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Male and female sexual dysfunction: is hypertension an innocent bystander or a major contributor?

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ABSTRACT

Sexual dysfunction represents a major quality-of-life-related health problem, and available data indicate that essential hypertension is a risk factor for sexual dysfunction in both men and women. Male and female sexual dysfunction is more prevalent in hypertensive than normotensive individuals, and several mechanisms have been implicated in the pathogenesis of sexual dysfunction in hypertensive patients. Several factors affect the sexual function of hypertensive function, such as severity and duration of hypertension, age, and antihypertensive therapy. Older antihypertensive drugs (diuretics, ß-blockers, centrally acting) exert negative results while never drugs have either neutral (Ca-antagonists, ACE-inhibitors) or beneficial effects (angiotensin receptor blockers). Female sexual dysfunction, although more frequent than the male one, remains largely underinvestigated possibly due to the lack of effective treatment. A better understanding of sexual functioning and appropriate education of doctors at medical schools and specific seminars would result in a more effective approach of sexual dysfunction by practitioners dealing with hypertensive patients.

KEY WORDS

Erectile dysfunction, female sexual dysfunction, essential hypertension, hypertension treatment, quality of life.

INTRODUCTION

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 it is obvious, sexual dysfunction affects both men and women. However, although male sexual dysfunction has attracted great scientific interest after the discovery of phosphodiesterase-5 (PDE-5) inhibitors, female sexual dysfunction still lies on the shadow. Sexuality represents an important issue and sexual dysfunction has a great impact on patients' and their sexual partners' quality of life.

Erectile dysfunction is defined as the persistent inability to attain and/or maintain penile erection sufficient for sexual intercourse[1]. Recent reports estimate that over 150 million men all over the world have some degree of erectile dysfunction and the projected prevalence for 2025 is 322 million men worldwide[2].

The definition of female sexual dysfunction is more difficult, since womens' perception about sex is much more complicated and there is no objectivity in female sexual function. Although several mechanisms 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[3]. Thus, female dysfunction covers all four aspects of women sexuality: desire, arousal, orgasm, and pain (dyspareunia). It came as a big surprise when the US National Health and Social Life Survey reported that female is more frequent than male sexual dysfunction[4]. Although several studies have confirmed this finding, female sexual dysfunction remains remarkably understudied.

Sexual dysfunction has been considered of psychogenic origin since ancient times, however it is currently believed to

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Rev Bras Hipertens vol.14(3): 139-147, 2007.

be a disease of organic (mainly vascular) etiology in the majority of cases. 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, hyperlipidemia) might impair sexual function.

Arterial hypertension is considered a major public health epidemic and affects more than 25% of the general population, with its prevalence increasing with age. Since blood pressure is a major contributor in the atherosclerotic process, and vascular and perivascular genital tissues exhibit profound damage with increasing blood pressure, it's of no surprise that essential hypertension has been linked to erectile dysfunction. The fact that several areas of male and female reproductive embryology and sexual physiology are similar has lead researchers to investigate the relationship between essential hypertension and female sexual dysfunction.

The relationship between essential hypertension and sexual dysfunction has raised a very important issue: is hypertension *per se* the cause of sexual dysfunction or do the drugs used in treating high blood pressure impair sexual function? Although several studies have addressed this topic, the question remains largely unanswered.

In our point of view, the data presented in this review provide several substantial reasons for hypertension specialists to become familiar with sexual dysfunction and deal with this important problem, since:

i) a significant proportion of hypertensive patients experience sexual problems that impair their quality of life. Patients and their sexual partners will be offered a great benefit from resolving this problem. Since it is preferable to adopt a holistic approach in patients' management, hypertensive specialists have to deal with all patients' problems;
ii) some antihypertensive drug categories are implicated in sexual dysfunction. Thus, changing the drugs administered to the patients might result in resolution or significant improvement of the problem;
iii) many hypertensive patients take PDE-5 inhibitors by themselves (especially from the Internet), without medical advice and care. Since these drugs cause hypotension and interact with antihypertensive drugs, it seems prudent to offer a medical follow up instead of neglecting this issue;
iv) a substantial percentage of hypertensive patients suffer from coronary artery disease or heart failure. Since PDE-5 inhibitors may be extremely harmful in such patients, especially if co-administered with nitrates, it would be much safer for the patients to take appropriate consultation regarding sexual intercourse; and
v) sexual dysfunction is frequently accompanied by atherosclerotic lesions in other beds of the vascular tree. Since in many cases there exist no signs from the other affected organs, sexual dysfunction might be considered an early sign of vascular disease, and thus must be thoroughly investigated in hypertensive patients.

This review briefly presents the prevalence of male and female sexual dysfunction in the general population and hypertensive patients, outlines the pathophysiology of sexual dysfunction and underlines the specific changes observed in hypertension, comments on the factors contributing to sexual dysfunction in hypertensive men and women especially addressing the effect of antihypertensive drugs on sexual dysfunction, discusses the impact of sexual dysfunction on the quality of life and, summarizes the relationship between sexual dysfunction and cardiovascular disease as well as the cardiac risk of sexual activity in hypertension.

PREVALENCE OF SEXUAL DYSFUNCTION

An overview of existing data regarding the prevalence of erectile dysfunction in the general population and hypertensive patients follows, in the effort to clarify the effect of hypertension on male and female sexual function.

Prevalence of erectile dysfunction in the general population

The real advent of erectile dysfunction epidemiology followed the erectile dysfunction definition by NIH[1]. The prevalence of erectile dysfunction in the general population varies markedly among different countries. This could reflect different sample populations (age, cohorts of patients with recognized erectile dysfunction), different assessment methods (questionnaires, mail responses and telephone interviews), cultural differences in the willingness of individuals to discuss such issues and accept the social stigma of erectile dysfunction, and ethnic differences (genetic and environmental factors affecting erectile function).

The Massachusetts Male Aging Study in 1994 was the first longitudinal, community-based, wide-scale epidemiological study of 1,290 men[5]; the study reported an unexpectedly high rate of 52% erectile dysfunction prevalence, drawing the general attention of the scientific community. 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[6-16]. A recent study of 22,839 men in eight countries reported an overall prevalence rate of 16%, ranging from 10% in Spain to 22% in USA; however, although the study is very

large, the use of a single-item embedding question for erectile dysfunction assessment limits the validity of the study[17].

A need for large epidemiological studies in several representative countries worldwide, using the same assessment method (a standardized validated questionnaire), performed at a prespecified representative sample of the general population by specialized doctors or well-trained nurses and cross-checking of answers with the sexual partners, is essential for clarifying the prevalence of erectile dysfunction worldwide, a real "landscape in the mist" now.

Erectile dysfunction in patients with essential hypertension

Although essential hypertension is widely accepted as a risk factor for erectile dysfunction, available data is in part controversial and indicate that this relationship is not definitely established. Some older studies have reported a similar prevalence of ED in hypertensive pts and normotensive subjects; however, the majority of the available data indicate that ED is more frequent in pts with EH when compared to normotensive subjects.

In a study of 440 impotent men, arterial hypertension was not an independent predictor of vasculogenic erectile dysfunction (after adjusting for diabetes mellitus, hyperlipidemia and smoking), measured by penile arterial flow using duplex ultrasonography[18]. Similar results were obtained in a study of 132 patients evaluated by duplex echo after intracorporeal papaverine injection, where hypertension alone was not an independent risk factor for vasculogenic erectile dysfunction[19]. In addition, in a study of 32 men with mild to moderate hypertension and 78 normotensive men, no association between hypertension and arteriogenic impotence was found, as measured by penile blood inflow, peak systolic velocity and resistance index[20]. Larger epidemiological studies have found only marginal effects of hypertension on erectile function; only a "meager" relationship of erectile dysfunction and hypertension was observed in a study of 1,128 patients, aged 16 to 80 years[21]. Similarly, the 9-year follow-up MMAS study reported that, although hypertension was an independent predictor of erectile dysfunction, its effect was modest[22]. However, the majority of epidemiological studies report an increased prevalence of erectile dysfunction in patients with essential hypertension. The relative risk of erectile dysfunction in hypertensives compared to normotensives ranges from 1.3-6.9[6-16].

Essential hypertension is related to increased prevalence of erectile dysfunction, whichever the method of erectile dysfunction assessment. The vast majority of the available data indicate that erectile dysfunction is more frequent in patients with essential hypertension when compared to normotensive subjects[23-28].

The TOMHS study was the first large hypertension study to report the prevalence of erectile dysfunction in hypertensive patients[29]. The prevalence of erectile dysfunction at baseline was considerably low (14.4% in men and 4.9% in women); however, this could be due to several factors: 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 consumed in that issue, c) patients' age ranged from 45-69 years, excluding older patients, and d) it is a considerably old study and patients were not at that time familiar with the issue and willing to accept it.

In a recent open, prospective study of 2,130 men with essential hypertension from Spain, erectile dysfunction was detected in 45.8% of hypertensive men[30]. This percentage is significantly high compared to 18.9% that was found in the general Spanish population[8]. However, although the difference of prevalence is too high, these are two different studies and differences in baseline characteristics may account for the difference in prevalence. We have recently reported in a sample of 634 Greek men that erectile dysfunction was twice as prevalent in hypertensive than in normotensive subjects, since it was detected in 35.2% of hypertensive men compared to 14.1% of normotensive men[28].

A major limitation of the majority of these studies however, is that hypertension recognition relies on self-reporting, while no attempt was made to validate responses with medical records, physician or partner reports. Therefore, a multinational study with accurate blood pressure measurement and recording of all coexisting co-morbidities will clearly demonstrate whether hypertension is indeed a risk factor for erectile dysfunction.

Determinants of erectile dysfunction in essential hypertension

There exists no specific age at which sexual activity does or should end, and since life expectancy is constantly increasing, sexual function will become a crucial issue. Erectile and medical problems are frequently associated in the aging patient, resulting in a confusing mixture of normal age-related decline in sexual function and real pathological conditions.

It is well recognized that erectile function declines with aging. The prevalence of erectile dysfunction in the MMAS increased from 52% in men 40-70 years old to more than 95% in men over age 70 with diabetes[5]. All epidemiological studies confirm the steep decline in erectile function with advanced age. However, aging is accompanied by several diseases that affect erectile function, such as hypertension and diabetes[31]; thus, it is not unexpected that hypertension and erectile dysfunction coexist in older individuals. The likely worldwide increase in the prevalence of erectile dysfunction represents a major challenge

Rev Bras Hipertens vol.14(3): 139-147, 2007.

for the timely recognition and proper management of erectile dysfunction.

Duration of hypertension significantly affects erectile function. Studies addressing this issue in hypertensive patients reported that 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[28].

Hypertension severity is associated with erectile dysfunction as well. It seems that as blood pressure increases erectile function decreases, and erectile dysfunction is more prevalent in patients with severe hypertension[28,32]. Moreover, the severity of erectile dysfunction follows hypertension severity and patients with severe hypertension tend to not only have erectile dysfunction, but suffer from its severe form[28]. It is also noteworthy that the relationship between erectile function and blood pressure levels is significant even in prehypertension, indicating that appropriate counseling must be given at early stages[28].

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 analytic overview of available data regarding the effect of various antihypertensive drugs on erectile function has been recently published[33]. Briefly, old-generation antihypertensive drugs (central acting, ß-blockers, diuretics) negatively affect erectile function, while new-generation agents (calcium antagonists, ACE-inhibitors) seem to have neutral effects; preliminary data with the latest drugs (angiotensin receptor blockers) point to a beneficial effect on erectile function. Phosphodiesterase-5 (PDE-5) inhibitors, used for the treatment of erectile dysfunction, can be effectively and safely administered to hypertensive patients (even when on multiple agent antihypertensive therapy), with a caution regarding α-blockers. In the case when erectile dysfunction results from antihypertensive therapy, ARBs may substitute previous medications before using PDE-5 inhibitors.

No definite data exists regarding the role of smoking, alcohol intake, and the level of physical activity on erectile function in patients with essential hypertension.

Prevalence of female sexual dysfunction

Limited information is available on the prevalence and antecedents of female sexual dysfunction. It has come as a big surprise that female is more frequent than male sexual dysfunction (43% vs. 31%) when reported in 1999 based on the U.S. National Health and Social Life Survey[4]. The most common complaint was libido (51%) followed by arousal (33%) and pain disorders (16%). A recent English study reported that 53.8% of females had at least one sexual problem lasting at least one month over a 2 year period[34]. These results were confirmed recently, since 43% of women 40-80 years old worldwide reported sexual dysfunction[35]. In a mailed survey study of 1480 women (65% responders) 98.8% had one or more sexual concerns, including decreased sexual desire, orgasmic problems, insufficient lubrication, coital pain and above all unmet sexual needs in addition to inadequate information regarding sexual issues[36]. A study of physicians' chart notes revealed that only 2% of females reported sexual problems[37]; in contrast, the recorded sexual complaints increased about six fold after a physician inquiry about sexual problems[38]. All of the above, taken into consideration together with epidemiological findings, demonstrate the need for physician education in this topic, in order to dissolve this discrepancy.

Female sexual dysfunction in hypertension

The most widely accepted system for female SD was introduced in 1988 by the American Foundation for Urologic Disease (AFUD). In the sexual arousal disorder classification, it is claimed that potential etiologies include hypertension, among others[39]. However, data supporting this claim are substantially weak.

It is generally accepted that the prevalence of sexual dysfunction in a disease is higher than the prevalence in the healthy population[40,41]; however, data in hypertensive women are far from conclusive. No population-based controlled studies exist, capable of clarifying the association between hypertension, antihypertensive treatment and female sexual function. Existing data include: a) the TOMHS study that, though a large double-blind controlled randomized trial, has several limitations (see previous comment)[29], and b) a rather small case-control study, addressing female sexual dysfunction in 104 women with mild hypertension (67 on treatment) in comparison with 107 healthy controls[42]. It was reported that hypertensive women experienced decreased vaginal lubrication, less frequent orgasm, and more frequent pain compared to normotensive women. The study revealed that it was hypertension per se resulting in female sexual dysfunction rather than the antihypertensive therapy; moreover, in a recent study examining postmenopausal women with heart disease, antihypertensive medication was not a predictor of sexual problems[43].

We have recently studied the sexual function of 417 women; 216 of them had hypertension (136 treated, 80 untreated) while the remaining 201 were normotensive[44]. Sexual dysfunction was found in 42.1% of hypertensive women compared to 19.4% of normotensive women, with an odds ratio of 3.2. Increasing systolic blood pressure, increasing age, and ß-blockers administration were significant predictors of sexual dysfunction, while adequate blood pressure control was related to lower prevalence of female sexual dysfunction.

The relative lack of data regarding female sexual dysfunction in hypertension does not imply that hypertensive women are

free of sexual problems; it suggests, rather, that no adequate studies have been performed and appropriate questions have not been asked. Sexual dysfunction must be routinely addressed in hypertensive patients in a very sensitive way, dedicating adequate time and using appropriate tools.

The findings of recent surveys have posed a metatheoretical question regarding the role of the pharmaceutical industry in defining female sexual problems[45]; however, the National Health and Social Life Study was based on funding from government and other foundation sources, and no pharmaceutical industry funds were used for either the original study or data reanalysis[39,46]. Notwithstanding industry's current interest in the sexual dysfunction area, it seems highly misleading to imply that this topic derives from this source; the term "sexual dysfunction" has been based on the work of Master and Johnson, Kaplan and other sex therapists in the early seventies.

PATHOPHYSIOLOGY OF SEXUAL DYSFUNCTION

Male physiology

The penis contains the corpora, two cylinders of a syncytium of vascular smooth muscle cells that are histologically undifferentiated smooth muscle cells of the peripheral vascular system. The main elements of peripheral vascular function are three: a) the nerves that regulate the function through the release of various neurotransmitters, b) the smooth muscle cells that are subject to modulation by several substances with opposing effects and c) the endothelium that is affected by several factors and subsequently releases vasoactive substances.

Penile erectile function is the result of a complex interplay between psychologic, neurologic, hormonal and vascular factors. A successful erection and a satisfactory sexual intercourse is a very complex process, implicating at least neurosensory and neuromotor pathways, hormonal and vascular changes, interpersonal and psychosocial relationships and cultural and personal beliefs.

In brief, erection begins with a central brain stimulation of arousal centers. Signals are then transported to the penis through preganglionic parasympathetic nerves, leading to nitric oxide release, which in turn results to smooth muscle relaxation in cavernosal arteries and within the cavernosal tissue. The latter is accompanied by increased arterial inflow, relaxation of sinusoids, passive blood restriction and erection. After ejaculation, a massive sympathetic discharge occurs, resulting in vasoconstriction and detumescence.

Male pathophysiology in essential hypertension

The structural and functional abnormalities induced by hypertension may be implicated in the pathophysiology of erectile dysfunction. Based on the physiology of erection, any factors impairing: a) signal transportation from the central nervous system to penis, b) the basal sympathetic tone in the flaccid state, c) the blood arterial inflow to the corpora and d) the nitric oxide (NO) production and release in the corpora, may result in erectile dysfunction.

Experimental studies indicate that hypertension results in structural changes in the penile vasculature[47-49]. Cavernous vessels are affected by high blood pressure in the same way as vessels all over the vascular tree are. Recent data shows that 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 fibers are significantly increased[50,51].

In addition, functional alterations in rat penile resistance arteries have been reported[52]. 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[53]. Although the expression of nNOS gene and NOx levels after electrical stimulation are similar in hypertensive and normotensive rats, the impairment of NO-dependent relaxation in hypertensive rats is caused (at least partially) by the increased oxidative stress (as indicated by reduced superoxide dismutase activity and increased thiobarbituric acid reacting substance)[53]. 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[54]. In addition, the responsiveness to a_1-adrenergic stimulation of corporal smooth muscle in hypertensive rats is altered, maybe due to a change in the expression of adrenoceptor subtypes.

Angiotensin II is known to induce contraction of the corporal smooth muscle in vitro and in vivo, via AT1 receptors[55,56]. The human corpus cavernosum contains 200-fold higher Angiotensin II levels than the human plasma[57]. Angiotensin II induces vascular hypertrophy in hypertension and induces endothelial dysfunction through NO reduction[58]. Thus RAS activation resulting in enhanced angiotensin II production may be responsible for the structural and functional changes in penile vasculature observed in hypertension. Recent animal data suggests that angiotensin receptor blockers exert beneficial effects on penile structural effects caused by hypertension[51]. Interestingly enough the intracavernosal injection of angiotensin II decreases intracavernosal pressure and terminates spontaneous erection in anaesthetized dogs; in contrast, the intracavernous injection of an angiotensin receptor blocker (losartan) increases dose-dependently the intracavernosal pressure[57]. The role of angiotensin II in human

Rev Bras Hipertens vol.14(3): 139-147, 2007.

erectile function has been recently established by Becker providing in vivo data[59]. Angiotensin II levels in the cavernous blood were higher than in the peripheral blood of healthy volunteers; in addition, angiotensin II levels increased during the detumescence phase of erection, underlining the role of Angiotensin II in the termination of penile erection.

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[60]. In addition, morphological studies revealed the presence of mast cells that produce chymase in the cavernosal area[60]. These findings, if confirmed in humans, can lead to the hypothesis that angiotensin receptor blockers will be more advantageous than ACE- inhibitors in protecting the penile tissue from the negative effects exerted by angiotensin II.

Bradykinin is a potent vasodilator peptide that has been recently implicated in erectile function. Functional B_2 kinin receptors have been found in the human erectile tissue and activation of these receptors result in NO release and subsequent corpus cavernosum relaxation[61]. Since ACE-inhibitors result in angiotensin II decrease and bradykinin increase, their use in the treatment of hypertension may exert beneficial effects on erectile function, having advantage over utilization of angiotensin receptor blockers.

The available data regarding the relationship between endogenous male sex hormones and blood pressure are controversial[62-64]. Some studies show lower testosterone levels in patients with hypertension, while others show no significant difference between hypertensive and normotensive subjects.

Another possible link between erectile dysfunction and hypertension is endothelin-1 activity. Several studies indicate the importance of endothelin-1 in the regulation of smooth muscle tone of corpus cavernosum[65-67]. It seems that endothelin-1 augments the contractile responses of other vasoconstrictors (like phenylephrine) present in the human corpus cavernosum[68].

Carbon monoxide (CO), a neurotransmitter with vasodilatory properties that is produced by heme oxygenase (HO-2), has been recently implicated in the pathogenesis of erectile dysfunction[53]. Since animal data is controversial, indicating species specificity, further studies are needed to clarify the role of CO in human erection[69,70].

The occurrence of a single base polymorphism (894 G/T) in the endothelial nitric oxide synthase (eNOS) has been associated with erectile dysfunction[71]. In contrast, although data is not always consistent, the angiotensin converting enzyme I/D polymorphism does not seem to affect erectile function[72,73].

Female physiology and pathophysiology

Although sexual problems are common in both sexes, female sexual arousal disorder is less well-characterized, understood and managed than its male counterpart, erectile dysfunction. Arousal disorders are usually organic and can often result from neural and peripheral vascular diseases, pelvic disorders and various medications, including antihypertensive agents (ß-blockers, clonidine, diuretics, calcium antagonists and α-blockers).

The female genital arousal response is a neurovascular process characterized by genital engorgement, swelling and lubrication. Disorders of arousal include decreased labial and clitoral sensation and engorgement as well as lack of vaginal smooth muscle relaxation. It appears that NO plays a key role in clitoral smooth muscle relaxation, while its role in the vagina remains controversial. Phosphodiesterase-5 inhibitors result in significant increase of genital blood flow and vaginal lubrication. Functional adrenergic receptors are expressed both in clitoris and vagina and mediate norepinephrine induced genital smooth muscle contraction. Thus, it seems that the main mediators of male sexual function (NO and catecholamines) exert the same effects on female genital tissue as well. However, available data is remarkably insufficient and further research is needed in the physiology of female sexual dysfunction.

Preliminary data indicate that high blood pressure induces structural abnormalities in the female genital tissue that resemble the alterations 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. Since research in female sexual dysfunction has lagged significantly, intense efforts are needed for the clarification of sexual pathophysiology in essential hypertension.

QUALITY OF LIFE

Erectile dysfunction compromises the overall quality of life and is associated with loss of self-esteem, anxiety and depression[2,74,75]. Erectile dysfunction directly affects men's confidence on the ability of a successful sexual performance; this confidence is an important psychological aspect of sexual function. Negative thinking about sexual ability results in increased anxiety, poorer sexual performance and finally any efforts to avoid sexual activity. On the contrary, increased confidence results in greater spontaneity and less concerns about ability during sexual intercourse. The uncertainty may persist even after successful medical management of erectile dysfunction, since men still

believe that they are reliant on treatment and experience a loss of manhood.

Erectile dysfunction exerts a significant impact on men's social and psychological well-being, their quality of life, and their relationship with their sexual partners[76-78]. Couples affected by sexual dysfunction frequently lose emotional and physical intimacy, and may experience lower satisfaction with their sexual life and their relationship[79]. Erectile dysfunction adversely affects patients' sexual partners, since almost 60% of women whose partners experience erectile dysfunction report reduced interest in sex compared to only half (30%) of those with healthy partners[80].

A major challenge in the assessment of the impact of erectile dysfunction on QOL is that the tools used in the recent past were not sensitive enough. General quality of life measures assess the impact of diseases on specific areas, such as physical, emotional and social domains, and pain; these topics are not relevant to men and their sexual partners[81]. Quality of life assessment in studies of erectile dysfunction is mostly done by generic measures or by questionnaires developed for other conditions. Both methods lack the sensitivity to detect erectile dysfunction changes and are insufficiently comprehensive to mirror erectile dysfunction issues and related symptoms.

Several studies demonstrate a weak correlation of QOL results and erectile function, maybe due to the fact that they are different entities. The individual reaction to erectile dysfunction varies among men, and erectile dysfunction has a different impact on their quality of life. Some men do not seem to be considerably bothered by poor erectile function, while other may exhibit particular concern and anxiety resulting in impaired QOL[82].

Erectile dysfunction related quality of life is different from functional ability, and thus should be estimated separately but combined with erectile function assessment. The Erectile Dysfunction Effect on QOL (ED-EQOL) questionnaire represents an example of a simple, short, easy to complete instrument and can be routinely used in clinical practice. Assessment of erectile dysfunction treatment should include psychological, behavioral and relationship factors that are of significant concern to men and their partners.

ERECTILE DYSFUNCTION AND CARDIOVASCULAR DISEASE

Normal erectile function involves a delicate balance between vasoconstricting and vasodilating agents; the disruption of this balance results in erectile dysfunction. Erectile dysfunction and cardiovascular disease may not simply occur by coincidence in the same patients. In conditions such as hypertension or diabetes the underlying pathophysiological process usually causes erectile dysfunction. Erectile dysfunction represents a unique opportunity for an effective management that will result in long-term improvement of cardiovascular and overall health, since erectile dysfunction can either be a risk marker of the first symptom of cardiovascular disease[83,84] or cardiovascular complications in hypertensive patients[85]. Recent animal data suggest that erectile dysfunction may be an early marker for hypertension since the onset of erectile dysfunction is detectable before the onset of hypertension[86]. Thus, physicians treating patients with erectile dysfunction need to be aware of the possibility of underlying cardiovascular disease, in terms of a holistic patient approach.

Studies deserving special attention show that the extent of cardiovascular disease is related to the risk of concomitant erectile dysfunction. It has been shown that erectile dysfunction correlates with the number of coronary vessels occluded on angiography[87]; in addition, subjects with erectile dysfunction have an increased risk of suffering from asymptomatic, severe coronary heart disease[83,88,89]. Studies investigating NO bioavailability in penile and coronary arteries support the hypothesis that vasculogenic changes in the penile vascular bed in erectile dysfunction mirror those in the coronary arteries[90,91].

CARDIAC RISK OF SEXUAL ACTIVITY IN HYPERTENSIVE PATIENTS

Sexual activity doubles the risk of a cardiac event through sympathetic nervous system activation. However, since the absolute risk for a cardiac event is extremely low in subjects without cardiovascular risk factors (one in a million) it seems rational to assume that sexual activity is rather safe in low-risk individuals.

According to the Second Princeton Consensus Conference[92] patients with controlled hypertension are considered low-risk patients and may safely proceed to sexual intercourse. On the contrary, high-risk patients have a 10-fold increased risk for a cardiac event during the sexual intercourse and the following two hours. Thus, patients with untreated, poorly controlled, accelerated, or malignant hypertension are considered high-risk patients, and sexual activity should be deferred until the patient's condition has been stabilized by treatment or a decision has been made by a cardiologist and/or internist that sexual activity may be safely resumed.

Since many hypertensive patients have an easy access to phosphodiesterase-5 inhibitors through the Internet, without previous medical counseling, hypertension specialists need to pay special attention in this issue in order to avoid undesirable incidents.

CONCLUSIONS

Male and female sexual dysfunction are frequently found in the general population, thus representing a serious health problem that remains largely under-explored. Essential hypertension seems related to sexual dysfunction, since the latter is more

prevalent in hypertensive than normotensive subjects. The pathophysiology of erectile dysfunction has been in great part clarified thanks to intense investigational efforts, while the effects of hypertension and the pathogenesis of female sexual dysfunction merit further substantial work. Antihypertensive drugs exert different actions on sexual function, with older drugs presenting negative and newer drugs neutral or even beneficial effects. Antihypertensive drugs can be safely co-administered with phosphodiestrase -5 inhibitors (some caution with ß-blockers). The significant impact of sexual dysfunction on patients' and their sexual partners' quality of life suggests that physicians have to make every possible effort in dealing with this problem in order to offer relief to their patients.

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