Hypertension and sexual dysfunction

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Abstract

Data from epidemiological and pathophysiological studies are far from complete, but despite some conflicting results, several tentative conclusions can be drawn, which can then be fitted into the prevailing view of an association between sexual dysfunction, hypertension and cardiovascular disease. The medications used by patients with hypertension and coronary artery disease may also contribute to the increased prevalence of sexual dysfunction in these patients. The therapeutic management of erectile dysfunction has advanced significantly in recent years with the advent of phosphodiesterase-5 (PDE-5) inhibitors; these drugs may be safely and effectively co-administered with antihypertensive drugs. Although sexual dysfunction is highly prevalent in the general population and significantly affects patients' and their sexual partners' quality of life, it is frequently neglected in everyday clinical practice. It is of utmost importance for physicians to become familiar with sexual dysfunction and realize that this issue requires both in-depth knowledge and extreme sensitivity.

Key words: erectile dysfunction, female sexual dysfunction, hypertension, antihypertensive drugs, coronary artery disease.

Introduction

The continuous prolongation of life expectancy has resulted in population aging, which combined with the economic prosperity in developed countries has created the need for improvements in quality of life of older individuals. Sexual dysfunction impacts the quality of life of patients and their sexual partners, resulting in anxiety, depression, and low self-esteem [1, 2]. It has been shown that human sexuality, although declining with aging, does not come to an end at any specific age. Despite its commonplace occurrence, sexual dysfunction is a notoriously under-reported, under-recognized, and under-treated chronic illness. It can be rationally speculated that the majority of cases with sexual dysfunction remain undiagnosed. The discovery of PDE-5 inhibitors marked the beginning of a new era, since these drugs seem to satisfy a silent social demand.

More than 25% of the general adult population suffers from arterial hypertension, and it has been estimated that by the year 2025 almost 1.5 billion people worldwide will be affected by this disease, thus placing hypertension among the major public health epidemics [3]. Since atherosclerosis of the arteries supplying genital tissues greatly affects sexual function, it seems rational to assume that conditions predisposing

to atherosclerosis (hypertension, diabetes, obesity, hyperlipidaemia) might impair sexual function. Increased blood pressure is currently considered a major contributor in the atherosclerotic process, and vascular and perivascular genital tissues exhibit profound damage with high blood pressure; thus, it is of no surprise that essential hypertension has been linked to erectile dysfunction. A vast amount of data indicates an association between arterial hypertension and sexual dysfunction, either as a consequence of the disease itself or as an adverse effect of the medications used for blood pressure lowering. However, the recognition of sexual dysfunction in hypertensive patients remains elusive in everyday clinical practice.

Cardiovascular disease represents the leading cause of mortality, and although many patients experience angina symptoms, sudden cardiac death can be the first manifestation of coronary heart disease. Thus, the identification of asymptomatic coronary artery disease seems of paramount importance, but thorough diagnostic evaluation cannot be applied to the general population. Erectile dysfunction is considered a disease of primarily vascular origin; its occurrence is mainly driven by the generalized atherosclerotic process, and may represent an 'early diagnostic sign' of silent coronary artery disease.

This review endeavours to address the challenge of sexual dysfunction management in the 21st century, outlines the association between sexual dysfunction and cardiovascular disease, focuses on the relationship between hypertension and sexual dysfunction in men and women on patho-physiological, epidemiological, and pharmacological grounds, and concludes with the use of phosphodiesterase-5 (PDE-5) inhibitors in hypertensive patients.

The challenge of sexual dysfunction in the 21st century

One of the most important characteristics that define living beings is their capacity to reproduce, an ability that relates directly to their sexuality. The complexity of sexual behaviour reaches its peak in humans, where a network of factors (biological, psychological, social, cultural, religious, etc) interact in a different way in every individual, thus conferring uniqueness in this aspect on each one of us. However, the finer the resolution the greater the complexity, and the greater the uncertainty.

The changes that took place during the second half of the previous century have affected human sexuality dramatically. The discovery and the wide application of oral contraceptives has allowed for the separation between reproduction and recreational sex. Mass media, fashion and the film industry have created new role models, the 'macho man' and the 'femme fatale', characterized by sexual liberty and intense sexuality. This 'false reality' has generated a lot of distress in women and men trying either to be like these models or to be involved with a person like this. Although the increased psychological pressure might have contributed to some extent to sexual dysfunction, the new era has also permitted an open discussion of previously unspoken realities.

Another significant step forward was the development of a definition of sexual dysfunction that is generally accepted. Impotence, a word with disrespectful and negative connotations, has been abandoned and replaced by sexual dysfunction, which is more neutral and "chic". Sexual dysfunction is defined by the WHO as "the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish". As is obvious, sexual dysfunction affects both men and women. Erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse [4]. The definition of female sexual dysfunction is more difficult, since female perception regarding sex is much more complicated and there is no objectivity in female sexual function. Although several definitions exist, the most descriptive defines female sexual dysfunction as the persistent or recurring decrease in sexual desire or in sexual arousal, or the difficulty or the inability to achieve an orgasm, or the feeling of pain during sexual intercourse [5]. Thus, female dysfunction covers all four aspects of women's sexuality: desire, arousal, orgasm, and pain (dyspareunia). It has to be emphasized that: a) the vast majority of patients with sexual dysfunction suffer from the vasculogenic form of the disease, and b) any dysfunction in sexual activity becomes a problem only when it creates distress to the individual. However, reliable studies truly evaluating the bother for the patient with sexual dysfunction and the concurrence of sexual disorders for the couple are lacking.

Although erectile dysfunction commands a great deal of attention in medical care, physicians seldom focus on uncovering this problem. The recognition and diagnosis of sexual dysfunction should be regarded as a routine aspect of everyday clinical practice. The primary goal of the diagnostic approach is to uncover the existence of unreported sexual dysfunction as well as significant comorbidities that contribute to the appearance of sexual dysfunction. A reliable and effective relationship between patients and physicians is of paramount importance when approaching a patient with sexual dysfunction. Physicians must earn patients' trust and should strive to maintain comfort and flexibility throughout the clinical examination. Every possible

effort has to be made in order to ensure privacy and confidentiality that will result in patients' openness, comfort, and trust, while the physicians have to avoid judgementalism and provide realistic therapeutic expectations. The initial assessment should always include a detailed medical, psychosocial, and sexual history.

One of the most significant hurdles for the majority of men with erectile dysfunction is admitting that they have a problem, since the social stigma associated with this dysfunction is devastating, and prevents men from seeking help. The fear of embarrassment further restricts patients in discussing this issue with their treating physicians. On the other hand, health care professionals seem to be poor communicators when it comes to discussions about sexuality [6, 7], and the main reason is that sexual issues have not been covered in undergraduate studies or during the basic training. Overcoming these obstacles and unmasking erectile dysfunction represents a serious challenge for health care professionals. Given the high prevalence of erectile dysfunction in the general population, the pressure and the challenge is upon the primary care physicians who are being asked to deal with this problem without appropriate education. The prospect of several new therapeutic modalities being available for clinical use in the near future makes the management of erectile dysfunction even more challenging, and the need for appropriate education even more necessary. Some efforts towards better education of general practitioners in this field have been initiated [8], but have to be widely implemented if we aim at the effective management of sexual dysfunction in the general population.

Involvement of the sexual partner in the therapeutic approach represents another significant challenge. The vast majority of patients with sexual dysfunction consult their physician alone, in the absence of their sexual partner. The most efficient way to engage the partners in the therapeutic plan is by encouraging the patients to bring their partners into the office and by pointing out the significance of this approach. However, clinical practice proves that several obstacles have to be overcome, since their sexual partners are at first intimidated and do not show up, especially when they are not married. Thus, physicians have to establish a very good relationship with their patients, earn their trust, and then proceed to the engagement of patients' sexual partners in the therapeutic plan. Using this 'step-by-step' approach, we have managed to involve the majority of the sexual partners in the therapeutic management of patients with sexual dysfunction, thus achieving realistic treatment expectations and improving the couple's relationship (personal unpublished data). This therapeutic approach is a potentially rewarding experience for all: patients, their sexual partners, and treating physicians.

We believe that the management of sexual dysfunction can be simplified by using a step-by-step approach, which we have named the 'six-E' approach:

- earn the patient's trust,
- evaluate the patient's medical, sexual, social, and psychological history,
- engage the patient's sexual partner,
- establish the diagnosis of vasculogenic sexual dysfunction,
- ensure absence of CAD and appropriate control of CV factors,
- elaborate a realistic therapeutic plan.

Cardiovascular disease and sexual dysfunction

Back in the 1920s, the famous French surgeon Leriche observed that the majority of patients with occlusive disease at the bifurcation of the aorta into the common iliac arteries suffered from erectile incapacity [9]. Recent studies revealed that erectile dysfunction is more frequent in patients with atherosclerotic disease at other sites of the vascular tree, such as coronary and peripheral artery disease [10-12]. In the Rancho Bernardo Study, small vessel lower extremity arterial disease was significantly and independently associated with the severity of erectile dysfunction [13]. On the other hand, narrowing of the larger arteries of the lower extremities is more common in patients with erectile dysfunction [14], and arterial lesions in the pudendal arteries are more frequent in men with sexual dysfunction compared to the general population [15].

During the last decade, accumulating data point towards a significant relationship between erectile dysfunction and cardiovascular disease. This association seems rational, since erectile dysfunction is currently considered a disease of vascular origin and atherosclerotic lesions in the penile arteries leading to reduced blood supply represent the predominant pathophysiological mechanism of erectile dysfunction. In addition, endothelial dysfunction is a common denominator [16] and nitric oxide bioavailability is reduced in both clinical entities [17, 18]; nitric oxide-induced vasodilation is thus defective and penile arteries are unable to dilate sufficiently in order to attain an erection. In a recent study, coronary flow velocity reserve was reduced in patients with erectile dysfunction compared to control individuals, but was similar compared to subjects with impaired glucose tolerance [19]. Furthermore, branchial endothelial-dependent and -independent vasodilation is reduced in patients with erectile dysfunction [20-22], while signs of endothelial cell activation have been observed in patients with erectile dysfunction but without clinical coronary

artery disease [23, 24]. In addition, a recent study reported that the existence of vasculogenic erectile dysfunction in patients with hypertension is associated with subclinical atherosclerosis, impairment of arterial function, and systemic endothelial and inflammatory activation [25].

Association studies suggest that erectile dysfunction is highly prevalent in patients with coronary artery disease, either overt or asymptomatic [26, 27]. Indeed, in 300 consecutive patients with angiographically documented coronary artery disease, erectile dysfunction was present in 49% of them [27]. Vice versa, patients with erectile dysfunction have coronary artery disease very frequently [22, 28]; in a patient with vasculogenic erectile dysfunction, coronary arteries are likely to have more than 50% stenosis [26, 29, 30]. Moreover, erectile dysfunction correlates with the number of occluded vessels and predates angina symptoms in many patients [22, 27, 31]; the mean interval between onset of erectile dysfunction and coronary artery disease was as long as 39 months in one study [27].

Of note, several traditional cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidaemia, and smoking) are also risk factors for erectile dysfunction [32, 33]; consequently patients with erectile dysfunction have a higher prevalence of these comorbidities [34-36] and are at higher risk for cardiovascular disease. Given the association between erectile dysfunction and cardiovascular disease, an important question arises: is this association independent or dependent on the comorbid conditions (hypertension, diabetes mellitus, hyperlipidaemia)? Although existing data are far from conclusive, studies in this field consistently suggest that erectile dysfunction remains an independent risk factor for cardiovascular events, even after correcting for other known traditional cardiovascular risk factors. In particular, erectile dysfunction has been shown to be independently correlated with coronary artery calcification [22], and left ventricular diastolic dysfunction [37]; in addition, it was the most significant predictor of asymptomatic coronary artery disease in patients with type 2 diabetes mellitus, independently of other risk factors [38]. However, the most important data come from prospective studies evaluating the association between erectile dysfunction and hard endpoints, such as major cardiovascular events. In the Prostate Cancer Prevention Trial, erectile dysfunction – either prevalent or incident – predicted over a long-term follow-up period the occurrence of cardiovascular events (myocardial infarction, stroke, transient ischaemic attack, congestive heart failure, fatal cardiac arrest, coronary revascularization, or cardiac arrhythmias requiring therapy); the increased cardiovascular risk was independent of traditional risk factors, with an adjusted hazard ratio of 1.45 (95% CI 1.25-1.69, P<0.001) that was of the same magnitude as that of hyperlipidaemia, smoking, or positive family history of myocardial infarction [39]. In another large study of more than 25,000 individuals followed for five years, patients with erectile dysfunction had a 2-fold increased risk of acute myocardial infarction compared with subjects without erectile dysfunction, after adjustment for confounding risk factors [40].

Two recently published studies in patients with diabetes mellitus provide further evidence on the association between erectile dysfunction and subsequent cardiovascular events [41, 42], and strongly suggest that erectile dysfunction should be considered a warning sign for cardiovascular events in patients with type 2 diabetes mellitus. In the first study of patients with no clinical evidence of cardiovascular disease, men with erectile dysfunction had a 1.6-fold increase in risk of experiencing coronary events compared to men without erectile dysfunction during a 4-year follow-up; the hazard ratio was 1.58 (95% CI 1.08-2.30, P=0.018) after adjustment for other covariates, age, antihypertensive agents, albuminuria, and duration of disease. In the second study of patients with angiographically documented silent coronary artery disease, patients with erectile dysfunction were twice as likely to experience major adverse cardiac events compared to patients without erectile dysfunction; erectile dysfunction remained an important predictor of major adverse cardiac events even in multivariate analysis adjusting for other risk factors. Thus, erectile dysfunction seems to be a powerful predictor of serious cardiovascular events in patients with type 2 diabetes mellitus.

Therefore, two things seem to be of utmost importance: a) in patients with coronary artery disease, appropriate questioning to uncover unreported erectile dysfunction seems worthwhile in order to improve the quality of life of patients and their sexual partners, and b) patients with erectile dysfunction seem to deserve a thorough and profound investigation for coronary artery disease, while more aggressive treatment of traditional risk factors might be justified in these patients to prevent cardiovascular events. The recognition of erectile dysfunction provides physicians with the opportunity not only to mitigate existing comorbidities that are known risk factors for cardiovascular disease, but also to prevent the occurrence of cardiovascular events by appropriately managing these comorbidities.

Pathophysiology of sexual dysfunction

Male physiology

The acquisition and maintenance of penile erection is the foremost event required for male sexual activity.

This is primarily a vascular phenomenon which is triggered by neurological impulses, and is facilitated by an appropriate hormonal and psychological milieu. The anatomy of the human penis is unique since it is designed to transform central and/or peripheral psychoneurogenic sexual stimuli into a complex haemodynamic process resulting in erection. Thus, erection is a coordinated sequela of psychoneurogenic stimuli, neuromodulation through different pathways influenced by various hormones, and increased arterial blood inflow caused by arterial vasodilatation with simultaneous venous occlusion.

The penis is composed of three bodies of erectile tissue: the corpus spongiosum and the two corpora cavernosa. The latter represent a unique vascular bed consisting of sinuses (the trabeculae) that are supplied from the resistance helicine arteries and are drained by the subtunical venules. Histologically, the corpora are composed mainly of connective tissue and smooth muscle cells, joined by nerves, fibroblasts, and the vascular endothelium.

Erections initiate in response to erotic stimuli, sexual fantasy, or tactile stimuli to the penis or genital area, and the continuation of the erectile process requires an appropriate neural input to direct the blood flow into the corpora cavernosa. The blood flow into the corpora cavernosa and the bulbus spongiosum engorges the cavernosal spaces, and the subsequent elevation of intracavernosal pressure leads to occlusion of the emissary veins, which in turn results in further engorgement. In the flaccid penis, smooth muscle tone is heightened, while penile erection requires a decrease in the penile smooth muscle tone. Detumescence occurs when the nitric oxide-dependent vasodilation subsides due to cGMP catabolism that is mediated by type 5 phosphodiesterase. An appropriate hormonal environment permits a successful erection, with testosterone playing a pivotal role, while prolactin, thyroid hormones, and adrenal steroids have a secondary role.

Male pathophysiology in essential hypertension

Penile erection is based on increased blood flow into the corpora cavernosa and depends on the perfusion pressure, dilation of blood vessels, and the relaxation of cavernosal smooth muscle. Erectile dysfunction in hypertension probably reflects alterations in a number of the processes involved in normal sexual function. Atherosclerotic stenosis or increased wall-to-lumen ratio may result in lumen narrowing and decreased blood supply, while penile vasodilation may be impaired as well. Increased adrenergic nerve activity maintains the penis in the flaccid state and causes detumescence of the erect penis, while the injection of alpha-adrenoreceptor antagonists results in erection [43].

Structural and functional abnormalities induced by hypertension may be implicated in the pathophysiology of erectile dysfunction. Experimental studies indicate that hypertension results in structural changes in the penile vasculature [44-46]; apart from the marked vascular smooth muscle hypertrophy of the cavernous arteries, the smooth muscle layer in the cavernous space is increased in hypertensive compared to normotensive rats. Moreover, the extracellular matrix morphology is also affected in hypertensive rats, since collagen type III fibres are significantly increased [47, 48].

In addition, functional alterations in rat penile resistance arteries have been reported [49]. The neurogenic relaxation in response to electrical field stimulation is impaired in hypertensive compared to normotensive rats, due to the attenuated relaxation in response to NO [50]. Furthermore, the overproduction of endothelium-derived cyclooxygenase products in the corporal tissue results in increased vasoconstriction, thus rendering it more difficult for the corporal smooth muscle to relax and achieve an erection [51].

Angiotensin II is known to induce contraction of the corporal smooth muscle *in vivo* and *in vitro*, *via* AT1 receptors [52, 53]. The human corpus cavernosum contains 200-fold higher angiotensin II levels than human plasma; in addition, angiotensin II levels increase during the detumescence phase of erection, underlining the role of angiotensin II in the termination of penile erection [54, 55]. Recent animal data suggest that angiotensin receptor blockers exert beneficial effects on penile structural effects caused by hypertension [48]. Interestingly enough, intracavernosal injection of angiotensin II decreases intracavernosal pressure and terminates spontaneous erection in anaesthetized dogs; in contrast, intracavernosal injection of an angiotensin receptor blocker (losartan) increases dose-dependently the intracavernosal pressure [54].

The angiotensin-converting enzyme (ACE) and chymase that result in angiotensin II production present considerably high activity in the rat corpus cavernosum, and pretreatment with combination of an ACE inhibitor and chymostatin is needed to completely abolish the angiotensin I-induced contraction [56]. In addition, morphological studies revealed the presence of mast cells that produce chymase in the cavernosal area [56]. These findings, if confirmed in humans, can lead to the hypothesis that angiotensin receptor blockers will be more advantageous than ACE inhibitors in protecting penile tissue from the negative effects exerted by angiotensin II. The role of bradykinin [57], sex hormones [58-60], endothelin-1 [61-64], carbon monoxide [65, 66], Rho-Rho kinases [67], and gene polymorphisms [68-70] remains controversial and needs further clarification.

Female physiology and pathophysiology

The male and female sexual orgasm have several similarities, sharing even the same electrophysiological appearances [71, 72]. Functional adrenergic receptors are expressed both in the clitoris and vagina and mediate norepinephrine-induced genital smooth muscle contraction. On the other hand, nitric oxide plays a significant role in clitoral smooth muscle relaxation, while conflicting results exist regarding its role in the vagina. Phosphodiesterase-5 inhibitors result in significant increase of genital blood flow and vaginal lubrication. Therefore, although available data in women are substantially weaker than those in men, both catecholamines and nitric oxide seem to exert almost the same effects on female and male genital organs.

Hypertension induces structural alterations in the female genital tissue that resemble the abnormalities observed in male hypertensive animals. Moreover, angiotensin II seems to play a pivotal role in the structural and functional changes of the clitoris and vagina, while blockade of the renin-angiotensin axis protects the genital tissue from these abnormalities. Thus, the major players in female sexual dysfunction pathophysiology in hypertension appear to be nitric oxide, catecholamines and angiotensin II, just like in male sexual pathophysiology. However, current therapeutic approaches are mainly affected by the 'patriarchal' mode of society, attempting to resolve male sexual problems and largely ignoring female ones.

Prevalence of sexual dysfunction

As with almost all dysfunctions, sexual dysfunction is primarily a self-reported diagnosis, and only cross-checking with the sexual partner can provide further significant information. The evaluation of sexual dysfunction has evolved over the past two decades, and moved towards a questionnaire-based determination of sexual function. Several inventories have been proposed, with the IIEF (International Index of Erectile Function) and FSFI (Female Sexual Function Index) seeming to be the most appropriate for men and women, respectively. Sexual dysfunction is common among older men and inevitably co-exists with other diseases that are prevalent in this population, such as arterial hypertension, diabetes mellitus, hyperlipidaemia, and coronary artery disease.

Erectile dysfunction in the general population

Despite a paucity of longitudinal studies regarding the incidence of erectile dysfunction, evidence-based studies point to an incidence rate of 25-30 cases per 1000 person years. However, the incidence of erectile dysfunction has not been adequately studied, and large differences exist in incidence rates between available studies [73-77]. The only definite conclusion that can be drawn from these studies is that the incidence of erectile dysfunction increases with age.

In 1995, it was estimated that over 152 million men worldwide were affected by erectile dysfunction, while the projection for 2025 is a prevalence of 322 million men worldwide [78, 79]. A significant increase with age has been consistently reported, with men over 70 or 80 years of age showing a prevalence rate of erectile dysfunction between 50 and 75%. The prevalence of erectile dysfunction shows significant variation worldwide, and many reasons may account for this variation. Population samples, data collection methods, definition of erectile dysfunction, and tools for the assessment of erectile dysfunction vary between different studies and contribute to the conflicting findings regarding erectile dysfunction prevalence [80].

The Massachusetts Male Aging Study (MMAS) in 1994 was the first longitudinal, community-based, wide-scale epidemiological study of 1290 men [1]; the study reported an unexpectedly high rate of 52% erectile dysfunction prevalence, drawing the general attention of the scientific community. Complete erectile dysfunction was present in 15% of men with treated hypertension, and this was associated with the duration and severity of hypertension. Since then, many studies have reported the prevalence of erectile dysfunction in the general population all over the world, ranging from 15% in Brazil to 74% in Finland [73, 81-91]. Although these studies employed different methodologies and cannot be directly compared with one another, they nonetheless reveal that the prevalence of erectile dysfunction is high in the general population.

Erectile dysfunction in hypertensives

Despite arterial hypertension being currently considered as a risk factor for erectile dysfunction, existing information is in part conflicting [92-94]. Older studies evaluating the prevalence of erectile dysfunction in hypertensive patients and normotensive subjects reported similar results [15, 41, 95-97]. In addition, the Treatment of Mild Hypertension Study (TOMHS) reported a low prevalence of sexual dysfunction in hypertensives (14.4% in men, 4.9% in women), and largely contributed to the general opinion that erectile dysfunction is not very frequent in patients with essential hypertension [98]. Thus, it is of no surprise that all current guidelines for the management of hypertension either address sexual dysfunction superficially or do not mention this condition at all [99-101]. However, several drawbacks can be recognized in the TOMHS: a) the study included only

mildly hypertensive patients since diabetic and severely hypertensives were excluded, b) there was only one question assessing sexual dysfunction, without any particular interest or time spent on that issue, c) patients' age ranged from 45 to 69 years, excluding older patients, and d) it is a considerably old study and patients were not at that time familiar with the issue or willing to accept it.

Most of the studies consistently point to a higher prevalence of erectile dysfunction in hypertensive patients compared with normotensive subjects [102-108]. It has been estimated that hypertensives have a relative risk of 1.3-6.9 for erectile dysfunction compared to normotensives [73, 81-90]. Of note, two studies from the South of Europe reported a prevalence of erectile dysfunction in hypertensives (45.8% in Spain, 35.2% in Greece) that was considerably higher than in the general population in Spain (18.9%) or in normotensive subjects in Greece (14.1%).

In the currently performed ONTARGET/TRANSCEND study, a substudy assessing the effect of telmisartan on the sexual function of 1,357 patients revealed that 54.3% of them suffered from erectile dysfunction at baseline [109], thus confirming that erectile dysfunction is highly prevalent in patients with cardiovascular risk factors or cardiovascular disease. Although the results of this substudy are eagerly expected, we have to keep in mind that data derived from this study regard the addition of telmisartan in previous therapy, and thus may not offer information on the effect of ARB monotherapy on erectile function.

Determinants of erectile dysfunction in essential hypertension

Erectile dysfunction is more frequent and more severe in patients with long-standing hypertension (>5-6 years) compared to patients with recent onset of hypertension [107], underlining the effect of hypertension duration on erectile function. Erectile dysfunction is more prevalent in patients with severe hypertension, and the severity of erectile dysfunction follows hypertension severity [107]. It is also noteworthy that the relationship between erectile function and blood pressure levels is significant even in prehypertension, indicating that appropriate counselling must be given at early stages [107].

Treatment of hypertension has been largely associated with erectile dysfunction, and treated hypertensives are more prone to suffer from erectile dysfunction than untreated ones. An overview of available data regarding the effect of various antihypertensive drugs on erectile function follows in a separate section. Unfortunately, no definite data exist regarding the role of smoking, alcohol intake, and the level of physical activity on erectile function in patients with essential hypertension; however, implementing lifestyle changes in hypertensives is of paramount importance and every possible effort should be made in this direction.

Female sexual dysfunction in the general population

The social and cultural influence on female sexuality has been profound over the years. Women were not allowed to express their sexuality until some decades ago, and they still are not permitted to do so in some parts of the world. In retrospect, it seems impressive that, only fifty years ago, the publication of a scientific book regarding female sexuality by Kinsey resulted in several foundations halting all financial aid to Kinsey. This explains why only limited information is available on the prevalence and antecedents of female sexual dysfunction.

The 5-year incidence of female sexual dysfunction was reported to be approximately 40% in two studies from Scandinavia in the 1990s [110, 111], and the incidence was strongly age-related. However, almost nobody paid attention to these reports, and thus it came as a big surprise when reported in 1999 (U. S. National Health and Social Life Survey) that female sexual dysfunction is more frequent than male (43 vs. 31%) [112]. Although several studies have confirmed this finding [113-117], reporting a prevalence from 51.3% in Chile to 78.4% in Ecuador [118-120], female sexual dysfunction remains remarkably understudied, and research in this field represents an emerging topic.

Although biological factors have a pivotal role in human sexuality, it would be exceedingly simplistic to ignore psychological factors, especially in women. We have to keep in mind when evaluating studies on sexual dysfunction that sexual desire tends to decrease with longer duration of partnership [121], while routine elimination seems to be of utmost importance but is rarely implemented.

Female sexual dysfunction in hypertension

The TOMHS study reported a very low prevalence of female sexual dysfunction (4.9%); however, the limitations of this study have already been mentioned [98]. A well-controlled, although not very large, epidemiological study revealed that hyper-tension was associated with decreased lubricative function and with orgasmic dysfunction [122]. The same group reported that it is hypertension per se resulting in female sexual dysfunction rather than the antihypertensive therapy [123]; moreover, in a recent study examining postmenopausal women with heart disease, antihypertensive medication was not a predictor of sexual problems [124]. In contrast,

the use of antihypertensive drugs was a significant negative predictor of orgasmic function [125]; in addition, sexual interest was significantly decreased during antihypertensive therapy in 41% of middle-aged hypertensive females [126]. We have recently reported an increased prevalence of sexual dysfunction in hypertensive women (42.1%) compared to normotensive women (19.4%, odds ratio: 3.2); use of β-blockers was a significant predictor of sexual dysfunction in our study [127]. The relative lack of data regarding female sexual dysfunction in patients with high blood pressure does not imply that hypertensive women do not suffer from sexual problems; it rather suggests that appropriate studies have not been performed.

Antihypertensive drugs and sexual dysfunction

Erectile dysfunction in patients with essential hypertension could be caused by the disease itself or by the medications prescribed to lower the increased blood pressure. However, it has to be kept in mind that hypertension is an asymptomatic condition in the majority of cases, and thus antihypertensive drugs must have an acceptable side effect profile in order to ensure adequate compliance. The perception of patients regarding the effects of lifelong therapy with antihypertensive drugs on sexual function may have deleterious consequences on adherence to therapy, which in turn may play a particularly disruptive role in the management of hypertensive patients [128, 129]. However, this factor is often not taken into account in clinical trials, despite its significance in everyday clinical practice [130-132]. Another important issue is the placebo effect that has been recently re-suggested [133]; however, data supporting this hypothesis are also lacking. Furthermore, a recent study in patients who stopped antihypertensive drugs because of perceived effects on erectile function showed that most patients did not experience an improvement in sexual function despite treatment discontinuation [128].

The prevalence of erectile dysfunction has been found to be higher in treated hypertensives compared to untreated ones and normotensive subjects, while available data have been extensively reviewed in a previous article [134]. In the original MMAS study, a significant correlation between antihypertensive drugs and erectile dysfunction was observed [1]; however, a later analysis, after several adjustments, revealed that only the non-thiazide diuretics were associated with prevalent erectile dysfunction [135]. Erectile dysfunction has never been studied as the primary end-point in a large clinical trial, and therefore a causative relationship between specific antihypertensive drugs and erectile dysfunction has never been established in a definite way, without any doubt. Available data come from observational studies showing an increased prevalence of erectile dysfunction in patients taking certain antihypertensive drugs, large clinical trials reporting an increased incidence of erectile dysfunction with some antihypertensive medications, open clinical studies reporting a reversal of erectile dysfunction with the substitution of one drug by another, and small clinical studies comparing the effects of different antihypertensive drug classes on erectile function.

Whether one class of antihypertensive drugs is more likely to be associated with erectile dysfunction than another class is difficult to determine, since the appearance of erectile dysfunction depends on several factors: hypertension characteristics (severity, duration), existing comorbidities (cardiovascular disease, diabetes mellitus, hyperlipidaemia, depression), personal characteristics (age, body mass, cigarette smoking, alcohol consumption, physical activity), and co-administered medications. Therefore, only a well-designed, randomized, double-blind, large study may uncover without doubts any existing differences in the effects of various drug classes on erectile function.

Available data indicate that old-generation antihypertensive drugs (central acting, β-blockers, diuretics) negatively affect erectile function, while new-generation agents (calcium antagonists, ACE inhibitors) seem to have neutral effects [134]. Angiotensin receptor blockers and nebivolol [136, 137] seem to improve sexual functioning and may therefore be useful either for the initiation of drug therapy in hypertensive patients with pre-existing erectile dysfunction, or for the substitution of previous therapy in patients experiencing erectile dysfunction while taking other drug classes. A suggested algorithm for the evaluation and management of erectile dysfunction in hypertensive patients has been recently proposed [134].

Phosphodiesterase-5 inhibitors in hypertensive patients

The introduction of sildenafil citrate in 1998 has revolutionized the perception of erectile dysfunction [138], and has generated a multi-billion dollar market. Since then, two other PDE-5 inhibitors have been approved and entered the market (vardenafil, tadalafil), while several other drugs are in different stages of development, including PDE-5 inhibitors (mirodenafil, avanafil, udenafil, dasantafil, UK 369003, SLx 2101) and other substances: dopamine D4 agonists (ABT 670, ABT 724), melanocortinergic agents (PL 6983, bremelanotide was abandoned because of blood pressure elevation), poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors (INO 1001), Rho-kinase

inhibitors, hexarelin analogues, and guanylate cyclase activators.

Phosphodiesterase-5 inhibitors block the breakdown of cGMP. Erection was a very common side effect in the first clinical trials with sildenafil, and this observation re-directed research towards the evaluation of sildenafil in erectile dysfunction treatment [139]. However, sildenafil has some undesirable characteristics, such as short half-life, food interactions, and activity against PDE-6 resulting in visual disturbances; thus, newer PDE-5 inhibitors have been developed and joined sildenafil in the management of erectile dysfunction: vardenafil and tadalafil. Vardenafil is more potent than the other two, while tadalafil has a 17-h half-life, permitting more natural enga-gement in sexual activity, and its bioavailability is not influenced by food. In addition, tadalafil is less active against PDE-6 and thus lacks visual side effects [140].

The use of sildenafil in hypertensive patients has raised some concerns (because of its vasorelaxant properties), especially in patients taking complicated, multidrug, antihypertensive regimens, where sildenafil could be "potentially hazardous" [141]. However, accumulating data indicate that PDE-5 inhibitors result in small blood pressure reductions, both in normotensive subjects and hypertensive patients, which are usually clinically insignificant and thus do not affect patients' safety [142-150]. Orthostatic hypotension can be observed with the concomitant use of PDE-5 inhibitors and alpha blockers. According to the new FDA labelling α-blockers are not considered a contraindication for all three PDE-5 inhibitors; however, low starting doses of PDE-5 inhibitors are recommended in patients already taking α-blockers, and *vice versa*, low starting doses of alpha blockers in patients on therapy with PDE-5 inhibitors.

The use of PDE-5 inhibitors in hypertensive patients is not only safe, but can offer further benefits as well, regarding adherence to therapy and improved monitoring. In a recent study of 6,768 hypertensive men attending the New England Veterans Affairs Healthcare System, the use of PDE-5 inhibitors was associated with the addition of antihypertensive drugs in previous therapy (42.2%) rather than a decrease in used drugs (17.3%), as well as with initiation of antihypertensive medication (17.3%) instead of discontinuation of previous therapy (2.3%) [151]. It is thus not surprising that the initiation of PDE-5 inhibitors was accompanied by a significant decrease in systolic blood pressure, especially in patients with higher baseline blood pressure, probably due to better monitoring and a more aggressive therapeutic approach. In another recent report, more than 60% of patients taking antihypertensive drugs were non-adherent with their long-term medication therapy; among these non-adherent patients, 36% became adherent after initiating PDE-5 inhibitors to treat concomitant erectile dysfunction [152]. Of note, at least one PDE-5 inhibitor (SLx 2101) is currently in phase IIb trials for the treatment of essential hypertension.

Currently, PDE-5 inhibitors represent the most widely used treatment for patients with erectile dysfunction; however, they are not suitable or effective for all patients. Patients with untreated, poorly controlled, accelerated, or malignant hypertension are considered high-risk patients, just like several other categories of patients with significant cardiovascular disease [153]. Sexual activity should be deferred in these patients until their condition is stabilized by treatment and a decision has been made by a cardiologist that sexual activity may be safely resumed. The astute clinician has to fine-tune the treatment approach and individualize management for each patient.

Conclusions

Recent advances in the therapeutic management of erectile dysfunction with PDE-5 inhibitors have transformed the perception of erectile dysfunction for both patients and physicians. However, despite the major concern to patients, erectile dysfunction remains under-treated because of patients' reluctance to seek medical help and physicians' failure to recognize the disease. The challenge to uncover and appropriately manage patients with erectile dysfunction is growing, as is the need for the development of effective treatment for female sexual dysfunction.

There is accumulating evidence of a close pathophysiological relationship between cardiovascular disease and erectile dysfunction. The risk factors for both conditions are essentially the same, including hypertension, diabetes mellitus, hyperlipidaemia, and smoking. More importantly, several lines of evidence suggest that erectile dysfunction can independently predict future cardiovascular events, and may be considered an early sign of asymptomatic coronary artery disease.

Sexual dysfunction and hypertension seem to share common pathophysiological mechanisms; thus, the prevalence of sexual dysfunction is higher in hypertensives than in normotensives. Older hypertensive drugs seem to contribute to the more frequent appearance of erectile dysfunction in hypertensive patients, while newer generation drugs have either neutral or beneficial effects. Finally, available data indicate that PDE-5 inhibitors may be safely and effectively administered by hypertensive patients.

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