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Erectile Dysfunction: A Chronic Complication of the Diabetes Mellitus

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1. Introduction

Erectile dysfunction (ED) is defined as the persistent or repeated inability to achieve and/or maintain an adequate erection to accomplish a complete and satisfactory sexual activity. The term ED defines more accurately the nature of such dysfunction than the term impotence (National Institutes of Health (NIH) Consensus Conference, 1993; World Health Organization (WHO), 2000). ED manifests itself in the general population of adult males and increases with age. But it is more pronounced in individuals who suffer from diabetes, cardiovascular and metabolic problems. ED is one of the chronic complications of diabetes mellitus (DM), so the prevalence rate is very high in this group of men, and is one of the medical affectations with greatest impact on the quality of life of these patients. Because of the characteristic physiopathological alterations of DM, the damage caused mainly to the nervous and circulatory system favors the increased prevalence of ED (Kadioglu et al., 1994; Romero et al., 1997). In this chapter we discuss some aspects related to the epidemiology of ED and its prevalence in DM subjects, as well as the physiopathological mechanisms involved in this condition.

2. Epidemiology of ED

2.1 Epidemiology of ED in the general population

It has been estimated that ED affects around 100-150 million men worldwide and it is expected an increase of 322 million by 2025 (Bloomgarden et al., 1998; Laumann et al., 1999); being DM one of the main causes. It is important to note that ED is also reflected in

conditions that frequently coexist with DM, such as hypertension and cardiovascular disease (Benet & Melman, 1995). Epidemiological studies clearly show the high prevalence of this pathology. According with a number of studies, variables such as and the methodology employed, the estimated prevalence of ED varies from 19% to 75%. The data also showed that in addition to age, as an important factor, others such as lifestyle, food and tobacco consumption are highly associated to ED. It is estimated that the prevalence of ED varies according to the age of the population from 39% at the age of 40 years to 75% in men aged 80 years (Morley, 1986). In the Massachusetts Male Aging Study (MMAS), it was noted that the prevalence rate of ED of any grade was 52% (17% classified as a minimum, 25% moderate, and 10% severe) (Feldman et al., 1994). In another study performed in Spain known as EDEM [by its Spanish acronym: Epidemiología de la Disfunción Eréctil Masculina, (The Epidemiology of Male ED)], it was noted that the 19% of men between 25 and 70 years old have some degree of ED (16% classified as minimum, 2% moderate, 1% severe). This prevalence increases with age (8.6% in males aged from 25 to 39 years, 13.7% aged 40-49 years, 24.5% between 50 and 59 years, and 49% in people aged from 60 to 70 years) (Martin-Morales et al., 2001). Further information can be found in the work carried out by Kubin et al., in which they describe other several studies about the incidence of ED made around the world (Kubin et al., 2003).

2.2 Prevalence of ED in the diabetic population

Prevalence of ED is significantly higher in DM when compared to that found in the general population. The ED is associated with an increase in age (Fedele et al., 2001; McCulloch et al., 1980; Roth et al., 2003), poor metabolic control (Roth et al., 2003), time of evolution of DM (Klein, 1996; Roth, 2003), smoking (Bortolotti et al., 2001), consumption of alcoholic beverages, neurological damage (Lundberg et al., 2001), depression (Fedele et al., 2000), use of some drugs (Kleinman et al., 2000) and microvascular complications (Romeo et al., 2000) among other factors. Diabetic patients, with an inadequate control of their glycemic status, chronically suffer from neurological and vascular damages of penile smooth muscle, disruptions of endothelial function, a sustained increase in oxidative stress, formation of advanced glycation end-products, among others, all closely related to the physiology of erection. All these aspects are reviewed in detail in later sections of this chapter.

Epidemiological data show that the population of men with DM is more likely to develop ED. Data reported about ED in this population show a prevalence rate ranging from 35% to 78% depending on the age and general metabolic state of patients analyzed. In a study performed in 541 DM men aged 20-59 years, a prevalence rate of 35% of ED, and mainly attributed to microangiopathy; however, as mentioned before other factors such as age, type of treatment: oral hypoglycemic agents or insulin, the presence of retinopathy, symptomatic peripheral neuropathy, and symptomatic autonomic neuropathy (McCulloch et al., 1980) are also highly associated. Other studies report higher prevalence rates of 78%, of which 6% are mild, 36% moderate, and 36% severe. In this same study, it was found that the patients with non-insulin dependent diabetes that suffered of ED, had associated higher cardiovascular risks compared with the diabetic patients who did not have ED. Likewise, it was observed that the increase in cardiovascular risk factors is closely related to the severity of ED in diabetic patients (Meena et al., 2009). These elements suggest that ED is a common problem in diabetic patients and is a

direct consequence of an inadequate control of metabolic state in general and particularly of the glycemic state. ED has a multifactorial etiology but an appropriate diabetic patient's metabolic control is the best way to prevent this chronic complication of DM.

2.3 Prevalence of ED among patients with type-1 and type-2 DM

It is unclear whether erectile disorder is more common among men with non-insulin dependent diabetes (type-2, T2DM, late onset) or those with insulin-dependent diabetes (type-1, T1DM, early onset). Only a few studies include a prevalence of erectile disorder by diabetic type. In this regard, one study reported that men with elevated body mass index (BMI) and T1DM showed a significantly higher risk of ED than men with elevated BMI and T2DM. The same study also showed that the age-adjusted prevalence of ED was higher in men with T1DM (51%) than with T2DM (37%) (Fedele et al., 2000). But Miccoli et al., found that 40% and 52% of insulin-dependent and non-insulin dependent DM participants respectively had impotence (Miccoli et al., 1987). Fedele et al., in 2001 also reported that the incidence of ED in Italian men with diabetes was higher in T2DM than in T1DM (74 *versus* 45 cases per 1,000 person-years) (Fedele et al., 2001).

3. Basic mechanism of penile erection

Stimuli that can lead to penile erection include tactile stimuli to the penis and genitalia which will produce a reflex erection, while erotic stimuli, whether visual, auditory, olfactory or imaginative also produce penile erection by a mechanism which involves the paraventricular nucleus and medial preoptic area of the hypothalamus. A third mechanism is involved in the production of nocturnal erections that occur in all men during REM sleep (Eardley, 2002). The degree of contraction of the corpus cavernosum smooth muscle and the functional state of the penis is determined by the balance between proerectile and antierection mechanisms that operate physiologically in the penis. Vasoconstriction maintains the penis in the flaccid state. Erectile function is dependent on relaxation of the cavernous smooth muscle, and its mechanism of action is mediated by Nitric Oxide (NO). NO synthesized from L-arginine is the key mediator of endothelium-dependent smooth muscle relaxation, and likewise it is the key mediator of penile erection. After any stimulation, NO is released from non-adrenergic non-cholinergic (NANC) nerves through activation of neuronal nitric oxide synthase (nNOS). Binding of NO to soluble guanylate cyclase increases cyclic guanosine monophosphate (cGMP) levels and cGMP-dependent protein kinase-1 (PKG-1) activity, leading to smooth muscle cell relaxation and cavernosal dilation. Subsequent hemodynamic changes such as increased arteriolar shear flow stimulate the phosphatidylinositol-3-kinase/protein kinase B (Akt) pathway leading to activation of endothelial nitric oxide synthase (eNOS) in penile endothelium and further NO release. Occlusion of venous outflow is also required for sinusoidal filling and the maintenance of high intracavernosal pressure and erection. This veno-occlusion is achieved by the compression of the emissary veins that lie between the tunica albuginea and the expanding sinusoidal tissue (Hidalgo-Tamola & Chitaley, 2009).

Since erection is a complex process that involves the participation of vascular, endocrine, cellular and neuronal mechanisms; reason why any damage at these levels, favors the partial or total loss of erection. These damages are not only structural but also functionally. The figure 1 describes the main physiological mechanisms that regulate the erectile function, and the morpho-physiological organizations that might suffer damages during DM.

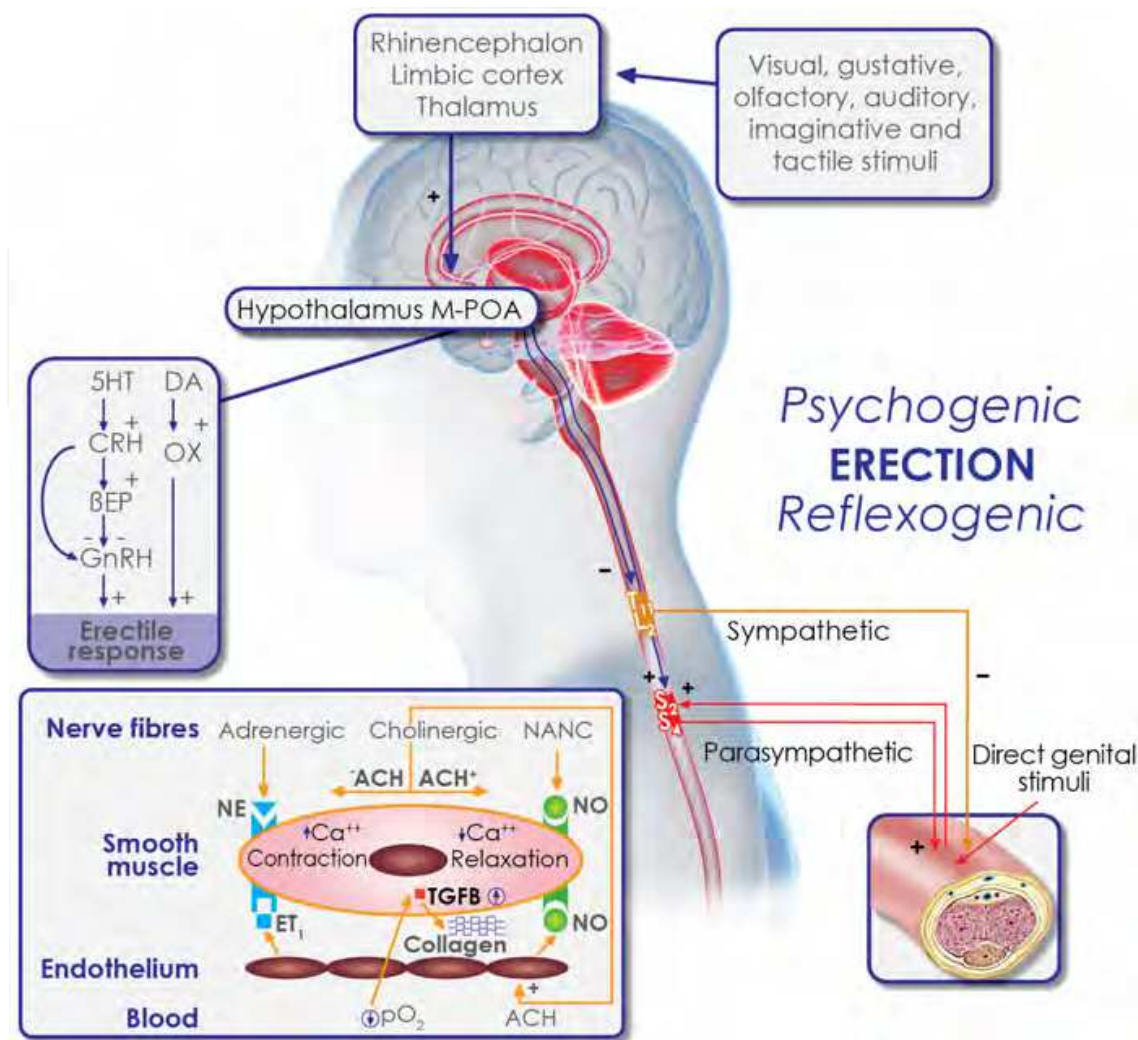


Fig. 1. Schematic representation of central and intracavernosal mechanisms involved in the control of erection. External visual, gustative, auditory, imaginative and tactile are transmitted to the rhinencephalon, the limbic cortex and thalamic nuclei, and are integrated into the hypothalamic medial preoptic area (M-POA) where they stimulate supraspinal erections (psychogenic erection). Up box: serotonin (5HT), corticotrophin-releasing-hormone (CRH) and β -endorphin (β EP) exert inhibitory effects, while gonadotrophin-releasing-hormone (GnRH), dopamine (DA) and oxytocin (OX) are the main stimulators of psychogenic erections. Hypothalamic projections (possibly oxytocinergic) to the spinal cord control thoracolumbar sympathetic (T11-L2) and sacral parasympathetic stimulation from (S2 to S4) fibers which inhibit and stimulate the erection, respectively. Direct genital stimuli initiate a local neural loop leading to parasympathetic stimulation from S2 to S4 and reflexogenic erection. Down box: intracavernosal mechanisms of erection involve cholinergic, adrenergic, and non-adrenergic non-cholinergic (NANC) nervous fibers. The main stimulators of smooth muscle cell contraction (detumescence) are norepinephrine (NE) and endothelin-1 (ET1), while acetylcholine (ACH) and nitric oxide (NO) are the main mediators of smooth muscle cell relaxation and erection via reduction of intracellular calcium (Ca^{+2}) content. Blood oxygen tension (pO_2) in the sinusoids inversely regulates smooth muscle cell transforming growth factor- β (TGFB) expression and collagen accumulation in the pericellular spaces. Modified from Fabbri et al., 1997.

4. Animal models of diabetes employed in the study of ED

In recent years, our understanding of human sexual function and dysfunctions has grown. Sexual responses are complex; therefore, different *in vivo* models exist, focused on the neurobiology, psychophysiology and different functional components of male sexual responses. When trying to understand how these preclinical models translate to humans, it should also be borne in mind that the primary purpose of sexual activity in animals is reproduction, while in humans it is predominantly recreational. The fact that animal sexual behaviors are highly stereotyped and species specific, it makes difficult to translate results in animal studies to humans (McMurray et al., 2006).

Erectile function monitoring intracavernosal pressure (ICP) is the most common method to preclinical monitoring the quality of an erectile response. ICP has been monitored in both conscious and anaesthetised animal models. The development of electronic data capture systems now allows various aspects of the ICP response to be measured. The typically measured endpoints include basal, peak, and plateau ICP, erection and detumescence time, duration of response, area under the ICP time response curve and the number of erections observed in a given time period. The aim is to use these end points to quantify the different phases and quality of the ICP response and the effect of the actions of drugs upon them (McMurray et al., 2006).

Despite this knowledge, clinical and epidemiological studies seldom separate type-1 (T1DM) and type-2 (T2DM) DM; however, this section will briefly highlight some of the T2DM animal models and animal models of DM induced by chemical treatments (T1DM) used to study the ED.

4.1 Rat models of T2DM

The obese diabetic Zucker rat (OZR) is a model for T2DM with glucose intolerance and an autosomal recessive mutation in the leptin gene. It develops hyperinsulinemia, insulin resistance, and hyperlipidemia at an early age with progression to proteinuria and glomerular injury (Kasike et al., 1992). Similar characteristics exist between the OZR and patients with T2DM including obesity, hypertension, and impaired vasodilation. The BBZ/WOR rat is a cross between the BB/WOR rat a model for autoimmune diabetes and a Zucker rat. Obese BBZ/WOR rats develop insulin resistance, and hyperglycemia with higher mean serum glucose levels compared with lean T2DM rats (Vernet et al., 1995). Otsuka Long-Evans Tokushima Fatty (OLETF) rats develop spontaneous diabetes by selective breeding. Male rats exhibit late onset hyperglycemia, hypercholesterolemia, and mild obesity. In this model, pancreatic islet cells changes mirror those seen in humans with T2DM (Kawano et al., 1992).

4.2 Mouse models of T2DM

Recently, mouse models of T2DM have been utilized to study ED. The high-fat diet fed mouse model was used as an ED experimental model (Xie et al., 2007). C57BL6 mice were fed a high-fat, high-simple carbohydrate, and low-fiber diet for 22 weeks, and developed obesity with a mean body weight of 39 g, and developed diabetes with a mean fasting serum glucose of 223.6 mg/dL. An additional mouse model of T2DM is the *db/db* mouse (Sharma et al., 2003). The *db/db* mouse has a mutation in the leptin receptor, and develops

spontaneous obesity, hyperglycemia, hyperphagia, hyperinsulinemia, and diabetic neuropathy, occurring from 10 days to 8 weeks of age.

4.3 Rabbit and rat models of T1DM induced by chemical treatment

The models of Alloxan-induced in rabbit (Chang et al., 2003; Vignozzi et al., 2007) and Streptozotocin-induced in rat (Vignozzi et al., 2007) of T1DM have been also used to study the ED.

Other animal models of T2DM and insulin resistance exist but have not been used to date to study mechanisms of ED during diabetes (Hidalgo-Tamola & Chitaley, 2009).

Findings gained from the study of some of these animal models have shed light on mechanisms underlying the cause of ED during DM. These factors include impaired vasodilatory signaling, cavernosal hypercontractility, and veno-occlusion, among others.

Although hyperglycemia is a common defining feature both: type-1 and type-2 DM, many unique characteristics distinguish these conditions, including insulin and lipid levels, obesity status, and inflammatory agent profiles. In the laboratory, the presence of ED has been established in animal models of both type-1 and type-2 DM. Impaired cavernosal vasodilation has been established in type-1 diabetic rodents. This dysfunction appears to be mediated by a severe defect in non-adrenergic-non-cholinergic nerve signaling, as well as impairment in penile endothelial function. In contrast, type-2 diabetic animals appear to have minimal impairment in parasympathetic-mediated dilatory function, but do have evidence of endothelial dysfunction. Type-2 diabetic models also exhibit a significant and striking increase in cavernosal contractile sensitivity, and a significant veno-occlusive disorder, neither of which is consistently reported in type-1 diabetic animals. With the distinct mechanisms underlying the ED phenotype in animal models of type-1 and type-2 diabetes, tailoring therapeutic treatments for diabetic-ED to the specific mechanisms underlying this disease complication may be warranted. Further examination of mechanisms underlying ED in DM patients may thus lead to significant changes in the way urologists diagnose, code, and treat diabetic-ED (Chitaley, 2009).

5. Mechanisms proposed to explain the ED in DM

From a historical perspective, theories pertaining to the pathophysiology of ED have changed as time has gone by. In the 1960's, the prevailing wisdom was that most ED had a psychogenic origin, and it was only in the second half of the 20th century, as we have gained increasing knowledge of the physiology of normal erectile function, that we have begun to understand the importance of vascular, endocrine, cellular and neural mechanisms in the development of ED (Eardley, 2002).

There are several ways of classifying the erectile dysfunction causes, for example as organic, psychogenic or mixed organic and psychogenic, with organic erectile dysfunction being the most common form (Maas et al., 2002). However, take into account the way in which disease can interfere with erection, the classification can be: psychogenic, vascular, neural, cellular, endocrine, and iatrogenic (Eardley, 2002). As was showed above by epidemiological studies (Feldman et al., 1994; Saigal et al., 2006), the risk of erectile dysfunction increases with diabetes and it is in relation with several pathogenic mechanisms in diabetes disease involved in precipitating and maintaining the ED.

As it is showed in the figure 2, the physiopathology of ED in DM is multifactorial and in the following section, we address some of these pathophysiological mechanisms being so far taken into account to explain the development of ED in DM.

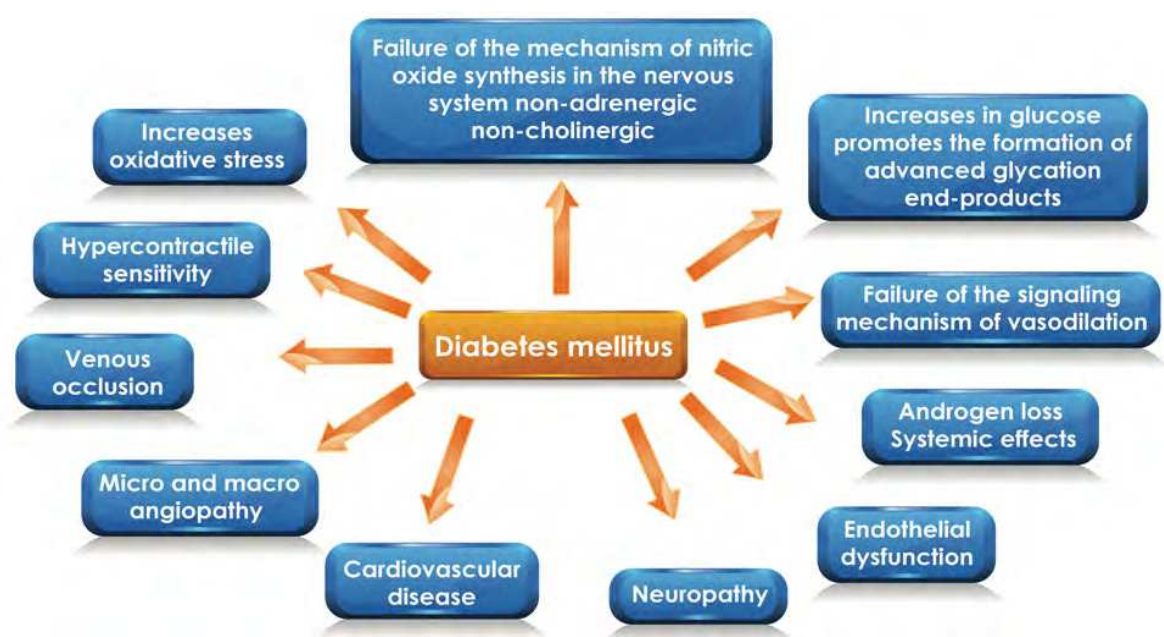


Fig. 2. Mechanisms of diabetes-associated erectile dysfunction.

5.1 Endothelial dysfunction

Several clinical and laboratory studies demonstrate that endothelial dysfunction is an important mechanism for the development of ED associated with T2DM. ED is usually described as a decrease in the bioavailability of NO, as a result of decreased expression and/or activity of eNOS, including increased removal of NO. Damage to the endothelium-dependent vasoreactivity has been demonstrated in various animal models of T2DM. Myograph in vitro studies in mice fed with a high fat diet, db/db diabetic mice and obese Zucker rats have shown that the ability of muscle relaxation of the cavernous tissue decreases even when stimulated with acetylcholine (Luttrell et al., 2008; Wingard et al., 2007; Xie et al., 2007). Jesmin et al., observed a decrease of the immunofluorescent staining of eNOS and the expression of this enzyme in the penile tissue of Long-Evans Tokushima Otsuka obese rats, with respect to controls (Jesmin et al., 2003). The decrease in eNOS mRNA expression suggests that reduced expression of eNOS is initiated at the gene transcription level. The alteration in the eNOS activation is another mechanism that contributes to decreased bioavailability of NO. eNOS activation occurs through phosphorylation of serine-177 residue by serine/threonine protein kinase Akt. In turn, the Akt-dependent pathway regulates the phosphorylation of eNOS mediated by the vascular endothelial growth factor (VEGF). The effects of VEGF include proliferation, migration, angiogenesis, and antiapoptosis in endothelial cells. VEGF increased the phosphorylation and expression of antiapoptotic proteins, mediated by eNOS. It is considered that in the ED, vascular repair mechanisms mediated by VEGF are damaged, probably because the expression of the VEGF and its receptors are altered in the cavernous endothelium, conditioning its angiogenic functions (Costa & Vendeira, 2007). In addition to the decreased

eNOS activity, the increased removal of NO by free radicals and oxidative agents has been shown to be important in the cavernous endothelial dysfunction in diabetes-associated ED models (Hidalgo-Tamola & Chitale, 2009). Endothelins (ET) are potent vasoconstrictor peptides that stimulate the contraction of trabecular smooth muscle of the corpus cavernosum. No one knows the exact involvement of ET on the pathogenesis of ED. High levels of ET-1 observed in diabetic patients could be enough to cause ED, although this does not happen. However, the high intracellular calcium concentration resulting from this condition modulates gene expression sufficiently to cause the proliferation of smooth muscle. Alternatively, alterations in ET receptor sensitivity in conditions such as diabetes and hypertension can enhance the processes of vasoconstriction. It is possible that the ET system may be relevant in ED, but under certain conditions where there is global endothelial dysfunction, such as diabetes and systemic sclerosis, the use of ET antagonists in these patients could be beneficial (Ritchie & Sullivan, 2010).

5.1.1 Failure of the signaling mechanism of vasodilation

Maintenance of cavernosal vasodilation has been hypothesized to occur through the activation of eNOS in endothelial cells, presumably in response to shear stress. Data from animal models of T2DM support the findings of impaired vasodilation in T2DM humans. Accompanying the impaired vasodilatory response, total penile NOS activity was found to be decreased in the BBZ/WOR rat model (Vernet et al., 1995). Similar result was showed by an age-matched case controlled study of 30 patients with T2DM and ED, where was found impaired the cavernosal vasodilation (De Angelis et al., 2001).

Vascular disease is probably the most common cause of ED, and of all the vascular causes, the commonest is atherosclerosis; however, DM joined with other risk factors, namely smoking, hypertension and hyperlipidaemia are also indirectly associated with the development of ED (Fig.3). A reduced arterial inflow leads to relative hypoxia within the penis with subsequent cellular effects. The crucial cellular mediator appears to be TGF-β1, which is increased in hypoxia and induces trophic changes in the cavernosal smooth muscle, and failure of the venous-occlusive mechanism (Feldman et al., 1994; Johannes et al., 2000).

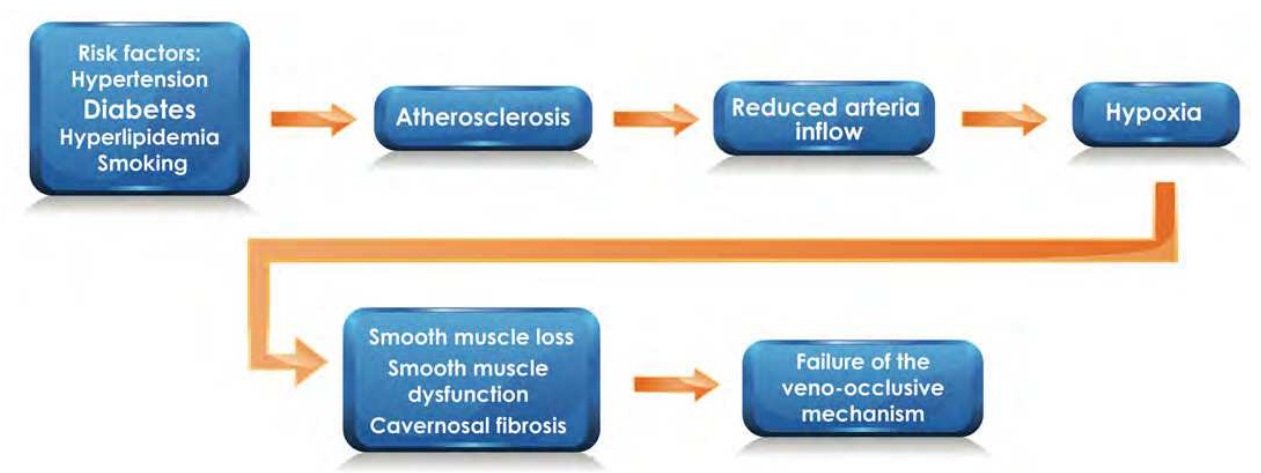


Fig. 3. Schematic representation of the relationship between the DM and other risks factors, with the development of vascular damages that favor the ED in the diabetic patient.

On the other hand, DM can injure cells and cause ED in a direct way. Diabetes damage the endothelium impairs the vascular response of the penis to neural stimuli. The structural changes in the endothelium that are produced by diabetes are accompanied by functional changes that result in impaired smooth muscle relaxation (Cartledge et al., 2001a; Saenz de Tejada et al., 1989). In the figure 4, it is possible observe the alteration of penile vascular endothelium of the rabbit with DM.

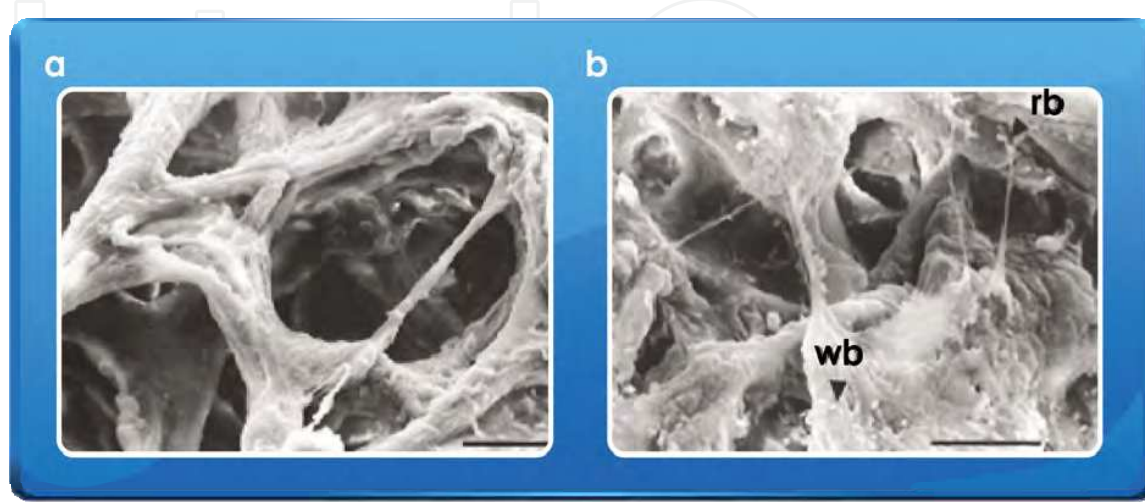


Fig. 4. Electron micrographs of normal penile vascular endothelium (a) and the effect of diabetes in the rabbit (b). Note the ragged appearance of the endothelium and the deposition of red (rb) and white (wb) blood cells in diabetes. (Micrographs published by the Dr. Ian Eardley in Pathophysiology of erectile dysfunction. (2002). *British Journal of Diabetes and Vascular Disease*, Vol. 2, No. 4, pp. 272-6, ISSN 1474-6514, by courtesy of Sullivan, M.

5.1.2 Venous-occlusive dysfunction

In ED, venous-occlusive dysfunction or venous leakage, involves the premature escape of blood inside the corpuses cavernous by incompetence of their drainage system and subsequent inability to reach the intracavernous pressure necessary to provide an effective stiffness. By Doppler studies and Pharmacocavernosometry, it has been observed that a high percentage of patients with T2DM present venous leak (Colakoglu et al., 1999; Metro & Broderick, 1999). Evidence from animal studies has demonstrated the importance of venous-occlusive dysfunction in the development of ED in T2DM. It is considered that the alteration in the process of veno-occlusion may be caused by changes in the structure of the penis, the cells and/or the content of the extracellular matrix. In this regard, the expression of VEGF has broad implications in the structure of the penis, resulting in changes in the rate of apoptosis. The decrease in VEGF expression correlates with elevated levels of pro-apoptotic proteins such as Bcl-2, so it is suggested that the decrease of VEGF in penile tissue in T2DM increases apoptosis and loss of erectile cells. In other studies with animal models of T2DM, there has been observed an alteration in the expression of collagen and the rate of smooth muscle/collagen in cavernous tissue. Likewise, decreased elastin has been found in the corpus cavernosum, specifically, decreased expression of tropoelastin mRNA, precursor protein of elastin and fibrillin-1. Structural alterations in the tunica albuginea caused by T2DM, could affect the compliance of the corpus cavernosum, required for veno-occlusion and intracavernous pressure maintenance (Hidalgo-Tamola & Chitaley, 2009).

5.1.3 Diabetic micro and macro angiopathy

Clinical and biochemical evidence support the participation of the microangiopathic complications of diabetes in the pathogenesis of ED. Multiple studies have shown that chronic hyperglycemia (which is the main determinant of the microangiopathic complications) is a strong risk factor for ED. Diabetes duration and other microvascular complications (i.e. retinopathy, neuropathy and nephropathy) are predictors of the occurrence of ED (Bhasin et al., 2007).

Somatic and autonomic nerve dysfunction is present in a large percentage of individuals with diabetes-associated ED (Chitale et al., 2009). Its presence is demonstrated by the existence of both, longer latencies in the evoked potentials of pudendal nerves and abnormal bulbar urethral and urethroanal reflexes. Diabetes causes degeneration of the nitrenergic nerves, which participates in the nitric oxide-dependent cavernosal smooth muscle relaxation. A central neuropathic mechanism has been postulated by several authors (Costabile, 2003).

Some of the biochemical mechanisms that induce endothelial dysfunction and decreased generation of nitric oxide participate also in the pathogenesis of diabetic neuropathy (Gur et al., 2009). An example is the oxidative stress. Superoxide radicals are present in high amount in cavernosal tissues. Superoxide anion reacts with nitric oxide to form peroxynitrite resulting in decreased nitric oxide bioavailability (Boulton et al., 2004). In addition peroxynitrite is a highly toxic compound for vascular cells and neurons. It causes mitochondrial dysfunction, oxidative DNA damage and apoptosis. Other examples are the activation of protein kinase C and the presence of advance glycation end-products (AGEs). 1,2-Diacylglycerol (DAG), a metabolite responsible of lipotoxicity in obesity and T2DM, activates protein kinase C (in particular the β isoform (PKC- β). These enzymes participate in multiple biological networks. This enzyme is activated also by free radicals. Experimental data suggest that activated PKC- β plays a major role in the hyperglycemia-related tissular damage; one of the possible explanations is the induction of the nuclear kappa B pathway. It is also involved in the cavernosal corpus smooth muscle contraction. On the other hand, chronic hyperglycemia causes the formation of AGEs which induces tissue damage by modifying molecules, activating inflammation and stimulating the synthesis of growth factors. AGEs modify cytoskeletal and myelin structure (England & Asbury, 2004). These changes correlate with a reduction in myelinated fiber density in peripheral nerves. Also, AGEs quench endothelium derived nitric oxide. As result, AGEs decreases smooth muscle relaxation and impairs erectile function (Thorve et al., 2011).

The macrovascular complications during the DM contribute to the development of ED (Chai et al., 2009). Vascular atherosclerotic disease of penile arteries is present in 70-80% of cases with ED. Occlusion of the cavernosal arteries could be a contributing factor in the long term. However, recent studies have shown that structural arterial changes in the penile vascular bed could exist even in cases with ED free of coronary heart disease.

5.2 Diabetic neuropathy

Neuropathy is a common complication of diabetes, in which there is nerve damage as a result of hyperglycemia. The damage involves both somatic and autonomic nerves. Autonomic nerves of the parasympathetic division stimulate relaxation of the muscles in the

penis; with the resulting erection, those of the sympathetic division are responsible for the contraction of muscles in the penis and thus maintain penile flaccidity. Although the mechanisms by which it occurs are not completely clear, it is known that nerve fibers are structurally modified by the effect of substances derived from the metabolism of excess glucose, which determines the loss of myelin. The loss of myelin promotes delayed nerve transmission, both reception of motor commands and other. Likewise, it is considered that the damage is caused in turn by the injury of blood vessels supplying the nerves. Neuropathy is another important mechanism responsible for diabetes-associated ED (Costabile, 2003). Diabetes is notorious for its microvascular complications, particularly autonomic neuropathy and peripheral neuropathy (Agarwal et al., 2003). It has been noted that patients with diabetic and neuropathic ED have similar frequencies of somatic and autonomic nervous system neuropathies, suggesting that neuropathy contributes significantly to the diabetes-associated ED. A recent study showed the connection between diabetic and neuropathic ED, demonstrating the presence of apoptotic pathways in the cavernous nerves in both disease processes (Mc Vary et al., 2006). The underlying cause of ED, which is the result of diabetic neuropathy, might be linked to selective nitrergic degeneration, which has been observed in the diabetic rat penis. This selective neurodegeneration seems to result in decreased nNOS activity and decreased NO production, which leads to damage nitrergic relaxation of corpus cavernosum in diabetic patients (Cellek et al., 1999). Additionally, NO could participate in the selective nitrergic degeneration through the formation of oxygen free radicals. It has been suggested that oxidative damage secondary to the production of peroxynitrite derived from NO may contribute to neurodegeneration (Cartledge et al., 2001a; Cellek et al., 1999). Several studies have shown that inhibition of NO synthase and NO production; prevent nitrergic degeneration, suggesting that this is a NO dependent process (Cellek et al., 1999).

5.2.1 Failure of the mechanism of nitric oxide synthesis in the nervous system non-adrenergic non-cholinergic

DM is one of the major risk factors to develop ED. Hyperglycemia is considered the cause of many vascular complications and metabolic alterations associated with both T1DM and T2DM. Diabetes-associated ED has been attributed to a reduction in the number of NOS-containing nerves, the impairment of NOS activity, and both neurogenic- and endothelium-mediated smooth muscle relaxation, and also to downregulation of the mediators downstream from NO, such as cGMP and PKG-1, in the corpus cavernosum (Musicki & Burnett, 2006).

In the cell, NO synthases have to compete, with other enzymes with activity of arginases, for the substrate L-arginine. Inhibition of arginase activity by 2(S)-amino-6-boronoheptonic acid (ABH) has been shown to cause significant enhancement of non-adrenergic, non-cholinergic nerve-mediated relaxation of penile corpus cavernosum smooth muscle, suggesting that arginase inhibition sustains L-arginine concentrations for be used in the NO synthesis (Cox et al., 1999). Moreover, another study demonstrated that diabetic corpus cavernosum from humans with ED had higher levels of arginase II protein, gene expression and enzyme activity than normal human cavernosal tissue. The impaired ability of diabetic tissue to synthesize NO was reversed by the selective inhibition of arginase activity by ABH. Increased expression of arginase II in diabetic cavernosal tissue may therefore contribute to

the diabetes-associated ED (Bivalacqua et al., 2001). Another explanation for decreased eNOS activity in the diabetic penis can be due to a reduced penile L-arginine content. Oral administration of L-arginine to diabetic rabbits increases endothelium-dependent relaxation of cavernosal tissue by improving the NO biosynthesis (Yildirim et al., 1999).

5.3 Oxidative stress

Oxidative stress occurs when there is an imbalance between pro-oxidants and the ability of the antioxidants to scavenge excess reactive oxygen species. However, its role in ED has not been investigated comprehensively but, significant associations between the production of reactive oxygen species and ED have been showed, especially in diabetic animal models.

NO is a highly reactive free radical that undergoes nonenzymatic reaction with oxyhemoglobin or that reacts with free radicals, such as superoxide anion, to form peroxynitrite (Beckman & Koppenol, 1996). This observation first highlighted the importance of oxidative stress in ED.

Reactive oxygen species (ROS) are formed during regular metabolism due to the univalent reduction of oxygen molecule. Superoxide (O_2^-) is the most important among the ROS. Hydrogen peroxide (H_2O_2), hypochlorous acid (HOCL), and peroxynitrite ($OONO^-$) are other important free radicals implicated in the pathophysiological mechanism of vascular disease. The vascular endothelium is the major source for these free radicals (Beckman & Koppenol, 1996). Superoxide dismutase (SOD) is an important enzyme that removes the superoxide radicals from the human body. There are 3 types of SOD isoenzymes: cytosolic, mitochondrial, and extracellular. Extracellular SOD reportedly plays a critical role in maintaining the redox state of vascular interstitium and thereby prevents the pathophysiological effects of superoxide in the vasculature.

The interaction between NO and reactive oxygen species (ROS) is one of the important mechanisms implicated in the pathophysiological process of ED. NO interacts with superoxide to form peroxynitrite, which has been reported to play a central role in atherogenesis. Peroxynitrite reacts with the tyrosyl residue of proteins, which inactivates superoxide dismutase and leads to decreased removal of superoxide. This further increases the formation of peroxynitrite and reduces the available NO concentration. Peroxynitrite causes smooth-muscle relaxation but is less potent than NO. Also, peroxynitrite and superoxide have been reported to increase the incidence of apoptosis in the endothelium. This leads to denudation of endothelium and further reduction of available NO (Agarwal et al., 2006). On the other hands a reduced NO concentration aggravates the adhesion of platelets to the endothelium, and the co-adhesion of neutrophils to platelets as well as the endothelium through the expression of adhesion molecules, releasing large amounts of superoxide which reduces more the available NO by the formation of peroxynitrite, countering erectile drive as well as promoting further more adhesion of platelets and neutrophils. Under this condition, is favored the releasing of substances (thromboxane A2 and serotonin) that cause vasoconstriction (Jeremy et al., 2000), taking place a vicious circle that generates the vasculopathic erectile dysfunction.

Another mechanism has been implicated in diabetes-associated ED is the activation of protein kinase C, this is an enzyme that modulates several cellular events, and increased levels of this enzyme are associated with increased production of ROS and reduced levels of NO, which can be prevented by administration of antioxidants (Ganz & Seftel, 2000).

The studies demonstrate that oxidative stress has a vital role in the development of diabetes-associated ED. Hyperglycemia is an important mediator of increased production of ROS leading to impaired endothelial function and structural impairment in the diabetic corpus cavernosum. The corpus cavernosum of diabetic rats and diabetic men with ED exhibits increased lipid peroxidation, upregulation of superoxide anion, and decreased antioxidants levels, suggestive of oxidative stress (Bivalacqua et al., 2005).

5.4 Involvement of advanced glycation end-products

The proposed mechanisms for ED in DM patients include: damage in the synthesis of NO, reduction in the activity of PKG-1, increased endothelin and endothelin B (ETB) receptor binding sites; ultrastructural changes in the endothelium, upregulation of the RhoA/Rho-kinase pathway, neuropathy, increased levels of oxygen free radicals and elevated concentration of advanced glycation end-products (AGEs) (Jiaan et al., 1995; Moore & Wang, 2006; Sullivan et al., 1997; Thorve et al., 2011).

Hyperglycemia in DM leads to AGEs, which are derived from non-enzymatic glycosylation reactions, actually known as glycation. Glucose reacts with amino groups, producing what is known as a Schiff base. Schiff base is modified to form more stable Amadori products. Some of these Amadori products undergo irreversible chemical changes and become AGEs (Brownlee et al., 1988; Cárdenas-León et al., 2009; Cartledge et al., 2001b) (Fig. 5). The action of AGEs is mostly via cell surface receptors, such as the receptor for AGEs (RAGE), P60/OST48 protein (R-1), 80KH phosphoprotein (R-2) and galectin-3 (R-3), scavenger receptor II, lactoferrin-like polypeptide, and CD-36 (Basta et al., 2004). Some of the receptors are likely to contribute to clearance of AGEs, whereas others may mediate many of the adverse effects, such as quenching of NO, impairment of extracellular matrix and tissue remodeling, modification of circulating proteins, and receptor-mediated production of ROS. AGEs can also form covalent bonds with collagen vascular, leading to thickening of blood vessels, decreased elasticity, endothelial dysfunction and atherosclerosis (Bucala et al., 1991; Singh et al., 2001). AGEs are accumulated during aging (Jiaan et al., 1995) and diabetes. They are formed abundantly when glucose remains high for prolonged periods (Bucala et al., 1991; Seftel et al., 1997). AGEs have been found elevated in the corpus cavernosum and tunica albuginea of the penis of diabetics rats and humans (Cartledge et al., 2001b; Cirino et al., 2006; Jiaan et al., 1995; Seftel et al., 1997). It is thought that AGEs may contribute to diabetes-associated ED, generating oxygen free radicals, which induce cell damage by oxidative processes and also remove NO, culminating with the decrease of cGMP and affecting the cavernous smooth muscle relaxation (Bivalacqua et al., 2005; Cartledge et al., 2001b). AGEs may take effect at the molecular level on different channels and receptors in cavernous smooth muscle cells, particularly on potassium channels, which facilitate the release of intracellular calcium and subsequent cavernous smooth muscle relaxation. Damage to the potassium channels could lead to lost of the relaxation capacity of the cavernous smooth muscle and to early onset of diabetes-associated ED (Cartledge et al., 2001b; Costabile, 2003). Also, AGEs are considered to be related to ED during diabetes by increasing the expression of mediators of vascular damage such as VEGF and ET-1, which have mitogenic and vasoconstrictor activities (Morano, 2003). Several studies have shown damage to smooth muscle relaxation in the corpus cavernosum and penile ED in diabetic rat in the presence of AGEs (Cartledge et al., 2001b; Usta et al., 2003). Also, it has been observed that under conditions of diabetes, the combined effect of AGEs and their receptor (RAGE), may increase the activity of ET-1 in the cavernous

tissue and thus promote the development of diabetes-associated ED (Chen et al., 2008). The involvement of AGEs in diabetes-associated ED has been demonstrated by using aminoguanidine, an inhibitor of AGEs formation (Usta et al., 2004) and ALT-711, a compound that breaks down formed AGEs (Usta et al., 2006), and observing improvement in endothelium-dependent cavernosal smooth muscle relaxation in vitro (Cellek et al., 2004) and erectile responses in vivo (Usta et al., 2003).

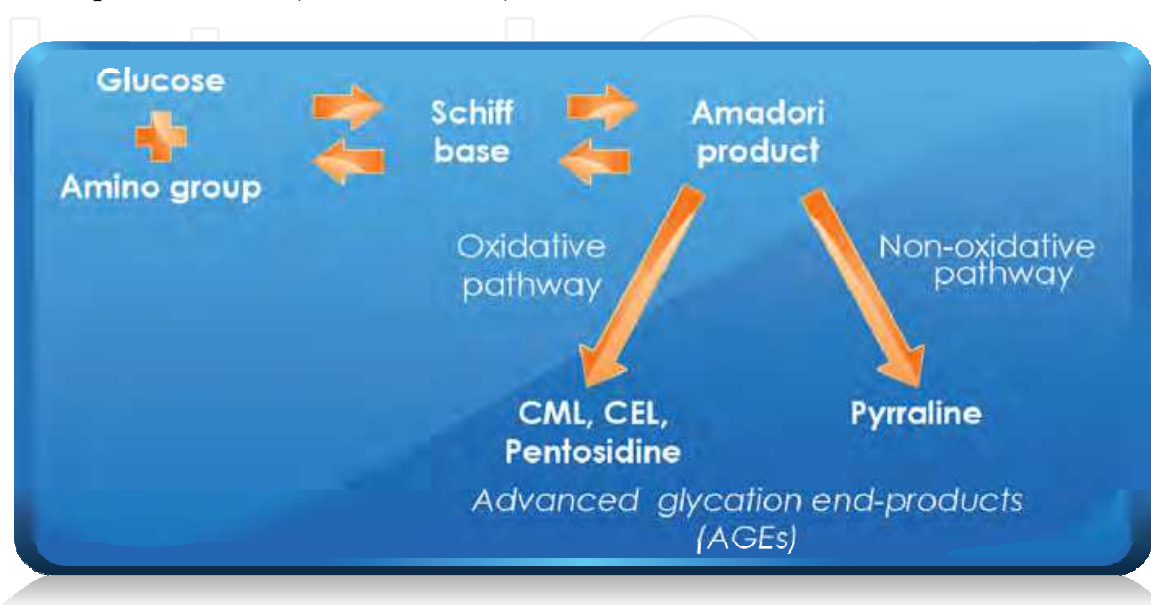


Fig. 5. Schematic representation: mechanisms of main Advanced Glycation End-products (AGEs) formation. CML: Carboxymethyl lysine; CEL: Carboxyethyl lysine.

5.5 Hyper-contraction of the cavernous body

ED is more common in diabetic patients. Hyperglycemia among others, leads to an altered vasodilator neural impulse, causing smooth muscle hyperkinesis and altered veno-occlusion process (Hidalgo-Tamola & Chitaley, 2009). Hypercontractility of corpus cavernosum may occur as a result of heightened sympathetic nervous system activity and/or increase in signaling to smooth muscle. The role of hyperkinesis of smooth muscle cells during T2DM-associated ED is difficult to discern from clinical studies, since most of them combine patients with T1DM and T2DM in the same group of evaluation. However, several animal studies suggest the importance of hyperkinesis in T2DM-associated ED.

Hyperinsulinemia and insulin resistance are associated with overactive sympathetic nervous system, which increases smooth muscle tone and keeps the penis in flaccid state. Currently it is unclear whether the increase in contractility is only due to sympathetic overactivity or the gloom of the signaling pathways in smooth muscle play a predominant role (Carneiro, 2008). The results obtained by using diabetic obese Zucker rats as an experimental model, suggest that increased smooth muscle tone is mediated by protein kinase C and RhoA/Rho-kinase pathway (Wingard et al., 2007). During normal erection, this pathway is inhibited by NO (Mills, 2002), but during diabetes the RhoA/Rho-kinase pathway activity is elevated and suppresses eNOS gene expression and enzyme activity in the penis (Bivalacqua et al., 2004). It has been reported that corpus cavernosal tissue,

obtained from alloxan-induced diabetic rabbits, exhibits increased RhoA and Rho-kinase β expression (Chang et al., 2003). It is considered that other modulators of tone of smooth muscle cells might be involved in T2DM-associated ED. In addition to the altered vasodilator stimuli and increased contractility of the corpus cavernosum, which limit the flow of blood into the penis, the inability to limit the outflow of blood due to a disorder of veno-occlusion, may also be a factor in T2DM-associated ED. ED during diabetes is associated among others with decreased PKG-1. In smooth muscle a major target of the PKG-1 are the calcium-sensitive potassium channels (BK_{Ca}), the overactivation of which hyperpolarizes smooth muscle cells, causing relaxation. But during diabetes the activity of PKG-1 and therefore the activity of the BK_{Ca} are low and the relaxation mechanism is affected. It has been observed that the elimination of BK_{Ca} channels in an experimental model causes hypercontractility of the smooth muscle and ED (Werner et al., 2008).

5.5.1 Relationship between glycaemia, dyslipidemia, hypertension and its medical treatment with ED in DM patients

The hyperglycemia and dyslipidemia associated to DM favors the mechanisms of oxidative stress, endothelial damage and the development of atherosclerosis (Li, et al., 2011; Kumar, et al., 2010) leading to hypertension as consequence of endothelial dysfunction and loss of vascular relaxation. Due to these considerations, it is extremely important the metabolic control of DM subjects to avoid the appearance of ED.

Weight loss is the prime objective of therapy. Several studies in which intensive lifestyle programs or bariatric surgery were implemented to lose weight have shown that erectile function improves in direct proportion with the difference in body weight. The potential mechanisms include improved endothelial function and nitric oxide bioavailability, decreased inflammation, increased testosterone plasma levels, and improved mood and self-esteem. In addition, weight loss is the cornerstone for the treatment of hyperglycemia, hypertriglyceridemia, arterial hypertension and hypoalphalipoproteinemia (Khatana et al., 2008). Patients should be encouraged to quit smoking, to reduce their alcohol intake and to give up recreational drugs. Prescription drugs and over the-counter medications should be checked for possible contributors to ED. Relationship counseling and a psychiatric medication is useful to treat anxiety and depression.

An association exists between glycemic control and ED in men with diabetes. Hermans et al., analyzed 221 consecutive male outpatients with T2DM in whom ED was assessed using the International Index of Erectile Function (IIEF-5) questionnaire (Hermans et al., 2009). Patients with ED ($n=83$) were compared with an age-matched controls ($n=51$). Patients with poor control have increased risk for ED compared to patients with good control. Body weight and adiposity are significantly associated with ED. Obesity is associated with an odds ratio of 1.5 to 3 for having ED. Other measures of adiposity, including the waist-to-hip ratio and abdominal circumference, are also independently associated with ED. A sedentary life style increases the risk, independently of its effect on body mass index. Arterial hypertension and abnormal plasma lipid level, common co-morbidities of T2DM, are associated with ED. Both are linked with endothelial dysfunction, reduced nitric oxide synthesis and increased free radicals synthesis.

Several authors have proposed that treatment of hyperglycemia and cardiovascular risk factors should be part of the treatment of ED. Although this proposal is clinically sound, no

major randomized controlled studies are available to support it. Only the EDIC trial (Epidemiology of Diabetes Intervention and Complications study) have partially evaluated it. The EDIC study is an extension of the DDCT trial, a landmark study that demonstrated that the correction of hyperglycemia reduces the incidence of microvascular complications. A substudy of the EDIC trial (Uro-EDIC) was designed to evaluate the impact of the correction of hyperglycemia on the incidence of urologic complications. ED was assessed using the IIEFF questionnaire. The effect of treatment was evaluated separately in cases ($n=280$) with or without ($n=291$) microvascular complications. No difference was observed in the incidence of ED between men randomized to intensive *vs.* conventional therapy (OR 1.24, 95% CI 0.68-2.28) in cases free of microvascular complications at the beginning of the study. In contrast, intensive therapy resulted in a smaller incidence of ED among men with microvascular complications (OR 0.33, 95% CI 0.18-0.60). Regrettably, ED was not included among the study outcomes of the main trials that have evaluated the effect of intensive treatment of hyperglycemia (i.e. ACCORD trial) in men with T2DM. Future studies including validated ED measurements, adequate sample size and important potential confounders are needed to measure the benefit of intensive glycemic control in men with poorly controlled diabetes.

5.6 Androgen loss systemic effects

The erectile response in mammals is regulated by androgens; in particular it has been confirmed that testosterone is an important regulator of the erectile function (Yassin & Saad, 2008). It is known that 6-12% of men between 40 and 69 years old suffer from hypogonadism. In adult men the disease is manifested by erectile dysfunction, among others. Male hypogonadism, which is also called testosterone deficiency syndrome, is characterized by failure of testicular testosterone production and is especially common in men with T2DM, affecting one third of them. Testosterone acts on the penile tissues involved in the mechanism of erection, so deficiency of this hormone, impairs erectile capacity. The pathophysiological mechanisms of low circulating testosterone concentrations are unknown, but it has been suggested that obesity associated with T2DM, helps to reduce testosterone levels by increasing the conversion of testosterone to estradiol in adipose tissue. The increase in the concentration of estradiol leads in turn to a suppression of hypothalamic gonadotrophin releasing hormone (GnRH), which is evidenced by a reduced secretion of pituitary gonadotropins (luteinizing hormone, LH and follicle stimulating hormone, FSH), which reduces in turn the secretion of testosterone by the Leydig cells and spermatogenesis in the seminiferous tubules, thus manifesting as hypogonadism. This may explain the inverse relationship between BMI and plasma concentrations of testosterone (Dhindsa et al., 2004; Grossmann et al., 2008; Kapoor et al., 2007; Rhoden et al., 2005; Traish et al., 2009). Male hypogonadism is associated with increased adipose tissue. In men with more than 160% of ideal body weight, concentrations of plasma testosterone and sex hormone-binding globulin (SHBG) are usually low while estrogen levels, from the conversion of adrenal androgens in adipose tissue, increase. In men with morbid obesity weighing more than 200% over the ideal weight, free testosterone may decrease. The concentrations of free testosterone and SHBG show an inverse relationship with waist circumference (WC) (Osuna et al., 2006; Pasquali et al., 1997; Svartberg, 2007). With the increase in adipose tissue also increases the production of leptin; favors the insulin resistance and therefore the appearance of hyperinsulinemia. Under these conditions, both leptin and insulin act on Leydig cells and inhibit testosterone synthesis (Pitteloud et al., 2005; Soderberg et al., 2001) (Fig. 6).

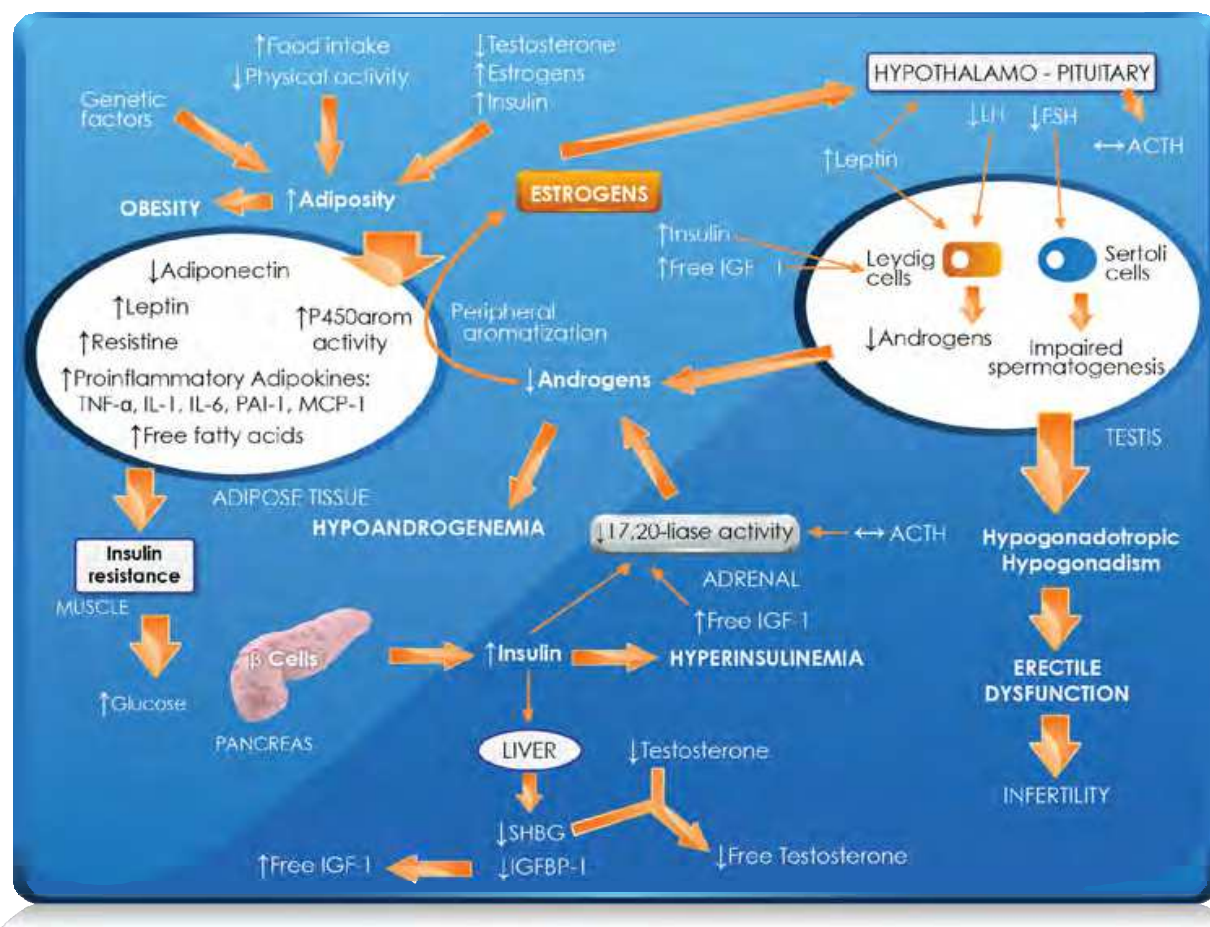


Fig. 6. Relationship between obesity, androgen deficiency (hypogonadism), metabolic syndrome and ED. The increase in adipose tissue and its accumulation in abdominal region, increases the production of adipokines and free fatty acids, this in turn, generates insulin resistance and hyperinsulinemia. The excess of insulin reduces the hepatic synthesis of SHBG and IGFBP-1 with the consequent increase of free IGF-1. The high concentrations of IGF-1 and insulin act synergically on the testis and the adrenals glands, reducing the androgens secretion. In the testis, moreover, because of the limited effect that the reduced LH concentration exerts on the synthesis of testosterone, the effect is more marked. Probably, the increase in aromatization of androgens by adipose tissue, contributes to the hypoandrogenemia, together with the low levels of FSH which limit the spermatic development, lead to ED and the hypogonadotropic hypogonadism condition, which is an infertility factor.

Androgen deficiency contributes to pathologies associated with the metabolic syndrome, such as obesity, T2DM, hypertension and hyperlipidemia, which affect the endothelium, resulting in multiple vascular diseases, including ED, representing the latter, an infertility factor (Akishita et al., 2007; Traish et al., 2009; Tripathy et al., 2003) (Fig. 6). Also, several studies have shown that low testosterone levels predict development of T2DM in men (Tomar et al., 2006). There is evidence that the treatment with testosterone to DM animal models improves erectile function by influencing the NO/cGMP/PDE5 pathway (Vignozzi et al., 2005). Testosterone supplementation to diabetic animals also down regulates RhoA/Rho-kinase signaling (Vignozzi et al., 2007) improving also erectile function. The use

of PDE 5 inhibitors like Sildenafil (Viagra), Tadalafil (Cialis) and Vardenafil (Levitra) for ED treatment has allowed a better management of this condition (Yassin & Saad, 2008). In particular, combined therapy of testosterone and sildenafil, improves erectile function in patients with T2DM (Hidalgo-Tamola & Chitaley, 2009).

5.7 Other causes of ED in diabetes

5.7.1 Viral and Bacterial pathogens

A role for viral and bacterial pathogens in the development of atherosclerosis has been suggested by multiple studies. Most evidence for this infection theory comes from seroepidemiological and experimental studies with *cytomegalovirus* (CMV) and *Chlamydia pneumonia* (CP), which are intracellular pathogens and can directly infect vascular wall cells, including endothelial cells and smooth muscle cells. Although still under debate, there appears to be an association of CMV and CP with the presence or development of atherosclerotic vascular disease in diabetes. Direct infection of endothelial cells leads to pro-coagulant activity and a local vascular pro-inflammatory response. Although the exact pathogenesis of ED in men with DM is still unclear, endothelial dysfunction plays a pivotal role and some studies suggested an association between ED and CMV and/or CP seropositivity in men with diabetes. Also, levels of the inflammatory markers as C-reactive protein and fibrinogen were elevated in patients with diabetes-associated ED (Blans et al., 2006).

5.7.2 Drugs used in the diabetic patient

A large number of drugs used in the managing of the DM patients may impair sexual function, either by an effect upon erectile and ejaculatory function or sex drive. Some of them are used as part of the diabetes treatment or others associated conditions like hypertension, anxiety and depression. The use of these drugs very rarely produces ED by themselves. Side effects usually appear adjunct to another pathophysiological mechanism (Eardley, 2002; Elías-Calles & Licea, 2003) (Table 1).

Type of drug:	Secondary sexual effect:
Antihypertensive (Diuretics):	
Spironolactone	Diminution of the libido, ED
Thiazide	Diminution of the libido, ED
Agents of central action:	
Methyldopa	Diminution of the libido, ED
Clonidine	ED
Reserpine	Diminution of the libido, ED and depression
Alpha-adrenergic blocking agents:	
Prazosin	Retrograde ejaculation

Type of drug:	Secondary sexual effect:
Terazosin	Retrograde ejaculation
Beta-adrenergic blocking agents:	
Propranolol	Diminution of the libido, ED
Metoprolol	Diminution of the libido, ED
Alpha and Beta Blocking Agents:	
Labetalol	Inhibition of the ejaculation
Blocking of the sympathetic ganglia:	
Guanethidine	ED, Retrograde ejaculation
Inhibitor of the angiotensin-converting enzyme:	
Lisinopril	ED in 1% of the cases
Psychiatric drugs (Tricyclic Antidepressants):	
Amitriptyline	ED, Inhibition of the ejaculation
Amoxapine	Diminution of the libido, ED
Desipramine	Inhibition of the ejaculation
Imipramine	Inhibition of the ejaculation
Maprotiline	Inhibition of the ejaculation
Nortriptyline	Inhibition of the ejaculation
Protriptyline	ED, Inhibition of the ejaculation
Atypical agent:	
Trazodone	Priapism
Inhibitors of Monoamine oxidase:	
Isocarboxazid	Inhibition of the ejaculation
Phenelzine	ED, Inhibition of the ejaculation
Antipsychotic:	
Thioridazine	Diminution of the libido, Inhibition of the ejaculation
Chlorpromazine	Inhibition of the ejaculation
Mesoridazine	Diminution of the libido, Inhibition of the ejaculation

Type of drug:	Secondary sexual effect:
Fluphenazine	Diminution of the libido, Inhibition of the ejaculation
Serotonin reuptake inhibitor:	
Fluoxetine	Anorgasmia
Trifluoperazine	Inhibition of the ejaculation
Chlorprothixene	Inhibition of the ejaculation
Haloperidol	Inhibition of the ejaculation
Anti-mania:	
Lithium carbonate	Possible ED
Anti-ulcer:	
Cimetidine	Diminution of the libido, ED, Gynecomastia

Table 1. Drugs used in the managing of the metabolic and psychological state of the diabetic patients with potential capacity to induce sexual dysfunctions including ED.

6. Conclusions

DM is one of the more important risk factors to the development ED. The uncontrolled metabolic state (characterized by hyperglycaemia, dyslipidemia, insulin resistance, hyperinsulinemia) induce oxidative stress, failure in the signaling mechanism of vasodilation, venous-occlusive dysfunction, atherosclerosis, angiopathy, neuropathy, alterations of the NO-mediated pathways, the formation of advanced glycation end-products, hypercontractility of the cavernous body, overweight and androgen loss systemic effects, and ED as consequence.

Although hyperglycemia is a common defining feature in type-1 and type-2 DM, many unique characteristics distinguish these diseases, including insulin and lipid levels, obesity status, and inflammatory agent profiles. Impaired cavernosal vasodilation has been established in T1DM rodents. This dysfunction appears to be mediated by a severe defect in non-adrenergic-non-cholinergic nerve signaling, as well as impairment in penile endothelial function. In contrast, T2DM animals appear to have minimal impairment in parasympathetic-mediated dilatory function, but do have evidence of endothelial dysfunction. T2DM models also exhibit a significant and striking increase in cavernosal contractile sensitivity, and a significant veno-occlusive disorder, neither of which is consistently reported in T1DM animals. With the distinct mechanisms underlying the ED phenotype in animal models of type-1 and type-2 DM, the therapeutic treatments for diabetes-associated ED most be adjustment to the specific mechanisms underlying this disease complication. Further examination of mechanisms underlying ED in DM patients may thus lead to significant changes in the way urologists diagnose, code, and treat diabetes-associated ED. An adequate metabolic and psychological control is the more effective way to avoid the ED in DM; for these reasons it is of extreme importance the opportune and specialized medical intervention and support.

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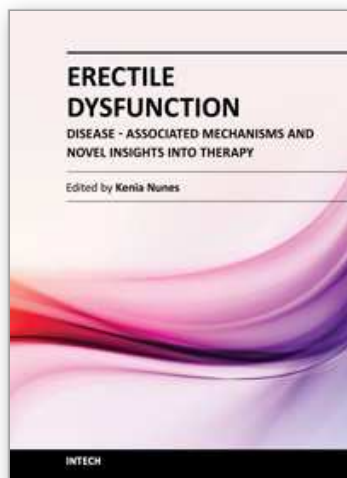
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Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy

Edited by Dr. Kenia Nunes

ISBN 978-953-51-0199-4

Hard cover, 214 pages

Publisher InTech

Published online 29, February, 2012

Published in print edition February, 2012

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.

How to reference

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Eulises Díaz-Díaz, Mario Cárdenas León, Nesty Olivares Arzuaga, Carlos M. Timossi, Rita Angélica Gómez Díaz, Carlos Aguilar Salinas and Fernando Larrea (2012). Erectile Dysfunction: A Chronic Complication of the Diabetes Mellitus, *Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy*, Dr. Kenia Nunes (Ed.), ISBN: 978-953-51-0199-4, InTech, Available from:
<http://www.intechopen.com/books/erectile-dysfunction-disease-associated-mechanisms-and-novel-insights-into-therapy/erectile-dysfunction-a-chronic-complication-of-the-diabetes-mellitus>

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