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Sexual Dysfunction in Male Patients with Hypertension

Influence of Antihypertensive Drugs

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Abstract

Evidence suggests that arterial hypertension, in addition to being a cardiovascular and renal risk factor, may also be associated with an impairment of male sexual function. Since other cardiovascular risk factors, especially diabetes mellitus, have also been shown to correlate with impaired sexual function it has been proposed that sexual and especially erectile dysfunction may, at least in part, represent just another manifestation of atherosclerotic vascular disease.

In addition to hypertension itself, sexual function in male hypertensive patients may also be affected by antihypertensive drug treatment. Available evidence suggests that centrally acting sympatholytic agents, β-adrenoceptor antagonists (β-blockers) and diuretics may have the potential to further impair sexual function. Calcium channel antagonists and ACE inhibitors may be neutral with respect to this endpoint. Preliminary data from several randomised and open studies have suggested that angiotensin II $(AT)_1$-receptor antagonists may even be associated with an improvement of sexual function.

However, many aspects of the interaction between hypertension, antihypertensive drug treatment and male sexual function remain unclear. Among other factors, the relative contribution of disease labelling both to the higher incidence of sexual dysfunction in hypertensive versus normotensive males and to the

negative impact of treatment remains an open question. Furthermore, dose dependence of the observed effects of antihypertensive agents on sexual function, the role of combination therapy and the anticipation of proposed adverse effects of treatment are unresolved issues. Thus, more data from studies of high quality using standardised definitions and procedures are urgently needed to at least partially resolve some of the many open questions.

Arterial hypertension has traditionally been associated with vascular, cardiac and renal endpoints such as stroke, coronary heart disease, congestive heart failure and renal failure.[1] Over the past decades, other consequences of long-standing hypertension have been proposed such as an impairment of cognition and disturbances in male sexual function.[1-9] The inter-relationship of hypertension and alterations in male sexual function is complex, since diminished sexual function is a natural part of the aging process and the incidence of hypertension increases with age.[8,9] Furthermore, several drugs including commonly used antihypertensives such as diuretics and β-adrenoceptor antagonists (β-blockers) have also been claimed to impair male sexual function.[10,11] Therefore, despite a substantial amount of epidemiological data on the strong inter-relationship of hypertension and sexual function, few data are available on the precise role of hypertension *per se* on male sexuality. In addition, sexuality depends on the integrity of various domains such as sexual desire, and erectile and orgasmic function. These domains, again, are influenced by separate, interacting regulatory mechanisms such as psychological and endocrine factors, the sympathetic nervous system, vascular endothelial function, and alterations within the macro- and microcirculation. Within such a complex regulation it may be difficult to establish alterations in separate domains (e.g. erectile function) since these are closely inter-regulated.

The biggest caveat in assessing the role of hypertension (and antihypertensive treatment) on male sexual function from the published literature, however, is the lack of consensus with respect to definitions and methods in the many studies available. Thus, while earlier studies in hypertension report 'impotence' to describe male sexual dysfunction, most of the more recent studies investigated 'sexual activity' or specifically 'erectile dysfunction' (ED), which were assessed by a variety of questionnaires using different scores and definitions.

The aim of the present review is to analyse the data available and attempt to make some careful judgments on the topic of arterial hypertension, antihypertensive drug treatment and male sexual function.

1. Male Sexual Dysfunction

Male sexual dysfunction includes problems related to libido, orgasm/ejaculation and, most often, erection. ED is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance.[12] Sexual dysfunction is strongly age-related. The first reference to the relationship between ED and age was given in the pioneering work by Kinsey and coworkers[13] in 1948.

The MMAS (Massachusetts Male Aging Study) has recently described an approximately 2- to 3-fold increase in the prevalence of moderate-to-severe ED between the ages of 40 and 70 years.[8] This study was a community-based, random sample observational survey of men aged 40–70 years. A self-administered 9-item sexual activity questionnaire was used to characterise erectile potency. Nil, minimal, moderate or complete impotence was defined using data from a calibration sample of 303 individuals. The total combined prevalence of minimal, moderate and complete impotence in the MMAS was thus determined as 52%. The prevalence of complete impotence tripled from 5% to 15% between individuals aged 40 and 70 years, respectively. In the MMAS, subject age was the variable most strongly associated with ED and impotence.[8]

In the Cologne Male Survey in Germany, a newly developed and validated questionnaire focusing on male erectile function was mailed to a representative population sample of 8000 men 30–80 years of age in the Cologne urban district.[14] The return rate of the questionnaires was 56.1% (n = 4489). Regular sexual activity was reported by 96.0% in the youngest age group (30–39 years) and by 71.3% in the oldest group (70–80 years). The average prevalence of ED was 19.2% with a steep age-related increase (2.3–53.4%). The increase was linear in the age groups from 30 to 59 years, while the age groups from 60 years upwards showed an exponential increase in the prevalence of ED. ED markedly contributed to dissatisfaction with the subject's sex life in this population.[14]

In a community-based sample of 1688 men aged 50–80 years from The Netherlands, sexual function was assessed by self-reported questionnaires.[15] In this sample, the prevalence of significant ED (erections of severely reduced rigidity or no erections at all) increased from 3% in men 50–54 years old to 26% in men 70–78 years old. Another epidemiological study of 5198 randomly selected men aged 50–76 years from rural New York, USA, was conducted using questionnaires sent by mail.[16] The response rate was 44.7% and the participation rate among respondents was 71.0%. The overall prevalence of ED was 46.3%. Age-specific prevalence was 26.0%, 34.9%, 46.9%, 57.8% and 69.4% among men aged 50–54, 55–59, 60–64, 65–69 and 70–76 years, respectively.[16] In a cross-sectional study from Italy, 2010 randomly selected men ≥18 years old were interviewed.[17] ED defined as the impossibility to achieve an erection sufficient for satisfactory sexual performance averaged 12.8%. The prevalence of ED increased with age, from 2% in men aged 18–39 years to 48% in those >70 years of age.[17]

Recently, the association between age and several aspects of sexual functioning has also been investigated in the Health Professionals Follow-up study.[9] This study investigated the association between age and several aspects of sexual functioning in 31 742 men >50 years of age. Several aspects of sexual function (including overall function, desire, orgasm and overall ability) decreased sharply by the decade after 50 years of age. The relative risk for ED was 5.7 (odds ratio [OR]) [95% CI 5.2, 6.3] among those aged 75–79 years compared with those aged 55–59 years.[9]

These studies and several others show that the incidence of ED in aging males is high. The absolute numbers and the slopes of the age-dependence of ED given in the cited studies vary and this may be due, to a large extent, to different methods (questionnaires) and criteria used in the different studies and, possibly, by intrinsic differences in the population samples investigated.

2. Hypertension and Male Sexual Function

Arterial hypertension is the most prevalent risk factor for cardiovascular and renal disease. Data from the NHANES (National Health and Nutrition Examination Survey) point to ≥50 million patients with hypertension in the US alone.[18,19] The incidence of hypertension is strongly age-related with approximately half of people aged 60–69 years old and approximately three-quarters of those aged ≥70 years affected.[1,20] Because of its high prevalence and significant impact on total mortality and cardiovascular morbidity and mortality, hypertension is regarded as a major public health challenge. Several guidelines by national and international societies and agencies have been published to increase awareness, prevention, treatment and control of high blood pressure.[1,21,22] Among the more recent guidelines published, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) stands out as the only one to comment on 'ED and hypertension'.[1] The main conclusions of their analysis are as follows.

- The age-dependent decline in erectile function is accelerated in patients with hypertension.
- Antihypertensive drug therapy may further impair erectile function, in part because blood pressure lowering itself may cause reduction of perfusion of genital organs.

- On the basis of the results of the TOMHS (Treatment of Mild Hypertension study),[23] the Veterans Administration Cooperative trial[24] and two other studies[25,26] it is suggested that while centrally acting α-agonists (e.g. clonidine) have been associated with ED, other antihypertensives have not been observed to increase its incidence.

While the first conclusion of the JNC-7 on hypertension and ED cannot be argued, the two further statements require some comment. In the TOMHS, 557 hypertensive men aged 45–69 years of age were treated with one of five active drugs (acebutolol, amlodipine, chlortalidone [chlorthalidone], doxazosin or enalapril) in addition to intensive lifestyle counselling.[23] The number of patients in the separate groups was small and the employed methods were rather crude. Thus, each participant was asked, "During the past 12 months, have you had a problem with sexual activity?" If the participant answered "Yes" additional questions were asked: (i) "During the past 12 months, have you experienced difficulty obtaining an erection?"; and (ii) "During the past 12 months, have you experienced difficulty in maintaining an erection?". At 24 months, men in the chlortalidone group experienced the highest incidence of problems obtaining an erection (15.7%), which was significantly higher (3.2-fold) than placebo (4.9%) ($p < 0.01$). Among the active treatments, only doxazosin had a lower rate (2.8%) than placebo (4.9%) at 24 months, but this difference was not significant. The acebutolol (7.9%), amlodipine (6.7%) and enalapril groups (6.5%) had incidence rates only slightly higher than the placebo group. The test for comparison of the five active groups showed a significant difference between the doxazosin and chlortalidone groups ($p < 0.01$). Most of the participants in the chlortalidone group who developed erection problems experienced the problem in the first year, a majority (but not all) of them continued on diuretic medication. Differences among groups in the incidence of erection problems through to 48 months were smaller than at 24 months. The difference in the incidence of problems obtaining an erection at that time point was not significant between the chlortalidone and placebo group (16.9% vs 11.9%). This narrowing of the difference between the chlortalidone and placebo groups was due to 11 participants in the placebo group reporting a new erection problem at 36 or 48 months of follow-up, compared with only one in the chlortalidone group. Of the 11 patients randomised into the placebo group who experienced a new erection problem at 36 or 48 months, five had been taking antihypertensive medication in the year before reporting the sexual problem (four on medication by their private physician). These factors may be taken as arguments to rely more on the results obtained at 24 months. The authors of that study therefore conclude that "the incidence of erection problems was relatively low but was higher with diuretic treatment".[23]

The second study quoted by JNC-7 with respect to hypertension treatment and ED is the Veterans Administration Cooperative trial.[24] In this randomised, double-blind study, 1292 men aged 59 ± 10 years with diastolic blood pressures of 95–109mm Hg, after a placebo washout period, received placebo or one of six drugs: hydrochlorothiazide (12.5–50 mg/day), atenolol (25–100 mg/day), captopril (25–100 mg/day), clonidine (0.2–0.6 mg/day), a sustained-release preparation of diltiazem (120–360 mg/day) or prazosin (4–20 mg/day). The drug doses were titrated to a goal of <90mm Hg for diastolic pressure, and the patients continued to receive therapy for at least 1 year. Diltiazem therapy had the highest rate of success with a response rate of 59% of the treated patients, atenolol was successful by this definition in 51% of the patients, clonidine in 50%, hydrochlorothiazide in 46%, captopril in 42% and prazosin in 42%; all of these agents were superior to placebo (success rate, 25%). In that study, a 31-item checklist was used to inquire about patients' symptoms. The patients were encouraged to describe their symptoms at each visit. All withdrawals from the study protocol were evaluated blindly by the study chairman and classified as administrative or medical. Medical withdrawals were further analysed blindly to determine whether they were due to an adverse drug reaction. Several

adverse reactions occurred with the different treatment options. With respect to erectile function, on the basis of the answers provided on the described checklist the study concludes that "no drug was associated with a significant increase in the frequency of impotence".[24]

The third study quoted by JNC-7 is an open trial investigating the effect of the angiotensin II $(AT)_1$-receptor antagonist valsartan alone or in combination with hydrochlorothiazide on sexual activity in hypertensive patients.[25] A total of 2202 patients (mean age 54 ± 8 years) with hypertension, untreated (913) or pretreated, were included. Sexual activity (intercourse episodes per week) was determined in three groups (n = 27, conventional therapy [48% β-adrenoceptor antagonists, 24% ACE inhibitors, 11% calcium channel antagonists, 17% diuretics]; n = 1899, valsartan group; n = 276, valsartan in combination with hydrochlorothiazide) at baseline and after 8 and 16 weeks of treatment, respectively. Systolic and diastolic blood pressure decreased significantly in the three groups of patients. Sexual activity decreased slightly in the conventional therapy group from an average of 1.3 to 0.9 times per week (not significant), whereas it increased in the valsartan group from 1.0 to 1.6 times per week during follow-up ($p < 0.0001$). Similarly, sexual activity increased in the combination group from 0.9 to 1.3 times per week during follow-up ($p < 0.0001$). The authors concluded from their results that the AT_1 receptor antagonist valsartan "increases the rate of sexual intercourses per week, whereas conventional therapy affects sexual activity adversely".[25]

The fourth study acknowledged in JNC-7 is a randomised, double-blind, crossover study including 160 hypertensive men aged 40–49 years, all married and without any previous sexual dysfunction.[26] After a 4-week placebo period, the patients were divided into two groups: (i) 120 patients were randomised to receive the β-adrenoceptor antagonist carvedilol 50mg once daily or the AT_1-receptor antagonist valsartan 80mg once daily for 16 weeks. After another 4-week placebo period, patients were crossed over to the alternative regimen for a further 16 weeks; (ii) 40 patients were treated with placebo according to a single-blind design for 16 weeks. Blood pressure was significantly lowered by both treatments. During the first month of therapy, sexual activity (assessed as the number of sexual intercourse episodes per month) declined with both drugs as compared with baseline, although the decrease was statistically significant in the carvedilol (from 8.2 to 4.4 episodes per month; $p < 0.01$) but not in valsartan-treated patients (from 8.3 to 6.6 episodes per month). With ongoing treatment, sexual activity further worsened with carvedilol (3.7 episodes per month; $p < 0.01$ vs baseline), while it fully recovered and also tentatively improved with valsartan (10.2 episodes per month; not significant vs baseline). The difference between the two drugs was highly significant ($p < 0.01$). The results were confirmed by the crossover. When the first and second treatment periods of each drug were combined and compared with the placebo group, the following picture emerged: after 4 weeks of treatment, sexual activity tended to decrease in all patients, but particularly in those receiving carvedilol. With ongoing treatment, placebo did not affect the intercourse rate, whereas carvedilol progressively worsened it by approximately 50% at 16 weeks and valsartan increased the intercourse rate at this timepoint by about 19%. The authors concluded from their study that the β-adrenoceptor antagonist carvedilol "induces a chronic worsening of sexual activity, whereas valsartan not only does not significantly worsen sexual activity but may even improve it".[26]

The conclusion of JNC-7 describing a nonspecific negative effect of blood pressure lowering on erectile or sexual function, at least from the cited references, is somewhat difficult to follow. In particular, the statement that centrally acting α-agonists have been associated with ED, and that other antihypertensives have not been observed to increase its incidence, cannot be accepted on the basis of the studies cited.

3. Association between Hypertension and Erectile Dysfunction (ED)

3.1 ED in Patients with Hypertension

Some of the cited epidemiological studies have also investigated other determinants than age on the incidence and severity of ED.

In the MMAS, after adjustment for age, a higher probability of impotence was directly correlated with heart disease, diabetes mellitus, indexes of anger and depression, and hypertension.[8] In a prospective continuation of that study, 513 men aged 40–70 years without ED, diabetes or heart disease at baseline were followed from 1987/9 to 1995/7.[27] ED was again assessed from responses to a privately self-administered questionnaire. A composite coronary risk score, being overweight and active (and passive) cigarette smoking were associated with a significant higher risk for ED, while the prospective association of hypertension was weaker.[27]

In the Cologne Male Survey the age-adjusted risk for ED was markedly enhanced in patients with diabetes (OR 3.95; 95% CI 2.98, 5.23) and hypertension (OR 1.58; 95% CI 1.29, 1.93).[14] In the Italian study, a history of cardiac disease, diabetes, neuropathy, stroke, peripheral vascular disease, smoking and hypertension all increased the risk for ED.[17] In comparison with non-diabetic and non-hypertensive men, the OR was 1.4 (95% CI 0.7, 3.2) for hypertensive men without diabetes, 4.6 (95% CI 1.6, 13.7) in diabetic men without hypertension and 8.1 (95% CI 1.2, 55.0) in men with diabetes and hypertension.[17]

The Health Professionals Follow-up study provides a thorough insight into the association between ED, some modifiable health behaviours and comorbid conditions.[9] This study also showed that many risk factors associated with atherosclerotic vascular disease were also associated with ED. As comorbid conditions increasing the incidence of ED, in an age-adjusted analysis, diabetes (OR 1.5; 95% CI 1.5, 1.6) and hypertension (OR 1.3; 95% CI 1.3, 1.3) could be identified.

Age-adjusted ORs for ED and comorbid conditions are also available from an Austrian study performed in 832 men aged 30–69 years from Vienna.[28] This study evaluated the patients based on questions from the International Index of Erectile Function (IIEF).[29] The IIEF is a 15-item questionnaire addressing five domains of male sexual function, that is erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. It is readily self-administered in research or clinical settings, is validated in many languages and is characterised by high sensitivity/specificity. It is increasingly used in studies on male sexuality and may, therefore, help to better compare studies in different populations and societies. As in the other studies cited, a strong dependence of ED on age could be established in that cohort. Age-adjusted risk for ED was increased in cardiac disease (OR 1.39; 95% CI 0.82, 2.37), diabetes (OR 2.65; 95% CI 0.65, 9.44) and hypertension (OR 1.77; 95% CI 1.02, 3.05).[30] Several studies in different countries with various cultural backgrounds have confirmed the finding that hypertension is one disease, among others, with an enhanced risk for ED.[30-34]

3.2 Hypertension in Patients with ED

In addition to analysing the prevalence of ED and identifying comorbid conditions with a possible impact on the incidence and severity of ED, studies have been performed including men with impotence or ED only.

Thus, in a study including 154 men aged >55 years with ED, the prevalence of obesity, hyperlipidaemia, diabetes, tobacco use and hypertension was determined. In this study, 44% of the patients with ED had arterial hypertension.[35] In another study including 472 impotent patients, 117 (24.8%) had a history of hypertension.[36] In a third study, the distribution of four main arterial risk factors (diabetes, smoking, hyperlipidaemia and hypertension) was investigated in 440 impotent men (mean age 46.8 years).[37] In this study, the frequencies of hypertension in the group of impotent men and in the general population were not significantly different. In summary, these three studies in patients with ED or impotence add little to the concept of an inter-

relationship between ED and hypertension. This could, at least in part, be due to a bias in the selection of patients included in these cross-sectional analyses.

3.3 Clinical Studies

In a large Spanish multicentre study including a total of 2130 men aged 25–75 years (mean 55.5 years) with treated essential hypertension, the prevalence of ED was determined using an abbreviated version of the IIEF.[38] The Sexual Health Inventory for Men (SHIM) uses questions 2, 4, 5, 7 and 15 of the IIEF. It is simpler to use than the IIEF. An overall score of >21 points defines a patient with ED.[39] Time since the diagnosis of hypertension was established in the patients included averaged 8.8 years. In this population of hypertensive men, of whom 722 (33.9%) were diabetic, 660 (31%) were obese, 234 (11%) had coronary heart disease and 311 (14.6%) had moderate-severe chronic renal failure, 975 patients (45.8%) fulfilled the SHIM criterion for ED. Thus, the relative contribution of hypertension or other comorbid conditions to the manifestation of ED cannot be extrapolated.

A review of sexual dysfunction in hypertensive men from 1988 states that "the high prevalence of sexual dysfunction in hypertensive men is well established".[40] On the basis of two published studies at the time,[41,42] evidence could be presented that untreated hypertension *per se* poses a risk for ED. Both studies used identical questionnaires that were self-administered by subjects at home and inquired approximately 20 somatic symptoms commonly associated with hypertension or its drug therapy. Responses obtained from 99 newly diagnosed untreated hypertensive men, 78 normotensive controls and 477 patients undergoing long-term treatment of hypertension were compared in one study.[41] In this study, disturbances of sexual function were lowest in the normotensive group, higher in untreated hypertensives and even higher in the treated patients. In the Australian National Blood Pressure Study, patients with diastolic blood pressure values 95–109mm Hg were treated at random with either active drug or placebo.[42] In both studies, the prevalence of ED in untreated hypertensive men was about twice that in normotensive controls.

Another study from 1988 is also taken as evidence for an association of untreated hypertension and ED.[43] In that study, 626 pretreated and untreated hypertensive men were evaluated. Interestingly, 58% of patients taking antihypertensive therapy and 44% of men not receiving antihypertensive drugs reported distress over one or more sexual symptoms. However, on the basis of our present knowledge on the marked age-dependence of ED, the lack of precise matching for age (and other confounders, e.g. smoking, obesity, diabetes, etc.) in theses studies should be considered. Furthermore, in one of the cited studies, in patients who were originally diagnosed as hypertensive but who subsequently had diastolic blood pressures <95mm Hg, the prevalence of ED was similar to that among hypertensive men, suggesting a role of 'disease labeling'.[40]

With all of the methodological problems in these cited studies in mind, yet another study has made a strong statement for untreated hypertension being a correlate for sexual dysfunction.[44] In this study, 110 patients with newly diagnosed, uncomplicated and never treated hypertension and 110 healthy volunteers without hypertension or a family history of hypertension were included. All men were between 40 and 49 years of age and married. Exclusion criteria were diabetes, a body mass index (BMI) >28 kg/m^2 and an intake of alcohol >30 g/day. Patients in the two groups were closely matched with respect to age, BMI and waist **:** hip ratio. All participants were given a questionnaire with instructions for self-completion. Interestingly, sexual activity assessed as number of sexual intercourse episodes per month was significantly lower in hypertensive men than in normotensive men (5.9 vs 7.9; −25%; $p < 0.01$).[44] However, it should be kept in mind that this study did not specifically address erectile function and, thus, the observed differences in sexual activity could well be due to changes in some other domain of sexuality, for example libido. Furthermore, the results obtained may also be affected by disease labeling.

3.4 Summary

In conclusion, several studies show that hypertension may negatively affect sexual function and especially ED. However, in the epidemiological studies, the confounding effect of treatment may be responsible, at least in part, for the higher prevalence of ED observed in hypertensive men. In studies addressing untreated or placebo-treated hypertension, results may be affected by lack of matching for important confounders such as age, heart disease, diabetes and smoking. Furthermore, the precise impact of disease labeling on sexual function remains unknown. With all of these limitations of the available studies in mind, it may be concluded that ED and atherosclerotic vascular disease are comparable conditions with respect to their risk factors. Evidence suggests that hypertension *per se* negatively affects male sexual/erectile function, but further studies taking into account the described methodological problems are needed to define the magnitude and clinical relevance of this interaction.

4. Sexual Dysfunction as a Result of Antihypertensive Therapy

In the 1988 review article by Bansal[40] on sexual dysfunction in hypertensive men it was stated that while a high prevalence of sexual dysfunction is well established in hypertensive men it is commonly believed to be the result of a specific hypotensive agent and it is therefore usually managed by a change of medication. It was also acknowledged that "this clinical practice is without an established scientific basis" since in the studies available at the time "the assignment of causality of ED to the specific effects of a hypotensive agent is based on data relying on reports of patients to therapists, suffers from patient and therapist bias, and seldom has pretreatment data or adequate controls (or both)".[40] Thus, in the Veterans Administration cooperative trial, no significant difference in the reporting of impotence was seen after initiation of either placebo or active therapy.[45] In contrast, another study performed in a similar population of >1000 hypertensive men reported the frequency of impotence to be 3.4 times higher in active drug-treated versus placebo-treated patients.[46]

4.1 Sympatholytic Agents

Since the many options available for the drug treatment of hypertension markedly differ by their mechanisms of action, differences in adverse events are common. With respect to male sexual or erectile function, sympatholytic agents (adrenoceptor antagonists) were the first group of drugs suspected to exhibit negative effects upon these functions. Thus, guanethidine and reserpine were shown to exhibit a high rate of sexual dysfunction,[47] while methyldopa was shown to negatively affect sexual function in some, but not all studies available.[40,43,47-49] In a small single-blind crossover study including sexually dysfunctional male patients, in which each study drug was administered for 1 month, sexual adverse effects were more frequent with methyldopa and propranolol than with diuretics.[50] However, these studies were unblinded or single-blinded and, thus, open for patient and/or therapist bias. Most importantly, no effective effort was undertaken to take into account the important influence of confounders such as age. Controversy exists about such adverse effects with respect to clonidine, another sympatholytic agent. A low rate of sexual adverse effects was proposed on the basis of one study in which sexual adverse effects were observed in 10% of treated patients.[51] However, this report was disputed by others reporting a higher rate of sexual adverse effects during treatment with this agent.[52] In summary, while sympatholytic agents are very likely to negatively affect male sexual function, the scientific basis for this claim is small given the number and the quality of studies available.

4.2 Diuretics and β-Adrenoceptor Antagonists

Striking results with respect to the effects of drug treatment on the incidence of sexual dysfunction in male hypertensive patients were obtained in the Medical Research Council trial.[53] In this single-blind study, patients with untreated diastolic blood

pressures between 90 and 109mm Hg and systolic blood pressures <200mm Hg were randomly allocated to one of four treatment groups: the diuretic bendroflumethiazide (bendrofluazide; up to 5mg twice daily), the β-adrenoceptor antagonist propranolol (up to 320mg daily) or a placebo for either of these drugs. On the basis of 23 582 patient-years completed, 10 684 on active drugs and 12 898 on placebo, adverse effects of treatment were analysed. The participants were asked to complete a questionnaire listing possible adverse effects. According to the questionnaires, the prevalence of impotence (affirmative answers) after 2 years of treatment was 10.1% in the placebo group, 13.2% in the propranolol group and 22.6% in the bendroflumethiazide group. The difference between active drug and placebo was significant for the diuretic but not for the β-adrenoceptor antagonist. The incidence of withdrawal from randomised treatment because of impotence (rates per 1000 patient-years) was 0.89 in the placebo group, 5.48 in the propranolol group and 19.58 in the bendroflumethiazide group. The difference between both active drugs and placebo was significant at $p < 0.001$.[53] It is intriguing that the differences between active treatment and placebo are much more pronounced with respect to the incidence figures of the withdrawal rates compared with the prevalence data of affirmative answers in the questionnaires. This could point to the fact that not only the prevalence but also the severity of sexual dysfunction increased with active drug treatment. On the other hand, this was a single-blind study and clinical staff may have been less ready to stop placebo treatment as a consequence of an adverse event than they would have been if the patient had been on active treatment. Altogether, this study points to diuretics and β-adrenoceptor antagonists, at least when used in high doses, as causal factors for sexual dysfunction in treated hypertensive males.

Several studies support the concept that among the commonly used antihypertensive agents, diuretics and β-adrenoceptor antagonists may be implicated in the sexual disturbances so often observed in treated hypertensive men. With the methodological problems already mentioned (see section 2), the TOMHS showed that chlortalidone at a dose of 15 mg/day may also be suspected to negatively affect sexual function in men.[23] In the TAIM (Trial of Antihypertensive Interventions and Management), a total of 878 overweight patients with diastolic blood pressures of 90–100mm Hg received either placebo, chlortalidone 25mg once daily or atenolol 50mg once daily.[54] Erection-related problems worsened in 28% of the patients receiving chlortalidone, 11% with atenolol and 3% with placebo.[54] Smaller studies with substantial methodological limitations have also pointed to the diuretics hydrochlorothiazide and chlortalidone as causing loss of libido and impotence.[47,55,56]

A recent randomised, double-blind, crossover study has compared the β-adrenoceptor antagonist carvedilol 50mg once daily and the AT_1-receptor antagonist valsartan 80mg once daily in 120 never-treated hypertensive male patients aged 40–49 years.[28] Both treatments had similar effects on arterial blood pressure. Sexual function, assessed by anonymous, self-completed questionnaires, was markedly impaired at 4 and 16 weeks of carvedilol treatment. During the first 4 weeks, treatment with valsartan was slightly, but nonsignificantly, associated with a decline in sexual activity. In contrast to the effects of the β-adrenoceptor antagonist, sexual activity increased to values significantly above baseline at 16 weeks of treatment.[26]

Carvedilol is a nonselective β-adrenoceptor antagonist and also an α_1-adrenoceptor antagonist. Therefore, it is interesting to note that another β-adrenoceptor antagonist, the β_1-selective antagonist atenolol has also been compared with the ACE inhibitor lisinopril[57] and with the AT_1-receptor antagonist valsartan[58] with respect to the possible effects of these treatments on sexual function. In the first of these studies, 90 untreated hypertensive men, aged 40–49 years, without previous sexual dysfunction were randomly treated with atenolol 100mg or lisinopril 20mg for 16 weeks according to a double-blind, randomised, crossover design. During the first month of therapy, sexual activity, assessed as the number of intercourse episodes per month, significantly declined with both atenolol (from 7.8 to 4.5;

$p < 0.01$) and lisinopril (from 7.1 to 5.0; $p < 0.05$). With ongoing treatment, sexual activity tended toward recovery in the lisinopril (7.7 intercourse episodes per month; not significant vs placebo) but not in the atenolol group (4.2 intercourse episodes per month; $p < 0.01$ vs placebo). The percentage of patients who complained of sexual dysfunction symptoms was significantly higher in the atenolol- than in the lisinopril-treated group.[57] In the second study employing atenolol, 110 untreated hypertensive men, aged 40–49 years, married and without previous sexual dysfunction were randomly treated with atenolol 50 mg/day or valsartan 80 mg/day for 16 weeks according to a double-blind, randomised, parallel-arm study design.[58] After 8 weeks, the dose of either drug was doubled in patients with diastolic blood pressures >90mm Hg. Clinical evaluation was performed after 8 and 16 weeks of treatment. Despite similar blood pressure lowering effects, atenolol significantly reduced sexual activity from 6.0 to 4.2 intercourse episodes per month ($p < 0.01$). In contrast, treatment with valsartan tended to increase sexual activity from 5.8 to 7.4 episodes per month ($p = 0.058$). The difference in sexual activity between the atenolol and valsartan groups was significant at $p < 0.05$.[58] Several smaller studies have also reported negative effects of β-adrenoceptor antagonists on various parameters of sexual function.[43,59-62]

In conclusion, available data suggest that thiazide-type diuretics such as hydrochlorothiazide, bendroflumethiazide or chlortalidone may negatively affect male sexual function. However, additional data from prospective, double-blind trials in which the many confounding factors are corrected for are definitely needed. Also, the dose-dependence of the proposed effect has to be clarified.

Regarding β-adrenoceptor antagonists, available data suggest that both β_1-selective and -nonselective agents have a negative impact on sexual function in hypertensive men. However, it should be kept in mind that the more recent cited studies investigated sexual and not erectile function, and that treatment periods of up to 16 weeks may not be representative for 'long-term' effects. Also, it is interesting to note the results of a more recent study, in which the influence of patient knowledge of β-adrenoceptor antagonist adverse effects was investigated.[63] In this study, three groups of 32 hypertensive men each were given atenolol 50mg once daily over 3 months. Patients in group A were blinded regarding the type of drug given, group B patients were informed about the drug given but not on its adverse effects, and group C patients were informed about the adverse effects of atenolol. After 3 months the incidence of ED was 3.1% in group A, 15.6% in group B and 31.2% in group C. While the difference in the incidence of ED between groups A and B may support an association between β-adrenoceptor antagonist use and impaired sexual function, this study demonstrates that knowledge of (potential) adverse effects of treatment may yet be another factor participating in this complex interrelationship.

4.3 Calcium Channel Antagonists and ACE Inhibitors

The calcium channel antagonist nifedipine at a dose of 40–80 mg/day (slow release) was compared with the thiazide diuretic trichlormethiazide 2–4 mg/day, the β-adrenoceptor antagonist atenolol 50–100 mg/day and the ACE inhibitor captopril 37.5–75 mg/day for 1 year after a 2- to 4-week placebo period in 156 male hypertensive patients.[64] Sexual function was checked via a self-reporting questionnaire. During the placebo period, 5% of the hypertensive patients complained of some sexual disturbance. In the short-term (1–4 weeks) after the initiation of therapy, all antihypertensive therapies except captopril caused sexual dysfunction, while in the long-term (1 year) only patients taking atenolol experienced sexual dysfunction.[60] In another study not confined to hypertensive patients, 1 month after initiation of therapy nifedipine and diltiazem improved different markers of sexual function, verapamil had a neutral effect and hydrochlorothiazide had some negative effect.[64]

Finally, in a double-blind comparative study conducted in general practice in 451 patients of both sexes, after a 4-week placebo run-in, patients were allocated to either treatment with the calcium chan-

nel antagonist amlodipine or the ACE inhibitor enalapril for 50 weeks.[65] In this study, sexual functioning was not different between the two groups.

In conclusion, only few data from small studies are available with respect to calcium channel antagonists and ACE inhibitors and sexual function. The available information suggests that these groups of antihypertensive substances may have no major negative impact on this particular function.

4.4 AT_1-Receptor Antagonists

The finding from the cited studies that AT_1-receptor blockade may be associated with a tendency towards increasing sexual activity[25,26,58] has received support from another study in which patients on various antihypertensive medications, including ACE inhibitors and calcium channel antagonists, were switched to the AT_1-receptor antagonist losartan 50–100mg once daily.[66] In that study, a marked increase in the self-reported degree of sexual satisfaction could be observed in 82 patients with hypertension and pre-existing sexual dysfunction after 12 weeks of losartan treatment.[66] Thus, several studies suggest that AT_1-receptor blockade may have advantages over other antihypertensive treatment strategies with respect to male sexual function.

Since the controlled cited studies were performed in selected study populations with hypertension over short periods of time, extrapolation of these findings to the general hypertensive population is limited. Therefore, we have conducted an open and prospective study evaluating male sexual function in hypertensive patients before and after 6 months of therapy with valsartan using the IIEF.[10] Patients who were either newly treated or who were switched from other treatment regimens received valsartan 80–160 mg/day. At baseline, 75% of the total group of 3502 patients investigated and 65% of the subgroup of patients without previous antihypertensive treatment ($n = 952$) could be diagnosed as having ED according to the IIEF. Valsartan therapy markedly reduced ED in these groups to 53% and 45% ($p < 0.0001$), respectively. Improved ED was associated with highly significant improvements in orgasmic function, intercourse and overall satisfaction, in both the total group and the previously untreated subgroup. In addition, sexual desire averaged 5.64 ± 1.99 (SD) IIEF units in the total and 5.99 ± 2.03 in the group without antihypertensive treatment at baseline. Valsartan markedly increased these means to 6.82 ± 1.72 and 7.06 ± 1.68 ($p < 0.0001$), respectively. The results of our study give support to the concept that AT_1-receptor blockade may improve sexual function in hypertensive males.[10] However, it should be noted that the study is limited by its open design and also by the fact that no control group was included. Therefore, our results may, at least in part, represent a placebo or time effect. In this context, it should be emphasised that the aim of the study was to confirm the results from smaller but tightly controlled trials.

4.5 Summary

In conclusion, evidence suggests that antihypertensive therapy may be a factor contributing to impaired sexual/erectile function in treated hypertensive males. As with other adverse events, the various classes of antihypertensive agents differ with respect to their effects on sexual function. It is suggested that centrally acting sympatholytic agents have the potential to disturb male sexual function, but this claim has never been proven in larger studies of acceptable quality. Among the five classes of antihypertensive drugs generally considered for antihypertensive therapy, diuretics and β-adrenoceptor antagonists stand out as the two groups most often associated with negative outcomes on various endpoints regarding sexual function. The little information available on calcium channel antagonists suggests that this class of antihypertensive agents may be neutral with respect to sexual function. On the basis of slightly more and better evidence, the same claim may be made about ACE inhibitors.

Interestingly, the AT_1-receptor antagonists may even improve sexual activity and, according to our open study, positively influence erectile function and other domains of sexual function such as libido.[10] This is also supported by a recent study in which treatment with valsartan, but not with lisi-

nopril, increased sildenafil use in hypertensive patients with severe ED.[67] Also, in a recent study, 120 postmenopausal women aged 51–55 years, after 4 weeks of placebo run-in, received valsartan 80–160 mg/day or atenolol 50–100 mg/day.[68] At baseline and after 16 weeks of treatment, patients were given a questionnaire that comprised a self-evaluation of various aspects of sexual desire, orgasmic response and coital activity. In the presence of comparable effects on blood pressure in the two groups, differences could be observed in the effect of treatment on sexual function. Thus, in the valsartan-treated women, the scores for several of the items related to libido significantly improved, including sexual desire (+38%, $p < 0.01$) and sexual fantasies (+51%, $p < 0.001$). In contrast, scores for these parameters worsened in the atenolol group by −18% ($p < 0.01$) and −23% ($p < 0.001$), respectively.[68]

5. Conclusions

Arterial hypertension is a well known risk factor for cardiovascular and renal disease, and contributes significantly to the high cardiovascular morbidity and mortality observed in most industrialised countries. In addition, long-standing hypertension has more recently been associated with other morbidity endpoints. In this context, an impairment of male sexual function has been demonstrated in several studies which may reflect largely, however not exclusively, a decline in erectile function accompanying arterial hypertension. Male sexual dysfunction associated with hypertension may further be aggravated by antihypertensive treatment, especially when central sympatholytic agents, diuretics and β-adrenoceptor antagonists are employed. This is of importance since satisfying sexuality is an essential contributor to a patient's well-being.

It could be speculated that sexual dysfunction associated with antihypertensive treatment may contribute to the low compliance and persistence with antihypertensive treatment.[69,70] In this context, it is interesting to note that the newer classes of antihypertensives (calcium channel antagonists, ACE inhibitors, AT_1-receptor antagonists) may be associated with better compliance and persistence than therapy with diuretics and β-adrenoceptor antagonists.[71-74] However, hard evidence for such an inter-relationship between drug-induced impairment of sexual function and alterations in drug adherence is lacking.

It should also be kept in mind that two-thirds or more of hypertensive patients require combination therapy of at least two drugs to reach their blood pressure goals. Therefore, combination therapy or therapeutic strategies will have to be compared in the future with respect to their effect on sexual/erectile function.

It is an interesting phenomenon and uncommon in the medical literature that, with respect to the topic of hypertension, antihypertensive treatment and alterations in sexual function, review articles and comments far exceed reports of original studies. This fact alone documents the urgent need for more hard data on the subject. Interestingly, studies of male sexual function have been incorporated in ongoing studies such as the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) programme.[75] It is hoped that these and other studies will, with the given power of prospective, randomised, double-blind studies in large patient populations, help to further clarify some of the aforementioned open questions.

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