SEXUAL MEDICINE REVIEWS

Aging and Erectile Dysfunction

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ABSTRACT

Introduction: Erectile dysfunction (ED) has been identified as the most common sexual problem that affects mainly men older than 40 years. According to this, there is a strong evidence linking ED with a number of medical conditions and related risk factors that had been described in the literature, yet there is limited information about the specific mechanism involved in the establishment of ED among healthy older men.

Aim: The purpose of this study is to review the literature and mainly focus on the basic physiologic and vascular alterations and morphologic changes related to aging and its related risk factors, summarizing the main and the latest findings in basic research of tissue remodeling process involved in ED pathophysiology.

Methods: Data from the pertinent literature were examined to inform our conclusions.

Main Outcome Measure: This article defines the morphologic and physiologic mechanisms involved in the process of aging, which play a key role in the development of sexual dysfunction.

Results: ED has been considered as a nonlife-threatening condition, but the recognition of its multiple co-morbid conditions, the importance of aging process over the male sexual performance among them its relation with vascular and nitric oxide content alteration, as well as penile morphologic changes, and the fact that it is a widespread under-reported disease, have established the need of an early diagnosis and treatment of this common sexual problem within the general male population.

Conclusion: In this case, morphologic and physiologic mechanisms that are involved in the aging process play a key role in the development of sexual dysfunction in the absence of any other clinical or medical condition.

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Key Words: Aging; Erectile Dysfunction; Tissue Remodeling

INTRODUCTION

Erectile dysfunction (ED) is defined as a consistent or recurrent inability to achieve and/or maintain a penile erection sufficient for sexual activity. This condition has been identified as the most common sexual problem that affects mainly men older than 40 years.[1–3]

According to the World Health Organization (WHO), due to the increase in life expectancy, by 2025 about 15% of worldwide population will be over the age of 65 years. This will also relate with increased prevalence of ED (∼322 million of cases), establishing a serious demand of healthcare policies to prevent or diminish sexual dysfunction within the male population.[1,2,4,5]

Despite the fact that this disorder has been present since ancient times,[6] it is in the past few years that sexual medicine has played an important role putting together a wide overview about ED. There is a strong evidence linking ED with a number of medical conditions such as neuropsychiatric disorders, vascular and histologic changes, endocrine abnormalities and iatrogenic causes.[3] Besides these medical conditions, there are related risk factors associated with a higher prevalence of ED, being the most important diabetes, hypertension, dyslipidemia, and coronary heart disease.[7,8]

Even though these medical conditions and risk factors are well known and have been described in the literature, there is limited information about the specific mechanism involved in the establishment of ED among healthy older men.[5,7] To that end, there are morphologic and physiologic mechanisms involved in the process of aging that play a key role in the development of sexual dysfunction in the absence of any clinical or medical condition.[9–12]

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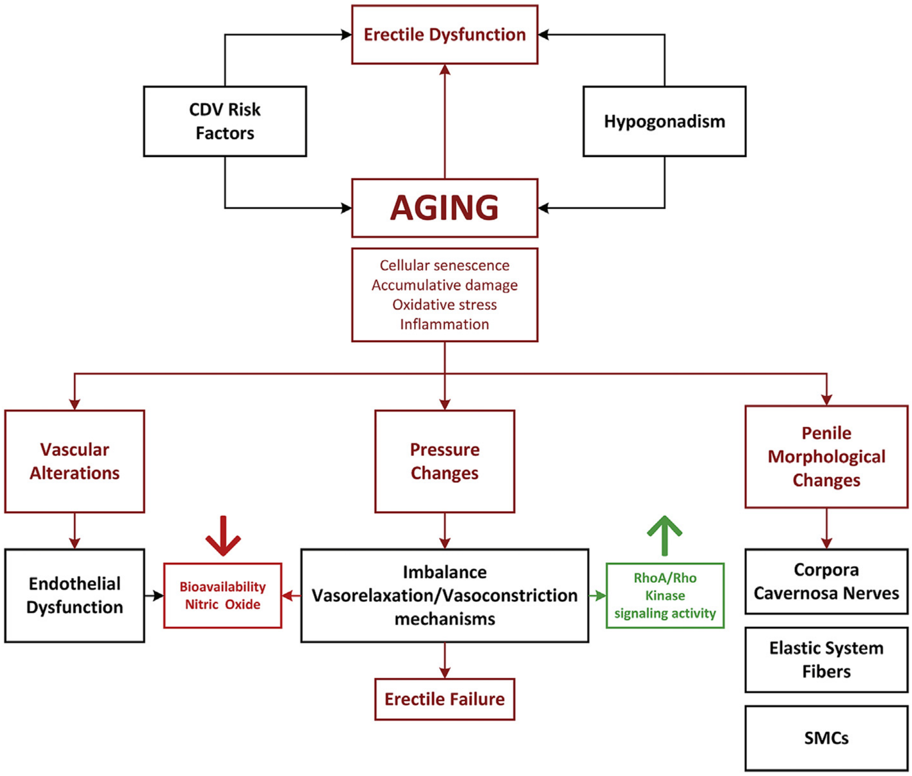

Figure 1. There are morphologic and physiologic mechanisms involved in the process of aging that play a key role in the development of sexual dysfunction. Cardiovascular risk factors and hypogonadism have a critical impact during the establishment of the aging process that could also lead to erectile dysfunction. Cellular senescence could induce oxidative stress and hence inflammation that with time leads to accumulative damage. With this overview, the main mechanisms of the aging process that drive toward erectile dysfunction include vascular and physiologic alterations and penile morphologic changes.

In this review, the authors will mainly focus on the basic physiologic and vascular alterations and morphologic changes related to aging and its related risk factors, summarizing the main and the latest findings in basic research of tissue remodeling process involved in ED pathophysiology (Figure 1).

ERECTILE DYSFUNCTION ETIOLOGIES

The NIH Consensus Statement determines that: "the multifactorial nature of erectile dysfunction, compromising both organic and psychologic aspects, may often require a multidisciplinary approach to its assessment and treatment",[3] which compels medical community to a full knowledge of its causes and age-associated risk factors, and its impact over the male reproductive system.

Regardless of multifactorial etiologies of ED, there are just few diseases that can be considered as the primary cause of ED such as hypertension, cardiovascular disease (CVD), and diabetes. In fact, ED has been considered as a possible marker for comorbid conditions including diabetes and CVD.[13–15] Despite this general clinical knowledge, most of the erectile dysfunction among older men takes place in those who are healthy but with existent numerous vascular risk factors.[5,7] Several epidemiologic studies have shown direct correlation between age and male potency: among men 40 to 70 years old showed decreased potency from 60% to 33%[9,16]; and it has been established that the risk of ED was about 26 cases per 1,000 men annually and increased with age from 1.2% per year for men aged between 40 and 49 years to 4.6% for men aged between 60 and 69 years, results from the Massachusetts male aging study.[17] Results from a population-based cohort study in Brazil showed that this condition also increased with age even with a 2.5-fold higher incidence of ED among Brazilian men compared with the Massachusetts male aging study,[18] among others.[5,7,10,19–24] According to this background, aging is considered as one of the most important risk factors for ED development.[7,12,25]

Historically, ED has been considered as a nonlife-threatening condition[26]; but it is in the past few years that recognition of its multiple comorbid conditions, the importance of aging process over the male sexual performance, and the fact that it is a widespread under-reported disease, have established the need for an early diagnosis and treatment of this common sexual problem within the general male population.[7,12,25,27]

Age Related to Vascular Alterations

Erectile function (EF) is described as a neurovascular phenomenon that demands an intact vascular endothelium;

therefore, any complication that affects the arterial vasculature may also affect the normal performance of the male reproductive system.[14,28–30]

The vascular endothelium is an active and dynamic tissue in charge of many regulatory functions such as proliferative processes, local homeostasis, vascular tone regulation, perfusion maintenance, coagulation, and inflammatory responses. It has been shown that the normal process of aging and its related risk factors could result in an accumulative endothelial damage that ultimately leads to endothelial dysfunction.[31,32]

It has been established that over 80% of ED cases account for organic causes, of which vascular alterations are the most common, suggesting that the severity of ED is directly related to the presence of vascular risk factors (hypertension, hyperlipidemia, atherosclerosis, and diabetes) that cause severe endothelial dysfunction.[14,29]

Gonzalez and Selwyn[32] described that the integrity of vascular endothelium is indispensable for the production of substances that regulate the vascular tone (ie, nitric oxide [NO]) and provide balance in processes such as cell adhesion, homeostasis of clotting, and fibrinolysis. Thus, it has been implied that progressive degeneration of endothelial tissue, associated with senescence, hypogonadism, and cardiovascular risk factors, results in a pathologic process causing ED by vascular dysfunction.[31–34]

A few years ago, it was not clear if low levels of total testosterone as a consequence of the aging process were related with the bad performance of EF. Nevertheless, currently it has been reported a direct relationship of an increased prevalence of ED and testosterone deficiency in old men with CVD. With time, several results have confirmed that there is a gradual decrease in androgen levels in men presenting ED and increased in prevalence related to the aging process (from age 40 to 55 years)[35–40]; however, the great variability and no clinical significance among the results limit its applicability, as well as the fact that hormonal changes are not the main determining factor within the decline of sexual function,[36,41–43] even in some circumstances bears no relation at all between ED and low serum testosterone,[44,45] also considering that it is frequent that sexual activity declines even in old men who are healthy.[46]

Despite the fact that variable degrees of hypogonadism frequently coexist with ED, it has been a controversial issue throughout the history of sexual medicine.[33,47–49] Recently, it has been reported that ED is in fact associated with low total serum testosterone levels in intermediate risk men,[50] in accordance with the significant improvement in sexual function in men with low and low-normal testosterone levels, receiving standard replacement therapy doses of testosterone compared with placebo.[51] However, in 2006, it was reported that the increased severity of ED was associated with a consistent prospective decrease in levels of testosterone throughout the 4 years of follow-up; however, some authors suggest that could be more related to the ultrastructural alterations because of the androgen depletion than by the results of its biochemical level.[52]

The mechanisms associated with an abnormal function of vascular endothelium are characterized by the alteration of vascular tone, due to marked deficiency in the relaxation process of smooth muscle cells (SMCs) located in the corpus cavernosum and the wall of the small arteries, and by occlusion of the cavernosal arteries due to atherosclerosis. Meaning that an impaired release of NO because of endothelial dysfunction could affect the SMC activity during penile erection and contribute to the loss of its anti-atherogenic protection.[14,31] It is important to know that testosterone has effects on the peripheral mechanisms of EF, which include endothelial production of NO by activation of NO synthase (NOS).[53–56] In agreement with this, animal data suggest that testosterone may act as a vasodilator in the penis, and that the use of replacement therapy prevents the 45% activity reduction of NOS in castrated rats.[57,58]

Solomon et al[59] reported that the presence of endothelial dysfunction should be described as an early marker for subclinical atherosclerosis; as a vascular risk factor it can lead to arteriogenic ED, through manifestation of macro- or microangiopathy of cavernosal penile arteries. In this sense, the underlying changes involve different structures, such as penile arteries, veins, and sinusoids,[2] being the damage to penile arteries—the alteration that accounts approximately for up to 80% of the cases of ED. This suggests that the remodeling process within the penile tissue that causes severe ED would be associated with increasing levels of biomarkers or specific inflammatory mediators related to thrombosis, endothelial cell activation, and dyslipidemia.[60–62]

Other results suggest that the process of structural alteration of penile arteries is due to endothelial cell activation (ECA), an initiating event of atherosclerosis that can be generated by oxidized low density lipoprotein providing an ideal environment for plaque formation.[31] This agrees with the increased biochemical measures of ECA, which associates with ED, independently of any cardiovascular risk factors and vascular damage, suggesting that ED may be considered as a sentinel of early atherosclerosis,[63] which is also possible because of the highly significant correlations between penile and systemic endothelial functions.[64] Also, it is possible to make an early detection of atherosclerosis through diagnosis of ED, since the effects of diffuse atherosclerosis unusually manifest simultaneously, and larger vessels can endure a plaque burden better than smaller ones. In agreement, this correlation might be related to the caliber of blood vessels, considering that the diameter of penile arteries is much smaller (1 to 2 mm) compared with coronary vessels, which could be twice the size, making penile vessels more susceptible to blockade under the proper pathologic environment.[65,66]

It is clear that beside the compromise of penile arteries, the vasculogenic structure also depends on the normal performance of venous system, more specifically the corporal veno-occlusive (CVO) mechanism during the normal physiology of erection. Some results also suggest that maybe testosterone enhances the process of erection by attenuation of the α-adrenergic activity in vascular smooth muscle (SM) of the corpus cavernosum,[67,68] as well as a vasodilator signaling mechanism in the microvasculature mediated primarily by peroxynitrite.[59] CVO consists of the relaxation of trabecular SM and dilation of the helicine arteries of the penis, achieving a significant expansion of the lacunar spaces that impede the return of the blood by compressing venules against the tunica albuginea.[3,69]

According to this, it has been established that the CVO dysfunction is correlated with SM alterations, affecting the function of corporal SMC, which might result in modification of cavernosal expandability and consequently CVO dysfunction. This alteration inside intracavernous structures could be related to testosterone deprivation that could lead to a process of tissue remodeling within tunica albuginea, with a large increase in collagen deposition and provoked by the loss of corporal SMC, in some cases causing fibrosis and leading to reduction of the size of cellular compartments and an inadequate NO synthesis, because of action maintenance of testosterone over NO production in the cavernosal arterioles. This process not only affects the veins but also sinusoids within the penis during penile erection.[70−77]

In summary, the vasculogenic ED is triggered by endothelial dysfunction that obeys to cardiovascular risk factors and to the accumulative damage generated by the aging process. ED has also been described as a vascular disease due to an interrupted production of NO, since the decreased amount of vascular NO translates into diminished sexual function.[78−80]

Age and Pressure Changes in the Cavernosal Space

The pressure changes in the cavernosal vasculature manage the balance between erectile/flaccid states of the penis. Among the mechanisms of cavernosal vasorelaxation, we can find NO, which is a neurotransmitter, involved in many regulatory functions, like control of vascular tone and proliferation of vascular SMCs. It has been reported that changes in its bioavailability trigger endothelial dysfunction, leading to increased susceptibility to vascular disease. NO is synthesized from L-arginine by the enzyme NOS; there are three different forms but just two of them, the endothelial (eNOS) and neuronal NOS, are thought to be important sources of NO, allowing it to function in an autocrine and paracrine way in the corpus cavernosum.[78,79,81−83]

Nocturnal tumescence induces production of neural NO (nNO), which diffuses into the contiguous corporeal SM, activates soluble guanylate cyclase increasing cyclic guanosine monophosphate (cGMP) levels, and decreasing calcium levels through inhibition of the phosphoinositol pathway, relaxing vascular SMCs.[84,85] Effective SMCs relaxation may also be induced through the activation of different mediators including neuropeptides such as vasoactive intestinal peptide, calcitonin-related peptide, and prostaglandin E1; these react with SMC membrane activating adenylate cyclase and converting adenosine triphosphate, in cyclic adenosine monophosphate[86−88]; consequently, eNOS phosphorylation translates into the decrease of free intracellular calcium levels and SMCs relaxation.[89]

Urotensin II is a cyclic peptide hormone with vasoactive effect mediated by the coupling to a GPR14 (urotensin-II [UT] receptor), present on the endothelium of human corpus cavernosum, which mediates an endothelium-dependent relaxation related to L-arginine/NO pathway activating eNOS, and therefore NO production, which induces and maintains erectile function in man.[90−93]

Normal performance of penile tissue during erection depends on cavernosal SM tone, conditioned by the balance of vascular relaxants and constrictors.[94] NO is considered as a potent vasodilator that acts to relax the cavernosal SM by stimulating second messengers,[79] resulting in a compression of the subtunical small veins, blocking the local venous return and making possible the process of erection.[2] Furthermore, mechanisms of cavernosal vasoconstriction include the activation of α receptors on the SMC, which leads to an enzymatic process with increased levels of Ca^{++} and the interaction of myosin and actin.[95] Additionally, the vascular endothelium also influences vascular tone through a variety of other signals including vasoconstrictors as angiotensin II, endothelin (ET)-1, and thromboxane, as well as other vasodilators like prostacyclin.[84,96] And finally, it has also been reported that vasoconstriction process is dependent on the small G-protein, RhoA, and a downstream target, the Ser/Thr kinase, Rho kinase.[97]

It has been reported that NO preserves vascular health of male penis maintaining low vascular muscle tone, opposing vascular SM proliferation, inhibiting platelet aggregation and inflammatory cells adhesion to the endothelium, and reducing oxidative stress and endothelial cell senescence. Taking note of this, NO has been considered as an important factor playing a major role in the performance of erectile process.[78−80] On the other side, the potential effects of RhoA/Rho kinase mediation in cellular contraction and penile flaccidity, it is through the regulation of the binding state of RhoA which activates this calcium sensitizing pathway by an increased myosin light chain phosphorylation through the inhibition of myosin light chain phosphatase by Rho kinase.[98,99] Both processes required by endogenous vasoconstrictors, such as norepinephrine and ET-1.[100−102]

The mechanisms of cavernosal vasorelaxation can be affected by several causes that alter the content of organic NO, concerning mostly endothelial damage and lifestyles. It has been reported that men with ED, independent of other clinical conditions, have elevated markers of ECA such as ET-1, indicating the initial stage of diffuse vascular disease.[63,103,104] Endothelium damage courses with pathogenic involvement of NO pathway leading to impairment of endothelium-dependent vasodilatation. Changes in the state of contraction to relaxation can be accomplished either by eliminating the contraction influences (ET-1, angiotensin-II and Rho kinase signaling pathway)[105,106] or by enhancing the effects of relaxant factors (NO and prostaglandin E2).[8,81]

Several authors have shown that low levels of NO are associated with risk factors of CVD, such as diabetes mellitus, atherosclerosis, and increased age. Obesity is also strongly associated with ED, and is an important risk factor for diabetes and atherosclerosis, which correspond to conditions classified as states of chronic inflammation due to the release of tumor necrosis factor-alpha and interleukin-6, causing systemic insulin resistance, raising circulating glucose, and reduction of insulin stimulation by NO production, leading to atherosclerosis.[81,107–109] Moreover, several reports suggest that impaired EF during the aging process involves elevated RhoA/Rho kinase signaling activity, as shown in the case of the neurogenic erectile response and its relation to systemic arterial pressure and the effect of a combined therapy with Rho-Kinase antagonism (Y-27632) and phosphodiesterase-5 (PDE-5) over the erectile response in young and old Brown Norway rats, which first of all demonstrate that erectile capabilities diminish with time, and that the administration of Rho-kinase antagonism provides an attenuation of the aging-related changes as well as the combined therapy, suggesting a possible derangement in penile hemodynamic mechanism.[110] In a more accurate molecular approach, it was confirmed that in Fischer 344 aged rats Rho-kinase activity is twofold greater than that in young rats and that the gene therapy with T19NRhoA reversed ED in aged rats.[111]

It has been established that there is an evident interaction between NO and RhoA/Rho kinase pathway. Initially it was demonstrated that the activation of RhoA/Rho kinase pathway mediates the downregulation of penile eNOS in the streptozotocin diabetic rat penis model[112,113] and that NO mediates the erectile response, in part, via inhibition of RhoA/Rho kinase Ca^{++} sensitizing pathway.[100,114] According to this, the presence of elements of the RhoA/Rho kinase signaling pathway in the penile SM is important, and it has been proposed on several occasions the potential use of Rho kinase inhibitors in the treatment of ED.[115–120] The inhibition of Rho kinase by Rho-kinase inhibitor Y-27632 can lead to erection process in rats and as well in a castrated rat model of ED, suggesting that could be independent of an NO-mediated pathway.[117,121] Moreover, it has been proposed that adjusting the imbalance between nNO and Rho-kinase activity through the administration of Y-27632 could improve the EF in old SD rats.[122] Soitis clear that even a subtle alteration of this equilibrium can lead to ED.[81,118]

ED and CVD, especially hypertension, are common clinical conditions among aging men.[15] Arteriosclerosis is also significantly associated with aging, and is one of the main causes leading to hypertension, as well as the possible involvement of Rho kinase in this pathogenesis.[26,123–126] Ferrini et al reported that the common alterations observed in the SMCs of both penis and peripheral vascular system in aging males leading to ED and hypertension suggest that both conditions may share a common etiology.[127,128] According to this, the reactive oxygen species (ROS), produced by xanthine oxidase, NO synthase, and nicotinamide adenine dinucleotide-reduced/ nicotinamide adenine dinucleotide phosphate-oxidase (NADH/NADPH) oxidase among many others, and mainly regulated by superoxide dismutase (SOD) acting as endogenous antioxidant, are considered important components of peripheral vascular disease through oxidative injury, causing endothelial damage, SMC proliferation, and collagen deposition in the vascular wall.[129–131] Jones et al reported that xanthine oxidase and SOD are present in the penile corpora cavernosa.[132] Smaller quantities of NO have been associated with risk factors that generate an increase of inflammation and oxidative stress conditions, which due to ROS have been postulated to be central to impaired cavernosal function in age-related ED.[132–134]

Nitrosative pathways have been proposed to be protective against ED by their influence over oxidative stress.[132] It has been reported by several authors that these pathways include the formation of peroxynitrite through which NO reduces ROS levels.[129,132,135–137] NO has been suggested as a control of collagen synthesis, inhibiting directly the production and generally lean toward collagen degradation, through metalloproteinases stimulation and downregulating the expression of their inhibitors (plasminogen activator inhibitor),[138] but if oxidative stress increases in an uncontrolled way, the reaction developed to maintain the balance of NO/ROS ratio will culminate in the reduction of NO concentration in the tissues, which in this case could lead to ED by a deficient SMC relaxation dependent of NO.[129,131]

It is clear, then, that an intact endothelium is essential, and every alteration impairing its biologic activities or disrupting its functional integrity will alter its endothelial ability of maintaining proper balance. Endothelial damage, dysfunction, and perpetuated inflammation will lead to irreversible changes in penile tissue morphology, especially structural vascular abnormalities, a condition considered as a common denominator between ED and CVD.[66,139]

Age and Penile Morphological Changes

It is well known that CVD is associated with endothelial dysfunction, and ED and testosterone deficiency is highly prevalent in old men with CVD.[59,140] Additionally, approximately one third of men with ED have androgen deficiency.[52] In line with this, a major impact of the mentioned conditions over the penile ultrastructures is possible.

Erection initiates by relaxation of the smooth muscle, reducing venous return, and thereby holding the blood within the penis. Integrity of the tunica albuginea that encloses corpus cavernosum defines smooth muscle fiber functionality as well as the right conditions to achieve a normal erection. According to this, any alteration of every structure within corpus cavernosum results in a down-regulation of muscle tonus leading to ED.[85,141]

Muscle tone regulates not just the erection but also detumenescence and flaccidity of the penis through the interaction of anatomic framework.[141,142] Corpus cavernosum is the main structure of the male penis, its tissue composed of functional endothelial cells, SMCs, blood vessels, extracelullar matrix with abundant collagen and elastic fibers, vascular lamina, and numerous unmyelinated and preterminal autonomic nerves.[85,143] Every one of these components plays a specific and fundamental role in the normal process of erection. Particularly, penile endothelial bed has been considered as a specialized extension of the peripheral vascular system, which plays an important role controlling vascular tone.[31,32]

Besides the vascular endothelium, also identified as a passive barrier, the smooth muscle cells network is considered as the main relaxing-contractile component of the corpora cavernosa; with numerous intracytoplasmic contractile filaments anchored in dense bodies.[143] Moreover, several researchers have reported that a good performance of the erection process demands an adequate percentage of SMCs,[144,145] which assemble a viable cavernosal SM tissue.[85,142]

Collagen and elastic fibers within penile tissue support SMC. Corpus cavernosum collagen mainly corresponds to types I, III, and IV. It is thought that within intracavernous structures, endothelial cells secrete collagen type IV as part of basement membrane of blood vessels; on the other hand, rigid bands of fibrils are formed by collagen type I, and collagen type III is found mainly in distensible elastic tissue, which makes it necessary for normal tensile strength.[146]

Aging has been reported to associate with a specific decrease in the amount of SM fibers, altering erectogenesis.[77,146–148] And testosterone deficiency is related with marked structural changes in cavernosal nerves, which in turn could lead to a diminished intracavernosal pressure,[149–151] as well a significant reduction in trabecular SM content and increased connective tissue deposition,[152,153] and an abnormal remodeling of tunica albuginea with a possible decrease in penile tensile strength induced by the replacement of elastic fibers with disorganized collagen deposition.[75]

Pathologic conditions and social habits related to risk factors play an important role in the beginning of ED; however, senescence has a huge impact over the human body, and as in other systems, the male reproductive system suffers several changes at the cellular and extracellular components of the penis affecting mechanic process or erection.[12,25,148] According to a comparative analysis of the penis corpora cavernosa between patients with ED and controls, they define penile erection as an elaborate neurovascular event that requires a specific teamwork of corpora cavernosa tissue, elastic system fibers and smooth muscle cells, that in the absence of this highly organized system could show alterations in the mechanical properties of erectile tissue, mainly related to the amount of elastic fibers.[143]

CONCLUSION

ED is the most common sexual problem among men older than 40 years.[1–3] Despite that some risk factors play an important role in the establishment of this condition, age by itself could be sufficient for the presence of diminished sexual function. In this case, morphologic and physiologic mechanisms that are involved in aging process play a key role in the development of sexual dysfunction in the absence of any other clinical or medical condition. Sexual dysfunction depends entirely on the integrity of the vascular endothelium, so minimal penile morphologic changes through the years could lead to accumulative damage generated by the aging process. Despite the fact that ED has been considered as a nonlife-threatening condition, its role as a sentinel of early atherosclerosis makes it a good marker for other comorbid conditions of worldwide huge impact, such as CVD.

In these circumstances, healthy lifestyles are not just preventing major diseases, but also contributing to maintaining sexual health, which can help to improve life quality of older male adults.

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