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REVIEW

To evaluate the etiology of erectile dysfunction: What should we know currently?

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Summary ***Erectile dysfunction (ED) is the inability to develop normal erection or an hardening problem at various extent that causes inability to maintain the erection for the sufficient time required for a complete sexual activity. It can be the result of neurologic, psychogenic, vascular, urogenital and hormonal abnormalities. It is reported that it affects 52-67% of men between 40 and 70 years old. Numerous theories and opinions are issued in the literature in order to explain the hemodynamic changea that occur during erection and detumescence. Especially the effects of chronic diseases and psychogenic factors on the pathophysiology of erectile dysfunction are common matters of discussion in recent years. In this review, we will evaluate the current developments in the literature about the etiology of erectile dysfunction.***

KEY WORDS: Erectile dysfunction; Ethiology; Erection.

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INTRODUCTION

Erectile dysfunction (ED) is defined as not providing or not continuing, when provided, the required penis hardening in order to perform a successful sexual intercourse (1). Various aspects have been introduced in order to explain the mechanism of erection. In 19th century, it has been hypothesized that the essential factor for the success of erection could be venous occlusion. In 1933, *Howell* revealed the role of the arterial system and, in the same years, *Oswald Lowsey* showed that there was no erection in dogs after ischiocavernous and bulbocavernous muscles ablation and that erection easily occurred as the result of separated plication of these muscles by catgut stiches and more plication caused priapism (2). *Newman et al. (1964)* have shown that erection may occur in volunteers and human cadavers simply by isotonic solution infusion without venous construction (3). *Shiari et al. (1978)* concluded that despite the increase of venous drainage, arterial flux was excessively increased to overtop venous drainage. *Wagner (1981)* demonstrated that arterial flux was increased and, in return, venous drainage was decreased. Various theories were developed as aterial muscular bolsters *(Von Enbner, 1990; Kiss, 1921)*, arterial and venous bolsters *(Conti, 1952)*, duct theory *(Deysach, 1939)*, arteriovenous shunt *(Newman et al., 1964; Wagner et al., 1982)* and cavernous smooth muscle contraction *(Goldstein et al., 1982)* (3). Most of the information regarding to erection physiology is obtained along 1980s and 1990s. In addition to the role of smooth muscles that regulate arterial and venous blood stream, the role of three dimensional structure of the tunica albuginea and its role in venous occlusion are explained. An important stage for understanding the nervous control was to determine that nitric oxide (NO) is the primary neurotransmitter for erection and that phosphodiesterases turns penis back to its flask condition for the adjustment of smooth muscle tone. Furthermore it was revelead the role of endothelium and the connection between the cells by "*gap junctions*" (3).

PREVALENCE OF ERECTILE DYSFUNCTION

ED is one of the primary problems that affect the quality of life of people and its incidence is gradually increasng. In 2025, it is estimated that more than 322 million men will be affected from ED (4). On the basis of the epidemiological data, patient population and definition of ED, it has been shown that ED prevalence is between 16-25% (5). The overall prevalence of erectile dysfunction in men aged > 20 years was 18.4% suggesting that erectile dysfunction affects 18 million men aged 16-20 in the US (6). According to the results of this studies about ED prevalence, it has been shown that ED prevalence increases with age. ED prevalence ratios in the study of "*National Health And Social Life Survey*" (NHSLS) is found as 7% between the ages 18 and 29, 11% between the ages 40 and 49 and 18% between the ages 50 and 59 (7). The prevalence of sexual activity declined with age to 73% among respondents who were 57 to 64 years of age, 53% among respondents who were 65 to 74 years of age, and 26% among respondents who were 75 to 85 years of age. Among men, the most prevalentsexual problems were erectile difficulties (37%). Fourteen percent of all men reported using medication or supplements to improve sexual function (8).
In a study performed in our country, it was determined that in men over 40 years old mild ED is foun in 35.7%,

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moderate ED in 23% and severe ED in 6%. In this study, it was determined that the factors increasing ED prevalence are advanced age, low educational level, *Diabetes Mellitus* (DM), hypertension, psychological stress and prostate diseases (9). In another study; ED prevalence in Turkey was measured as 69.2% and it was shown that especially the moderate-severe level of ED prevalence increased by age (10). In the study of *Massachusetts Men Aging* (MMAS), it was shown that 9.6% of men between the ages 40 and 70 have severe, 25.2% moderate and 17.2% mild ED. Rate of complete ED increased from 5.1% in 40-year-old to 15% in 70-year old (9). This and similar studies have obviously shown that ED increases by age and libido possibly decreases by loss of erections. There are some evidences showing that decrement rate of erection is related to the frequency of sexual activities and that men with more active sexual lives are better protected (10).

In various studies, it was observed that there is a strong relationship between diabetes and ED. ED incidence in diabetics treated at MMAS is about 28% (11). According to a study, more than 6% of USA population is diabetic and ED is present in approximately 8 million of them (13). ED is observed in 32% of men with Type 1 DM and in 46% of men with Type 2 DM (14). ED occurs in 50% of men with DM within 10 years and 12% of men with DM are diagnosed after they have applied for ED (15). ED in patients with DM is seen three times more frequently than in the normal population (11).

Cardiovascular diseases may affect potency with various mechanisms. Although ED has occurred up to 45% in men after myocardial infarction, there are also evidences that there is a high incidence in the period before having a cardiac attack. In a recent cross-sectional multicentered survey study among randomly selected males visiting a cardiologist, overall, 56% had ED, with up to 86% in patients with heart failure (16). *Oaks and Moyer* reported that 8 ± 10% of all untreated hypertensive patients had ED at the diagnosis of hypertension (17). A recent study using the validated *International Index of Erectile Function* questionnaire reported a higher incidence of severe ED amongst hypertensive men than in the general population (18). In spite of the fact that hypertension causes ED by itself, frequently used antihypertensive drugs can also be a cause of ED (19).

ED is more frequent after cerebrovascular events with up to 85% incidence of ED reported. There is strong relationship between various neurological diseases and ED. It is reported that ED incidence is high in men with multiple sclerosis (about 70-80%) and that more than 50% of such men have also complaint about decreased libido. Such effects are not only based on autonomic and somatic neuropathies that affect men with multiple sclerosis, but they are also related to concomitant psychological factors such as depression and anxiety.

Chronic renal insufficiency (CRI) is related to a decrease in erectile function, decrease of libido and infertility. ED incidence in men with CRI is about 40%. It is thought that occlusion of cavernous arteries, veno-occlusive dysfunction, lack of testosterone, increase in prolactin levels, various drugs used, autonomic and somatic neuropathy and especially psychological factors are the reasons for ED in patients with renal insufficiency (20, 21). After a successful renal transplantation, 50-80% of the patients may return to their potency levels before the disease (22, 23). The relationship between ED and psychiatric diseases, chronic alcohol usage and chronic liver disease, malignancies, trauma and smoking was shown in various studies (24).

Psychogenic reasons

Psychogenic ED generally occurs in young adults under the age of 40. Although psychogenic ED rate in men over the age of 50 is approximately 10%, 45% of all ED patients have psychogenic problems (25). Sexual behaviors and penile erection are controlled by hypothalamus, limbic system and cerebral cortex. Thus stimulating or inhibiting messages may be transferred to spinal erection centers in order to ease or prohibit erection. Psychogenic reasons may be emotional problems such as depression and anxiety, previous traumatic sexual experiences, lack of self-confidence, suspicions in sexual roles, physical disorders in spouses and lack of attraction and also interparental conflicts or cultural differences, sexual myths or socioeconomical factors such as job stress. Two possible mechanisms explaining the inhibition of erection in psychogenic ED are the direct inhibition of the spinal erection center of the brain by excessive normal suprasacral inhibition or over sympathetic discharge and the increased peripheral catecholamine levels that inhibit the relaxation required for erection by increasing the penis smooth muscle tonus (26). Clinically it is reported that serum norepinephrine level is higher in patients with psychogenic ED when compared to normal controls or patients with vasculogenic ED (27).

Organic reasons

1. Vascular pathologies

In middle aged men, ED is generally vascular-derived accounting for 40-50% of all the etiological factors. According to the general population, pudendal artery lesions are seen more frequently in men with ED (28). Apart from that, ED is frequently seen in men with atherosclerotic diseases such as ischemic heart disease and arterial foot disease. Furthermore ED and cardiovascular diseases have similar risk factors such as hypertension, diabetes mellitus, hypercholesterolemia and smoking (29). Such findings show that ED is a different form of vascular diseases. In a study it was observed that low penile brachial pressure index can be a predictive factor for myocardial infarction and cerebrovascular events (30). Arterial diseases causing atherosclerotic or traumatic occlusion in hypogastric-cavernous-helix arterial branching decrease perfusion pressure and arterial blood flow through sinusoidal gaps, prolong time to maximum erection and reduce the rigidity of the erected penis. In most of arteriogenic ED patients, the decrease in penile perfusion is common. At arteriography of atherosclerotic ED patients, it was observed bilateral diffuse pathologic involvement of penile and cavernous arteries. Focal stenosis in penile or cavernous arteries is mostly observed in young patients who have been exposed to pelvic or perineal blunt trauma (31). Long-distance bicycle riding is a risk factor for neurogenic and vascular ED (32). In cavernous arteries of old men and men with DM, it were frequently observed fibrotic lesions together with intimal

proliferation, calcification or lumen stenosis. Nicotine does not only reduce the blood flow of the penis but also inhibits the corporeal smooth muscle relaxation and thus the normal venous occlusion and may affect negatively erectile function. It was reported that ED rate is about 70% at 30 year age in patients who are consuming 1 package of cigarettes per day and at 15 year age in patients who are consuming 2 packages of cigarettes per day (33).

As a result of uncontrolled venous leak, blood cannot be maintained in the cavernous bodies and erection cannot be obtained. Such group of pathologies account for 20-25% of all ED cases. Veno-occlusive dysfunction that is an important reason of ED may occur following the below mentioned pathophysiological conditions:

1. Presence or development of wide venous channels that drains corpus cavernosum
2. Insufficient compression of subtunical and emissary veins that are formed after degenerative changes in tunica albuginea (Peyronie's disease, advanced age, DM) or traumatic damage (penile fracture). In fat tunica albuginea that has lost its elasticity during Peyronie's disease may inhibit the obstruction of emissary veins 107,108. Tunica albuginea alteration may contribute to ED in men due to the reduction in elastic fibers and modification of its micro structure. Although rare, in patients who underwent to surgery for Peyronie's disease, changes in the subtunical aerolar layer may violate the veno-occlusive mechanism.
3. Structural changes in the fibroelastic content of trabecula, cavernous smooth muscle and endothelium may also cause venous leakage.
4. Individuals with anxiety may have insufficient neurotransmitter release or excess adrenergic tonus; insufficient smooth muscle relaxation and subsequent insufficient expansion of sinusoids and insufficient compression of subtunical venules may result in ED. It is shown that the changes in α adrenergic receptors or the decrease of nNO release may increase smooth muscle tonus and reduce the relaxation related to endogenous muscle relaxants (34).
5. Acquired venous shunts, operative correction of priapism, permanent shunts between glans/cavernosal body or cavernous body/spongiform body may cause ED.

2. Neurogenic reasons

Neurogenic reasons explain approximately 10-20% of ED cases. Medial preoptic area (MPOA), paraventricular nucleus and hippocampus are important integration centers for penile erection and sexual drive. Pathological situations that affect these regions such as Parkinson's disease, stroke, encephalitis or temporal lobe epilepsy are generally associated with ED. The negative effect of Parkinson's disease on erectile function may occur as a result of the imbalance in dopaminergic pathways. Tumor, dementia, Alzheimer's disease, Shy-Drager syndrome and trauma are other important brain lesions accompanying ED.

The grade of erectile function in spinal cord traumatic patients is mostly related to the quality, location and prevalence of the spinal lesion. While reflex in the upper motor neuron complete lesions of spinal cord is conserved at about 95%, erection can be provided in only 25% in the lower motor neuron complete lesions (35). It is known that sacral parasympathetic neurons have an important role in the protection of reflex of erection. Furthermore thoracolumbar pathway may compensate the losses related to sacral lesion via synaptic connections. Other diseases at spinal level (spina bifida, discal hernia, syringomyelia, tumor, transverse myelitis and multiple sclerosis etc.) may affect the afferent or efferent nerve pathways similarly (36).

3. Post-trauma and post-surgery ED

The mechanism of ED that develops after radical prostatectomy or cystoprostatectomy is generally neurogenic but ED may also be due to vascular reasons. After radical surgery, neurogenic lesion may generally develop in the cavernosal nerves in the posterolateral of prostate or in the pelvic plexus. In the past ED frequency after radical prostatectomy or urinary bladder surgeries was estimated about 100%; today this ratio varies between 35% and 68% depending on the surgical clinic, clinical and pathological stage and age of the patient as the result of the development of neuroprotective techniques (37, 38). ED prevalence in the patients exposed to transurethral prostate resection (TUR-P) due to benign prostate hyperplasia (BPH) varies between 4-10% (39). Cavernous nerve progresses at 5 and 7 o' clock at prostatic urethra level, 3 and 9 o'clock at membranous urethra level and 11 and 1 o'clock at penile urethra level. During TUR-P, the nerves may be damaged due to the energy released. Deep resection and coagulation at cavernous nerve transition points may cause the loss of erection.

It is reported that ED develops in 59% after abdominoperineal resections performed for rectum cancer (40). After retroperitoneal lymph node dissection and lumber symphatectomy, and during aorta-iliac and aorta-femoral surgery, ED develops in 10-20% due to the damage of nerves who regulate the reflex of erection (41). Due to the surgeries performed for head trauma and intracranial pathologies, influence of limbic system, destruction of hypothalamo-hypophyseal axis and modification of hormonal control may cause ED. Like perineal trauma (like overriding) and penis fracture, ED may develop after the traumas causing amendments in the anatomic structure of the penis. Additionally traumas causing posterior urethra ruptures destruct the reflex pathways of erection and may cause ED development at a rate of 10-50%.

4. Endocrinologic reasons

Hypogonadism in ED patients is a commonly seen pathology. Any disorder in hypothalamo-hypophyseal axis may result in hypogonadism. As hypogonadotropic hypogonadism can be congenital, it may also develop depending on a tumor or trauma. Hypergonadotropic hypogonadism develops as a result of various causes such as tumor, trauma, surgery or mumps orchitis. Hypophysis adenoma or drug-induced hyperprolactinemy can also cause ED. In hyperprolactinemy cases, symptoms such as decrease in libido, ED, galactorrhea, gyneacomastia and infertility may occur. High serum prolactin levels suppress the releasing hormone levels and reduce the testosterone levels.

ED can be seen together with hyperthroidism and hypothyroidism. Hyperthyroidism is associated to loss of libido that may be caused by the increase of levels of cir-

culating estrogen and rarely with ED. In hypothyroidism, plasma testosterone is decreased because of the reduced testosterone binding globulin. As a result, hypothyroidism may participate in ED pathogenesis by causing low testosterone release and high prolactin level.

5. Diabetes mellitus and ED

DM is a chronic disease that is commonly seen throughout the world with a prevalence ranging 0.5-2%. ED prevalence is three times more frequent in diabetic men (%28/%9,6). Diabetic ED occurs in young age and its incidence is the course of the disease. Although ED is seen more frequently in patients with neuropathic complications, its relationship with vascular damage is not yet clear. DM causes ED due to various physiopathologic mechanisms involving psychological functions, central nervous system functions, androgen release, peripheral nerve activation, endothelial cell proliferation and smooth muscle cell contraction (42).

In comparison to non-diabetic men, major atherosclerotic vascular lesions are seen 40 times more frequently in diabetic men and frequently DM accompanies ED. In men with DM, it was demonstrated that there is a decrease in the quantity and rigidity of night erections during sleep. Again some studies have specified that penile arterial insufficiency occurred in men with DM with rate ranging 75-100% (43).

The presence of ultra-structural changes is seen in the cavernosal tissues of diabetic men. These can be summarized as increased collagen ratio at smooth muscle level, thickening in basal lamina and loss of endothelial cells (41). It was also shown that there is a significant decrease in the relaxation responses to endothelial and neuronal NO. It was observed that neurogenic NO formation was significantly decreased in men with vascular ED when compared to patients with non-vascular ED and controls. A possible etiology that explains all these findings is the advanced stage of glycation end products (AGE) levels that are seen in diabetics. In various studies there are evidences showing alterations of the mechanisms causing NO release in relation to the increase of free oxygen radical production in diabetes that causes the decrease of vasodilatator response.

6. ED related to ageing and chronic diseases

In the literature, it is shown that there is a progressive deterioration in sexual functions due to ageing in healthy men. Changes, as prolongation of time to erection, erection weakening, strong loss of ejaculation, decrease in the ejaculate volume and prolongation in the resting period between two sexual intercourses have been described in association with ageing. Hypertension is an independent risk factor in the development of ED (44) and ED is seen more frequently in the patients who are treated for hypertension. Complications developed after hypertension such as ischemic heart disease and renal insufficiency increase the prevalence of ED. Severe ED prevalence in men submitted to hemodialysis for *chronic renal insufficiency* (CRI) is reported as high as 45% (45) and risk increases with increasing age, DM and not using *angiotensin-converting enzyme* (ACE) inhibitors. Various physiopathological effects such as permanent uremia, deterioration in the hypothalamus-hypophysis-testis sex hormone axis, hyperprolactinemia, increase in atheromatous diseases and psychological diseases cause ED development (46). Chronical diseases such as tuberculosis, tumors, leukemia can also cause loss of libido and ED. In scleroderma the rate of ED is about 60% due to thin penile arteries. In a study performed in brucella patients it is reported a ED rate of 68% in parallel with the duration of disease.

7. ED related to priapism and Peyronie's disease

Priapism is a pathological penile erection that is not related to sexual stimulation or that continues after sexual stimulation. Sickle cell anemia, trauma, neuoplasias, leukemia, intracavernosal injection, total parenteral nutrition and drugs (anti-depressants, anti-psychotics, α blockers as prazosin, heparin, warfarin, cocaine, etc.) are the agents that cause priapism. ED is observed in patients with priapism at a rate of about 11% (47). Peyronie's disease is one of the pathologies that affect the penis anatomy. ED incidence in Peyronie's disease is related to the severity of the disease. It is reported that anomalies due to the plaque have been observed at nocturnal penile tumescence in 5-7%.

Conclusion

In historical literature erection physiology was explained by different mechanisms. Aristo described 3 nerve fibers that carry spirit and energy to the penis and explained penile erection by air ingress (13), in 1504 *Leonardo da Vinci* showed that there is blood in the penis of men who were hung on (14), in 1573 Varolio showed that ischiocavernous and bulbocavernous muscles constrict the penis stem to achieve erection. Finally in 1585 in the book titled "*Ten Books and Production Book about Surgery*", *Ambroise Pare* described the penis as formed of concentric layers including nerves, veins, arteries,two ligament (corpora cavernosa), an urinary system and four muscles in 1585 in the book titled "*Ten Books and Production Book about Surgery*" (11, 14). These observations show us that ED has been a popular research area throughout history. We suggest that researches will be effective in increasing the knowledge of the etiology and pathophysiology of ED especially at molecular level and will offer us a deeper insight in the future.

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