Review Article

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Review of the current information on erectile dysfunction in hypertensive males with 40 years of age or older

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Abstract

Hypertension (HT) is a prevalent disease, which origin frequently remains undetermined. Antihypertensive treatment (AHT) has been linked with erectile dysfunction (ED), mainly in middle-aged and older males. On the other side, some drugs used in AHT seem to be themselves associated with ED as a secondary effect. This led to the search of coadjuvant therapies for hypertensive patients with ED, considering that both illnesses cause high physical, psychological and economic burden. While the association between AHT and ED has been approached several times, the direct association between blood pressure and ED remains unclear. This review aims to summarize the current knowledge on the relationship between HT, AHT and ED specifically in males with age ≥40 years.

Keywords: antihypertensive treatments, erectile dysfunction, hypertension, nitric oxide

Introduction

Cardiovascular disease (CVD) is responsible for nearly 17 million worldwide deaths/year and about 55% of these deaths are recognized to be due to hypertension (HT) complications.[1,2] According to the World Health Organization (WHO) 1130 million people worldwide present this condition, which is a risk factor for cardiac events. Numerous people are asymptomatic or present mild symptoms (eg, headache, nose hemorrhages, and vision shift), yet others may have severe complications (myocardial infarction, congestive heart failure, cerebrovascular accident, renal failure). Essential HT comprises over 90% of the hypertensive patients, being modulated by both genetic and environmental factors. Among those, changes in nutrition, increment in exercise practice, reduction in body weight, and privation of alcohol and tobacco consumption could be considered ("https://www.who.int/health-topics/hypertension/#tab=tab_1"; Acessed in September 11, 2020).

HT is clinically defined as systolic blood pressure (SBP) ≥140 mm Hg and diastolic blood pressure (DBP) ≥90 mm Hg (Table 1) ("https://www.who.int/health-topics/hypertension/#tab=tab_1"; Acessed in September 11, 2020). A survey conducted in a pool of Portuguese population demonstrated that the overall HT prevalence in that group was 36%; males and elderly showing the highest rates. It further showed higher rates in those with lower levels of education and with no formal occupation.[1]

Studies have been supportive of HT as a risk factor for sexual dysfunction (SD). Unexpectedly, SD seems to be more frequent in hypertensive patients that are submitted to antihypertensive treatment (AHT) than in untreated patients, which has raised the premise that AHT may be associated with SD.[3,4] Treatment of hypertensive males with erectile dysfunction (ED) has made controversy over the prior years.[5] The leading ground for non-compliance to AHT is the complaint on SD, particularly, when treatment included older-generation drugs, namely central-acting drugs, diuretics and β-blockers. Newer-generations drugs [calcium antagonists, angiotensin-converting enzymes (ACE) and angiotensin receptor blockers (ARBs)], however, owing to its endothelium protective action have shown to exert neutral or even beneficial effects on sexual function[6,7] (Table 2). The main goal of this review is to briefly summarize the relationship between HT, AHT, and ED in males with age ≥40 years.

Material and methods

The main aim of this study was to summarize the current knowledge on the relationship between HT, AHT and ED specifically in males with age ≥40 years.

For the execution of this review PubMed and Google scholar database searches were conducted using combinations of the keywords [ED; HT; AHT; nitric oxide (NO)]. The inclusion criteria for this study were papers of human male population published between 1990 and 2020. Clinical trials were analyzed only if the studied population were males of 40 years old or older. Numerous human studies include adult patients (≥18 years) of all ages, which were excluded from this analysis. Other studies only included the mean age of the patients and not the range (minimum and maximum ages). Additionally, several studies, particularly studies of older-generation AHT were published before 1990, reason why were not included.

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Table 1

Classification of the clinical blood pressure categories and definition of the hypertensive degrees

Pressure category	Systolic (mm Hg)	And/or	Diastolic (mm Hg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
Normal-high	130–139	and/or	85–89
Mild hypertension (degree 1)	140–159	and/or	90–99
Moderate hypertension (degree 2)	160–179	and/or	100–109
Heavy hypertension (degree 3)	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Adapted from "European Society of Cardiology and European Society of hypertension (ESH/ECH) guidelines for hypertension treatment".

HT and ED are associated with several other conditions, such as cardiac diseases, and SD is a secondary endpoint in various studies including HT patients. Papers that included previously known conditions causative of SD were excluded from the analysis.

No in vitro nor animal model studies were considered.

Erectile dysfunction (ED)

SD is a common concern around the world for both males and females. The WHO has defined SD as "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish".[8] This condition often impacts the quality of life (QoL) of the individual and his partner, creating psychological fear, loss of self-esteem, anxiety and depression.[9,10]

In men, ED is described as "the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse".[11] An epidemiological review by Kubin et al[9] has suggested that 5% to 20% of adult men have moderate-to-severe ED. In Europe, 15% of men has experienced some difficulty in having/maintaining an erection for a prolonged period in their lifetime.

Incidence of ED has been related with not only several chronic diseases, namely diabetes,[12,13] coronary heart disease,[13–15] benign prostate hyperplasia,[16] post-traumatic stress,[17] hypogonadism[18] and HT, but also with antihypertensive drugs applied in HT treatment, as previously mentioned.[3,19,20] These illnesses are more frequent in older males,[13] which could explain the higher prevalence of ED in men over 60 years old.[9] With the increment of longevity in high-income countries, it is estimated that by the year 2025, 322 million men will suffer from ED.[21]

Table 2

Effect of antihypertensive drugs on erectile function

Antihypertensive treatments	Effect on erectile function
Central-acting	− − −
Diuretics	− −
β-Blockers	−
Calcium antagonists	±
Angiotensin-converting enzyme inhibitors	±
α-Blockers	+
Angiotensin receptor blockers	+

Adapted from "Doumas, M. and Douma, S. (2006), The Journal of Clinical Hypertension 8:359–363".[6]

−: negative effect; ±: neutral effect; +: positive effect.

Penile erection is a neurovascular manifestation that is both modulated by hormonal (eg, testosterone levels)[22] and psychological factors.[23] Upon stimulus, occurs release of neurotransmitters, mostly NO,[24] primarily secreted by neurons and further by endothelium, which diffuses to the smooth muscle cells and conducts to relaxation of the vascular system that supplies the erectile tissue, causing increased blood flow into the penis. Simultaneously, the relaxation of the smooth muscle in cavernous tissue enhances the distensibility of capillaries, which aids prompt filling and expansion. Venous flow is almost fully blocked by compression between the trabeculae and the tunica albuginea. The veno-occlusion process traps the blood within the corpora cavernosa and carries the penis from a flaccid position to an erection with an intracavernous pressure of nearly 100 mm Hg.[5,25]

HT can, at some point, interfere with this process, leading to ED.[5] Considering that penile circulatory system is part of the vascular system of each individual, alterations in the systemic circulation will also impact the blood flow in the penis, and the other way around.[26] However, the small caliber vessels of the penis are particularly prone to manifest loss of dilatation ability than larger vessels of the body. Loss of function (ED) indeed manifests earlier than systemic vascular disease (2–3 years prior).[27,28] Also, with rising age, collagen replaces the smooth muscle of the peripheral vascular system after degeneration of its cells. This results in decrement of blood trapped in cavernous vessels required for the erection to occur.[5]

Although the association between antihypertensive drugs and ED has been approached several times, the direct association between blood pressure and ED remains unclear.[29] In men of 40 years old or older, ED prevalence grows in parallel with age.[30]

ED in hypertensive males

A recent study by Foy et al[29] in a large sample of participants (N=1225) from the Systolic Blood Pressure Intervention Trial, has performed direct and rigorous measurements of blood pressure, sexual activity and erectile function in hypertensive men. The cohort was composed of males ≥50 years of age, with 60% of participants presenting ED. In multivariate analysis they have showed that although blood pressure was not associated with sexual activity, lower SBP, higher DBP and lower pulse pressure were associated with better erectile function. These findings could be justified by the vascular physiology of the penis. Contrary to other studies,[31] no association between antihypertensive drugs and ED was found in this study. However, only hypertensive participants were enrolled in this study. The authors further stated that younger age, higher education, lower body mass index (BMI) and lower number of comorbidities were associated with efficient erectile function.[29]

These findings oppose those reported by Korhonen et al,[32] which in multivariate analysis after adjustment for age, cohabiting status, waist perimeter, and education, found no association between HT and ED in a cohort of 924 men aged between 45 and 70 years. This study included both non-hypertensive and hypertensive participants subjected or not to AHT. One strength of the study was the exclusion of patients with previously identified comorbidities, such as diabetes, CVD or renal disease, cancer or neurologic conditions. The team reinforced that psychological factors, such as depression could result in ED.

ED and HT may be a double-edge sword, taking into account that both HT or AHT could lead to ED. However, ED seems to be

present also in newly diagnosed hypertensive patients. Huang et al[33] showed in a Chinese population of men aged 40 to 80 years that patients with ED presented higher rates of HT, among other illnesses.

With ageing, smooth muscle apoptosis and collagen deposition in the arteries causes stiffness, which leads to HT. This could explain why HT is a common comorbidity associated with ED and seems to indicate that both ED and HT may in fact be the same disorder that aggravates with ageing.[26]

NO is the main neurotransmitter involved in penile erection. In HT, maintained high blood pressure values lead to premature senescence and increased turnover of endothelial cells, which culminates in decreased NO release by endothelial nitric oxide synthase in the endothelium.[5] This is 1 proposed mechanism to explain the relationship between HT and ED.

AHT in males with ED

ED is a common complaint of medicated hypertensive men and one of the main reasons for refusal of AHT.[7] In mild-to-moderate hypertensive patients with ED, ED seems to have a higher impact in the QoL of middle-aged men than HT itself.[34] This conducted the search of therapies, both non-pharmacological or pharmacological, that would not trigger this secondary effect (ED) in the AHT.

Physical exercise

Lamina et al,[35,36] with the goal of understanding the effect of aerobic exercise in hypertensive man with ED, performed tests in men 50 to 70 years old. These were divided in 2 groups (exercise vs sedentary). In the first study,[35] an interval exercise was proposed to the exercise group and in the second study[36] a continuous exercise was proposed. All patients were asked to leave any AHT medication, being monitored daily. These studies demonstrated that both interval and continuous exercise improved erectile function in older hypertensive men with ED. Furthermore, this amelioration was associated with better endothelial function upon decrease of the inflammatory biomarker C-reactive protein. Long-term vessel relaxation can be achieved through modifications in biochemical, neural and hormonal factors resulting from physical exercise. These studies have come to demonstrate that routine changes can help improving HT and ED in middle-aged patients. However, data in physical exercise and eating habits are still scarce and more studies need to be performed in order to draw conclusions.[3]

β-Blockers

Among AHT, β-blockers are a class of great heterogeneity in terms of selectivity to adrenergic receptors, intrinsic sympathetic activity, and vasoactive effects. Some β-blockers, such as nebivolol, carvedilol and metoprolol, hold vasodilatory properties.[3]

Metoprolol and nebivolol are 2nd and 3rd generation β-blockers, respectively. Despite presenting similar antihypertensive efficacy of the cardio selective β1-adrenoceptor antagonists, metoprolol seems to negatively affect erectile function, while nebivolol seems not to lead to ED[37]; in fact, nebivolol seems to be the only therapeutic in this class not to interfere with erectile function.[3] However, another study comparing ED effects of atenolol (β-blocker) and nifedipine (calcium antagonist) in males between 60 and 70 years of age found no substantial variation in the sexual activity of the subjects.[38]

Angiotensin receptor blockers (ARBs)

Angiotensin II activity has been shown to have an impact in erectile function.[39] The ARB valsartan indeed was shown, not only, to decrease both SBP and DBP but also to increase the rate of sexual activity in males between 40 to 60 years of age, with better results in younger patients (40–47 years). Yet, in this study, the control group receiving conventional therapy is rather small, which might not reflect genuine variations during treatment.[7]

In another study, comparing treatment with the α- and β-blocker carvedilol with valsartan, it was shown in a cohort of patients between 40 and 49 years of age that while carvedilol treatment seems to contribute to ED, valsartan actually seems to enhance erectile function.[40] This was further validated in another study comprising 110 men in the same age range. Testosterone plasma levels were measured in patients on atenolol and valsartan. It was shown that while atenolol decreased sexual activity and testosterone levels, valsartan increased sexual activity when comparing to the atenolol group (but not when comparing to the placebo group). Furthermore, valsartan did not cause oscillation in testosterone plasmatic levels.[41]

Fogari et al[42] compared the effect of the AHT drugs lisinopril (ACE) and valsartan in patients between 46 and 65 years of age with ED. All patients were under simultaneous sildenafil treatment. The authors demonstrated that both drugs induced an analogous blood pressure lowering. Yet, the use of sildenafil rose in the period of treatment with valsartan. The authors suggested that angiotensin II antagonism may increase sexual desire in ED males with HT.

ED treatments in hypertensive men

Phosphodiesterase type 5 (PDE-5) inhibitors are the primary line treatment for ED. Sildenafil was the first PDE-5 inhibitor approved by the FDA for the treatment of ED in 1998.[43] Later, vardenafil and tadalafil were also approved. These drugs block PDE-5 isoenzyme, hampering the sequential breakdown of cyclic guanosine monophosphate (mode of action represented in Fig. 1).[44,45] PDE-5 inhibitors administration has not revealed adverse effects when in combination with most AHT, so far. So ED in patients submitted to AHT drugs can be safely treated with PDE-5 inhibitors.[3]

Regardless of intensified awareness, numerous cases of ED remain undiagnosed, in part because due to psychological matters men can take a long period of time before seeking treatment. PDE-5 inhibitors nonetheless, like any other pharmaceutical pose side effects, such as headache, flushing, nasal congestion, dyspepsia and myalgia. Given their vasodilatory effects, these drugs take action not only in capillaries of the penis but also in other parts of the body.[44]

Sildenafil treatment was formerly shown to lead to a decrease in SBP and reduced arterial wave reflection, seemingly through a mechanism related with NO release.[46] Javaroni et al[47] showed in a cohort of 74 hypertensive men aged between 50 and 70 years and without major CVD that daily vardenafil treatment for the period of 5 weeks improved erectile function.

Some patients are non-responsive to PDE-5 inhibitors, which could be justified by insufficient concentration of NO in the erectile tissue that may interfere earlier in the signaling cascade (Fig. 1) and hamper PDE-5 inhibitors action.[48]

El-Sisi et al[49] has evaluated the effect of atorvastatin, a widely used cholesterol-lowering therapy with pleiotropic effects, in patients that were non-responsive to sildenafil. Atorvastatin

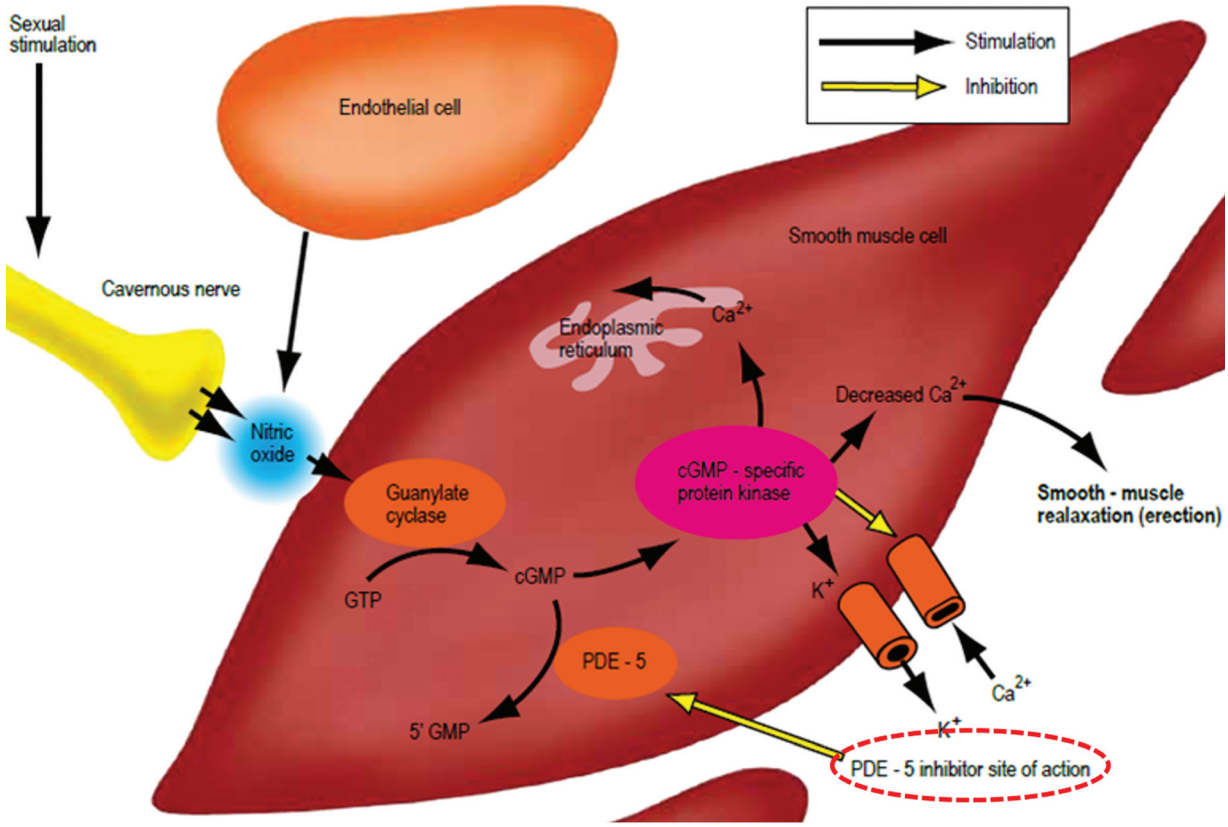

Figure 1. Mechanism of action of the phosphodiesterase type 5 (PDE-5) inhibitors. Nitric oxide is released from the neurons in the corpus cavernosum of the penis after sexual arousal, which culminates in accumulation of cyclic guanosine monophosphate (cGMP), produced from guanosine triphosphate (GTP). This causes smooth muscle relaxation leading to an erection. By preventing cGMP breakdown, (PDE-5) inhibitors (red dotted circle) enhance erectile function. (*Image adapted from "*Peate, I. British Journal of Community Nursing 2012 17:7, 310–317")[44,45].

treatment demonstrated anti-inflammatory and antioxidant effects, resulting in decreased IL-6, CRP and in increased glutathione peroxidase GPO. This drug also led to NO rise and ameliorated erectile function.

A large study including 8643 patients of age ≥65 years, showed that compliance to AHT seems to be associated with the adoption of newer-generation drugs, namely, ACE inhibitors and calcium channel antagonists. It further showed that good compliance was inversely associated with use of multiple pharmaceuticals. Although being a broad study, 1 major limitation is the inclusion of patients with other comorbidities, such as CVD. The existence of these conditions improved patient compliance.[50]

Final remarks

Epidemiological studies show that patients with ED present higher rates of HT. Yet, patients with newly diagnosed HT also present higher rates of ED. This evidence may indicate that HT and ED may result from the manifestation of the same condition in different vascular beds. In addition, several studies have been supportive that not only HT, but also, AHT could be underlying causes of ED in middle-aged and older men. Thus, ED should be actively screened by physicians in middle-aged and older HT patients.

Significant differences appear to exist upon the effects of AHT drugs on erectile function. While older-generation drugs, such as β-blockers seem to be associated with ED, newer-generation drugs, such as ACE and ARBs seem to have a neutral or even beneficial effect in erectile function. Alterations in lifestyle, such as the initiation/increase of aerobic exercise can be helpful in patients with ED and HT.

Conflicts of interest

Authors have declared no conflict of interest.

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