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Erectile Dysfunction Etiological Factors

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1. Introduction

The prevalence of ED in men between 40 and 70 years old is approximately 50%. (Massachusetts Male Aging Study). There are many ED etiological factors, such as psychological, vascular, neurological and hormonal disorders. (Tomada, 2010; Kavoussi, 2007; Glina 2002).

In accordance with the International Society of Impotence Research, ED may be classified into three subtypes: organic (that includes iatrogenic, neurogenic, vasculogenic and hormonal), psychogenic and mixed erectile dysfunction. A thorough investigation ought to be performed by a multidisciplinary team in order to avoiding misdiagnosis. (Kavoussi, 2007)

The basic assessment is suggested by ED guidelines: detailed anamnesis and physical examination, fast serum glucose, total cholesterol and fractions, triglycerides and testosterone level. Long history of diabetes, alcohol abuse and spinal cord injuries suggest neurological ethiology. (Kavoussi; Tanagho & McAninch, 2007).

Patients without contra-indications must be recommended to use 5 phosphodiesterase (PDE5) inhibitors after first visit. Vascular integrity may be tested by PDE5 inhibitors response and good drug response usually mean vascular integrity. (Tanagho & McAninch, 2007; Glina, 2002)

Recent studies have demonstrated the association between ED and cardiovascular diseases Zambon, 2010; Bal, 2007. Ultrasensible C Reactive Protein (CRP) is an early marker of cardiovascular risk, and patients with ED have higher levels of CRP. Risk factors such as hypertension, smoking, obesity, diabetes mellitus, metabolic syndrome and sedentary lifestyle are pretty common in patients with coronary disease and ED (Zambon, 2010; Bal, 2007).

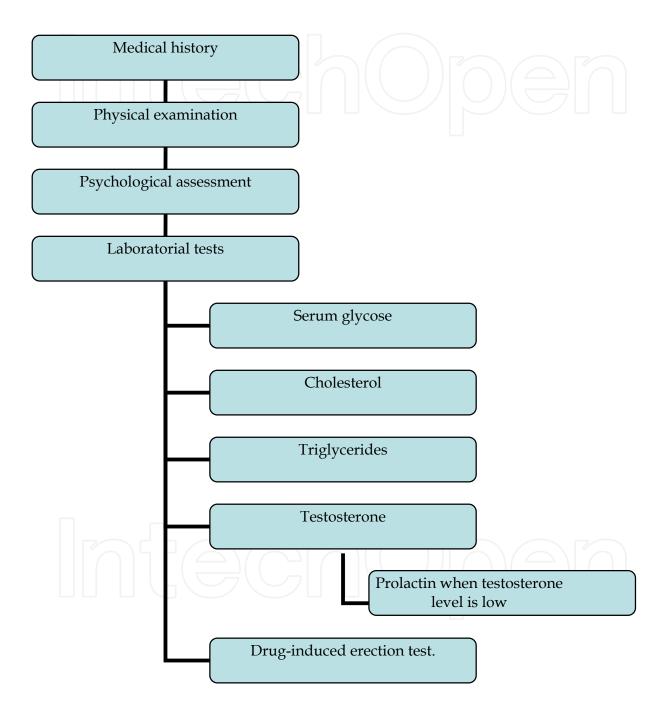
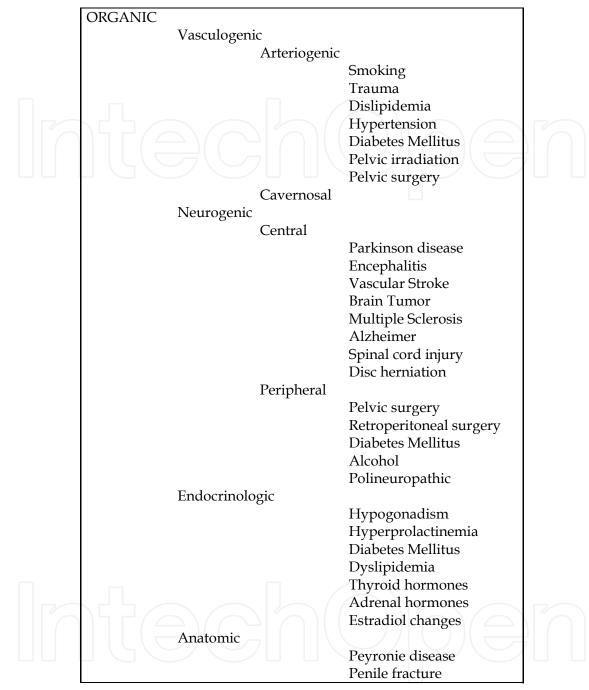


Fig. 1. Initial ED evaluation



2. Etiological factors

Table 1. ED organic causes

2.1 Anatomic factors

The most frequent physiopathology of these dysfunctions is low abnormal drainage, or severe alterations of penile geometry. Peyronie's disease, priapism and penile trauma are some examples of anatomic etiological factors. Physical examination can confirm penile shaft fibrosis, and Doppler ultrasound can identify the fibrosis with good sensitivity and specificity (Navarro, 2010; Persu, 2009).

2.2 Endocrinological factors

The endocrine disorders are directly or indirectly related with erection mechanism. Endocrine disorders can be associated or worsen the pre-existing ED. Among the etiological factors we can point out diabetes mellitus, obesity, hypogonadism, adrenals and thyroid dysfunction and Hyperprolactinemia. (Tanagho & McAninch, 2007; Kavoussi; Jabaloyas, 2010; Persu, 2009)

2.2.1 Diabetes mellitus

Diabetes Mellitus (DM) is one of the most frequent etiologies of ED. Patients with higher levels of glucose and glycated hemoglobin has higher risk of ED. The prevalence of ED in men with DM ranges from 10 to 90%. Risk factors for the emergence of ED in diabetic patients are: disease time, age, sedentary lifestyle and glycemic control. (Jabolayas, 2010)

Regarding PDE 5 inhibitors response, diabetic patients have lower response than normal patients. Furthermore, it is directly related to disease severity. Vascular and autonomic neuropathies are the main etiological alterations observed in diabetic patients. The main pathophysiological mechanisms proposed for ED in diabetic patients include the release of free radicals, increased endothelin receptor B, impaired nitric oxide synthesis and up-regulated RhoA/Rho-kinase pathway. (Jabolayas, 2010; Thorve, 2011; Moore, 2006)

2.2.2 Hypogonadism

Low testosterone level can decrease the libido, the morning erections and penile tumescence. It can also increase the risk of depression and psychiatric disorders. Furthermore, hypogonadic patients with ED have higher risk of early osteoporosis. (Tanagho & McAninch, 2007)

Studies have shown that hypogonadic men present high risk of metabolic syndrome and DM. The symptoms which are related to hypogonadism are common to many others diseases. It is advisable at least 2 consecutive dosages of total testosterone in the period between 7 and 11 a.m. The institution of compulsory treatment should be based on clinical and total dosage of testosterone. Moreover, hypogonadic patients may clinically present primary or secondary infertility. Thyroid, pituitary and adrenal disorders are less common etiologies, and in specific situations, alterations must be taken into account. (Traish, 2009)

2.2.3 Hyperprolactinemia

Hyperprolactinemia may be associated with reduced libido. The prevalence of hyperprolactinemia in men with ED varies between 2 and 13%. Prolactin above 35 ng/mL are associated with ED and decreased libido. (Jabolayas, 2010)

The mechanism by which elevated prolactin leads to ED, is not fully understood. This change is attributed to the reduction of testosterone and alterations in the pulsatile release of LH. There are several causes for elevated prolactin, for instance pituitary adenoma (most common cause), drugs (especially antipsychotics), chronic renal failure and herpes zoster. (Jabaloyas, 2010)

Guidelines recommended prolactin dosage when testosterone levels are low. The gold standard exam to evaluate pituitary adenoma is the magnetic ressonance imaging. (Tanagho & McAninch, 2007)

2.2.4 Changes in thyroid hormones

Changes in thyroid hormones are also associated with changes in libido, erectile function and ejaculation. The prevalence of thyroid diseases is variable and normalization of hormone levels can restore an adequate erection when the ethiology is the thyroid dysfunction .The hypothyroidism can decrease levels of free testosterone and SHBG, and hyperthyroidism appears to be strictly related to changes in libido. (Jabolayas, 2010; Cauni, 2009).

2.2.5 Dyslipidemia

Dyslipidemia is a risk factor for ED, and some patients are diagnosed during the ED investigation. The change in lipid metabolism is associated with endothelial dysfunction and abnormal relaxation of smooth muscle. (Vrentzos, 2007; Jabaloyas, 2010)

Hypercholesterolemia, high level of LDL and low HDL increase the risk of atherosclerosis, which may change the penile blood flow. Besides, hypercholesterolemia increases the proinflammatory markers and endothelial dysfunction. (Vrentzos, 2007; Bal, 2007)

Studies demonstrated a positive correlation between cardiovascular risks, hypercholesterolemia and erectile dysfunction (Zambon, 2010; Koenig, 2004) have demonstrated that men with ED had higher levels of C-reactive protein, which is an early marker of endothelial dysfunction and cardiovascular diseases. (Zambon, 2010; Koenig, 2004)

2.2.6 Changes of adrenal hormones

The role of adrenal hormones and their changes are not well established in the etiology of ED. Studies have correlated the low levels of dehydroepiandrosterone with ED. Androstenedione can be converted into testosterone and supplementation of this hormone may improve erectile function. Nevertheless, there is no justification dosage of adrenal hormones in the initial investigation of ED. In specific cases, the dosage of hormones produced in the adrenal, for example, cortisol, aldosterone, androstenedione, dehydroepiandrosterone, among others, is recommended. (Jabolayas 2010)

2.2.7 Changes in estradiol

The increased production of estradiol in men can be associated with ED. Elevated estrogen levels decrease the production of testosterone by inhibiting the LH production. The chronic liver disease may be related with the hyperestrogenism. Another uncommon etiology of hyperestrogenism is the endocrinologic neoplasms. (Jabolayas, 2010)

2.3 Vascular factors

The vascular dysfunctions are common in men with ED. Commonly, the vasoreactivity is reduced, and consequently low penile blood flow, hypoxia and fibrosis are the final results. These changes decrease the penile shaft stiffness over the time. (Tomada, 2010; Cauni, 2009; Odriozola, 2010)

ED seems to be an early marker of endothelial dysfunction, which can changes the vasoreactive substances production, such as nitric oxide and endothelin (Odriozola, 2010;

Hannan, 2010). Local growth factors seem also to be involved in the pathophysiology. Therefore, there is a reduced response to vasodilating substances and an increased sensitivity to vasoconstrictor agents. (Odriozola, 2010; Hannan, 2010)

Penile vascular abnormalities are strictly linked to cardiovascular risk factors such as hypertension, smoking, dyslipidemia, and DM among others. Diffuse and bilateral lesions in internal pudendal arteries, penile and cavernous as well are common in patients with atherosclerosis. (Odriozola, 2010, Hannan, 2010)

The evaluation of penile vascular function can be performed using Doppler ultrasound, magnetic resonance image or angiography, however, the real significance of these tests remains unclear.

2.4 Neurologic factors

The prevalence of ED as a consequence of neurological diseases ranges from 10 to 19%. In these cases, ED is moderate or severe, with poor response to oral therapy. (Cauni, 2009; Antuna, 2008)

The neurogenic etiology can be central or peripheral. Central disorders can be exemplified by Parkinson's disease, brain tumor, encephalitis, cerebral strokes, cranial trauma, epilepsy and multiple sclerosis. In the other hand, DM, spinal cord injury, and surgical trauma of the erector nerves during radical prostatectomy, polyneuropathy metabolic, toxic or congenital conditions among others, can be cited as peripheral neurogenic disorders. (Cauni, 2009; Antuna, 2008)

The basic neurological assessment must be performed in all patients with ED. Guidelines recommended the spinal cord reflexes evaluation, for example bulbocavernosum reflex, and sensitivity level. (Kavoussi, 2007)

2.4.1 Dysfunctional system

Multiple sclerosis is characterized by multiple areas of demyelization of the central nervous system. The prevalence of ED in men with multiple sclerosis is approximately 60%. Generally, multiple sclerosis is a progressive disease, with periods of acute crisis and remission. In the initial profiles, ED is mild; however, with the evolution of the disease, it becomes severe and unresponsive to conservative therapy. (Antuna, 2008)

Parkinson's disease is a neurodegenerative disease characterized by progressive decrease of gray matter's dopaminergic neurons. This process can achieve the mesolimbic and mesocortical regions and areas of the autonomic nervous system. Drug therapy with PDE-5 inhibitors can produce satisfactory results, but a careful analysis of these patients should be performed in order to improve the results and patient satisfaction. (Antuna, 2008)

In patients with epilepsy, the prevalence of ED is variable and the ethiology is multifactorial. ED secondary to cerebral strokes depends on many factors such as age, location and extent of stroke. Furthermore, co-morbidities and co-related diseases can worsen the ED prognosis. In general, traumas also can be associated with ED. Many patients develop psychogenic disorders, which may raise the ED incidence. (Antuna, 2008)

2.4.2 Spinal cord injuries

The spinal cord trauma is usually associated with automobilistic crashes. Generally, this kind of trauma affects the younger population who are economically active and the initial care of these patients should be performed by a multidisciplinary team, to avoid late sequel. (Kavoussi, 2007)

After the trauma, there is a phase of spinal shock, which has a variable duration, what occurs is a reflex abolition below the affected area. Over the time with spinal shock recovery, patients may have reflex erections. (Kavoussi, 2007)

The post spinal cord trauma depends on the level, extent and severity of trauma. In general, ED tends to be moderate to severe, and semen quality in these patients most frequently is poor. The use of medications can provide satisfactory results in some patients. A second option is the intracavernosal injections and penile prosthesis, which can be performed when other options did not have a good result. (Antuna, 2008)

In conclusion, the treatment of patients with spinal cord trauma should be individualized and carried out by a multidisciplinary team. (Antuna, 2008)

2.4.3 Peripheral dysfunction

The peripheral neuropathy may be related with many differents etiologies. The clinical manifestation is quite variable and the correct diagnosis must be made as always as possible to avoid unsuccessful treatment. ED is a symptom of this syndrome. In Brazil, in addition to DM, there is an increasing incidence of alcoholic polyneuropathy, due to the excessive consumption of alcoholic beverages. In this case, ED occurs late and is often irreversible. (Antuna, 2008; Abdo, 2006)

2.5 Pelvic surgery

Excluding skin cancer, prostate cancer is more common in men after age 60. Radical retropubic prostatectomy is the gold standard treatment of prostate cancer. The prostate-specific antigen (PSA) screening programs improve the early detection of this disease. (Zippe, 2006)

ED is a major surgical post-operative complication after pelvic surgery. The prevalence of ED after radical retropubic prostatectomy is approximately 50%, but depends on factors such as age, tumor stage, surgical technique, associated comorbidities, among others. The manipulation of the periprostatic nerve plexus can cause a transient neurological injury (neuropraxia) or permanent (neurovascular bundle injury). These lesions can induce hypoxia and collagen deposition in the corpus cavernosum. (Zippe, 2006; Gallina, 2010)

The vessel damage during surgery such as in the accessory pudendal arteries may cause a vascular insufficiency, by changing the irrigation of the erectile tissue. Furthermore, ligation of anomalous pudendal artery branches or venous plexus can induce the formation of fibrosis in the corpus cavernosum. (Zippe, 2006; Gallina, 2010)

ED can also occur after surgery to remove colon cancer, which is the most common cancers of the distal colon and at the junction between the rectum and sigmoid. Thus, the ED

incidence in patients undergoing colorectal cancer surgery varies between 10-60%. This incidence increases when there is need for neoadjuvant or radiotherapy adjuvant. A permanent colostomy also increases the rate of dysfunction to leading to alteration in body image. (Zippe, 2006; Gallina, 2010)

2.6 Cardiovascular risk factors

ED may be related to cardiovascular risk and may precede a cardiovascular event in 3-5 years. Studies have shown that ED is an early marker of endothelial dysfunction and atherosclerotic disease (Bryan, 2011; Blumentals, 2004).

The prevalence of ED in men with cardiovascular disease varies between 44 and 75%. (Muller & Mulhall, 2006). There is a strong correlation between cardiovascular disease and ED, since the risk factors are the same, such as hypertension, dyslipidemia, obesity, smoking, DM and sedentary lifestyle (Kupelian, 2006; Bal, 2007; Feldman, 2000; Derby, 2000)

The endothelium and the cavernous nerves are two sources of nitric oxide. Nitric oxide acts on smooth muscle relaxation during erection. The production and release of this substance depends on the integrity of endothelium. A nitric oxide response in men with ED is lower than in men with a preserved erection (Muller & Mulhall, 2006; Giugliano, 2004). Endothelial dysfunction is an early stage of vascular damage. Cardiovascular risk factors can cause endothelial damage leading to an impaired nitric oxide release, atherosclerosis and vascular stenosis. Endothelial dysfunction seems to play an important role in the development of both ED and cardiovascular diseases. Organic erectile dysfunction in a majority of men is due to the vascular diseases. (Muller & Mulhall, 2006).

Obesity is a multifactorial disease with high prevalence worldwide. Genetic, environmental and behavioral factors were identified as etiological factors. The incidence of obesity in men with ED is 30% higher than men without ED, (Muller & Mulhall, 2006). It is usually associated with other diseases such as, dyslipidemia, diabetes mellitus and hypertension.. In obese ones there is a peripheral resistance to insulin and a consequent hyperinsulinemia. Patients with higher body mass index are at greater risk of ED, even at the prospect of weight loss. Clinical factors like waist-hip ratio, body mass index and resting heart rate are significantly higher in patients with ED (Muller & Mulhall, 2006; Zambon, 2010).

Regarding hypertension, it has been demonstrated that the chronic changes in blood pressure, altering the flow of small vessels and penile vessels, which are associated with the development of the atherosclerotic disease can cause severe ED. A number of anti-hypertensive medications, such as beta-blocking drugs may have ED as a side effect (Muller & Mulhall, 2006).

Smoking as above mentioned is a risk factor for ED. It changes the mechanism of penile erection because it affects the smooth muscle relaxation. The prevalence among men with ED is 27.3% vs. 12.5% among men without ED. Not only the smoker, but passive exposure to cigarette smoke has a higher incidence of erectile dysfunction. Therefore, smoking increase the ED grade. (Feldman, 2000; Zambon, 2010; Muller & Mulhall, 2006).

Metabolic syndrome is also a significant risk factor in patients aged 40 to 49. In elderly men, this effect of metabolic syndrome on erectile function was not prominent, probably because

aging itself is a risk factor for erectile dysfunction. (Bal, 2007) ED may provide a warning sign and an opportunity for early intervention among men who had previously been considered to have lower risk of metabolic syndrome and cardiovascular disease (Kupelian, 2006; Muller & Mulhall, 2006; Zambon, 2010).

Preventive actions such as regular diet, physical activity, and hypertension and diabetes controls can decrease these risks and improve erectile function (Kratsky, 2009; Derby, 2000).

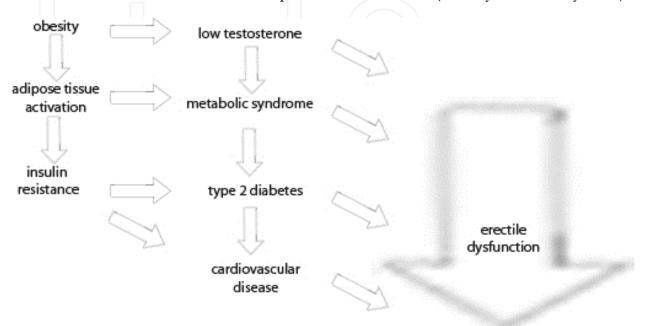


Fig. 2. Metabolic syndrome

2.7 Chronic renal failure

ED has a high incidence in patients with chronic renal failure (20-50%) and those underwent to renal transplantation. There is a positive relationship between the severities of both diseases. The cause of ED in these patients is multifactorial, including endothelial dysfunction, comorbidities, chronic hyperuricemia and psychogenic factors. Kidney transplantation can improve erectile function, due to the improvement of uremic neuropathy and anemia. (Phé 2008; Cauni, 2009).

2.8 Drug induced ED

Drug use may be responsible for up to 25% of all cases of ED. Among the medications that can induce it, we can highlight the drugs which affect the cardiovascular and autonomic nervous systems. Cauni, 2009).

Several studies have shown that intravitreal drugs such as bevacizumab (antivascular endothelial growth factor) can lead to a transient ED. The mechanism is not well established, but it is postulated that the systemic drug absorption may lead to an interaction with nitric oxide in the corpus cavernosum (Yohendran & Chauhan, 2010). Moreover, injection trauma can be associated with psychological effect, leading to temporary loss of erection. (Yohendran & Chauhan, 2010).

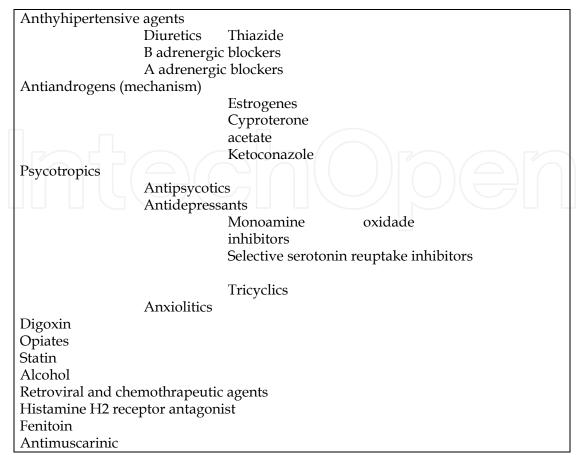


Table 2. Drugs induced **ED**

2.9 Psychogenic

In the past, psychogenic cause was considered the most important etiologic factor of ED, however, currently organic factors account for 60-90% of this condition. (Cauni 2009)

The pathogenesis of psychogenic ED is not well established. Many etiological factors have been studied, such as: neurotransmitters imbalance, autonomic dysfunction, etc. (Kavoussi 2007)

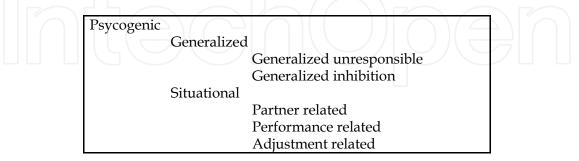


Table 3. Psycogenic ED causes

Performance anxiety related to several different causes ends up being the most common cause. Other causes are: an inappropriate sex education, traumatic childhood sexual experiences, a troubled marriage or relationship, stressful situations or psychiatric disorders. (Monseny, 2010)

Usually, psychogenic ED has short duration. Most commonly, patients have satisfactory erection in specific situations. (Abdo, 2006) Socioeconomic factors such as low income and poor educational background also have been associated withED. (Abdo, 2006).

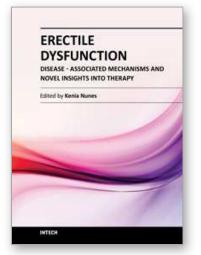
3. Conclusions

ED has a high prevalence in men over than 50 years. The incidence increase with aging and its ethiology appears to be multifactorial. The anamnesis and detailed physical evaluation ought to be performed in order to detect the main etiological factors. The best approach to obtain better results is to identify the main etiology. A multidisciplinary evaluation should be recommended for all patients.

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Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy Edited by Dr. Kenia Nunes

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Erectile dysfunction is a widespread problem, affecting many men across all age groups and it is more than a serious quality of life problem for sexually active men. This book contains chapters written by widely acknowledged experts, each of which provides a unique synthesis of information on emergent aspects of ED. All chapters take into account not only the new perspectives on ED but also recent extensions of basic knowledge that presage directions for further research. The approach in this book has been to not only describe recent popular aspects of ED, such as basic mechanism updates, etiologic factors and pharmacotherapy, but also disease-associated ED and some future perspectives in this field.

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