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Review Article

A Review on Erectile Dysfunction Among Hypertensive Patients on Pharmacotherapy

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Abstract: Hypertension and its related disorders have a high mortality as well as morbidity and require strict adherence to medications in order to mitigate these consequences. Sexual dysfunction is prevalent among patients with hypertension and can either be attributed to the disease progression or as a result of antihypertensive medications. Most patients report the symptoms after initiation therapy and sometimes leads to a spurious association with antihypertensive drugs. However, most drugs in the antihypertensive classes have been associated with sexual dysfunction in both men and women. The most implicated drugs are diuretics, beta-blockers, and centrally acting agents while angiotensin modulating drugs have proved to improve upon erectile dysfunction. The older generation of antihypertensive medications tends to have a negative impact on sexual performance. Females experience sexual dysfunction associated with hypertension and its treatment, but this is grossly under-reported compared to their male counterparts. The incidence in females is higher compared to men and it is sometimes erroneously considered as part of the post-menopausal period rather than hypertension. The impact of medications on sexual dysfunction has somewhat produced contrasting results with some studies showing an association with medications and others proving otherwise. Clinicians need to be aware of the impact of sexual dysfunction among hypertensive patients in order to make an informed decision regarding dosage and choice of medications while keeping target blood pressure in mind.

Keywords: Erectile Dysfunction, Hypertension, Antihypertensive Medications, Sexual Dysfunction

1. Introduction

Erectile dysfunction (ED) among hypertensive patients is a common disorder [1]. Sexual dysfunction is defined by World Health Organization (WHO) as the various ways in which an individual is unable to participate in a sexual relationship as he or she would wish. Females encounter the problem of sexual dysfunction but studies have probed more into the pattern of male sexual dysfunction [2]. Erectile dysfunction, as defined in 1992 by the National Institutes of Health Consensus Panel as the persistence with respect to achievement and/or maintenance of penile erection in the presence of appropriate stimuli for sexual intercourse [3]. Females tend to under-report the symptoms of sexual dysfunction which includes; lack of desire, arousal, orgasm and increased pain during intercourse [4]. In men, erectile dysfunction is a hurdle in the management of hypertension which presents as every physician's nightmare in deciphering if its aetiology is due to the medication taken [5]. Establishing a baseline sexual function in every patient is therefore imperative [6].

In the second Princeton consensus, knowledge of sexual function in hypertensive men is imperative in initiating antihypertensive therapy while planning for treatment of erectile dysfunction if it presents itself in the course of treatment [7]. Several studies have tried to mitigate this confusion by advocating for a thorough sexual history prior to

the commencement of antihypertensive therapy [5]. Erectile dysfunction has been erroneously limited to the shortfall in sexual function and activity but this stretches beyond this purview. ED is currently considered as a predictor of cardiovascular diseases and a premonitory sign to a general systemic vascular impairment [8]. Erstwhile, sexual dysfunction was considered more of psychogenic origin rather than organic but now it has been found to be due to vascular, neurogenic, drug-induced, metabolic, and hormonal etiologies [9].

Drug-induced erectile dysfunction can be ascribed to the increased prevalence of diseases such as obesity, hypertension, dyslipidemia and diabetes mellitus [10]. Advancing age in men has been associated with erectile dysfunction even in the absence of the aforementioned risk factors [11].

The objective of this review is to assess the impact of hypertension and antihypertensive drugs on erectile function.

2. Prevalence of Erectile Dysfunction in General Population

The existence of multiple data on the epidemiology of erectile dysfunction has warranted the need for a critical consideration in hypertensive patients. The impact of erectile dysfunction on the control of hypertension has generated a huge concern among the scientific community [12]. Age has been a strong predictor of sexual dysfunction in both genders [13]. In the famous Massachusetts Male Aging Study, a prevalence of 52% was observed with increasing age which was directly associated erectile dysfunction. At age 40, 40% of males had sexual dysfunction which increased to 70% at age 70. Worsening of erectile dysfunction was consistent with the presence of co-morbid conditions like diabetes mellitus and dyslipidemia [14].

In Brazil, a study on the prevalence of erectile dysfunction observed a prevalence of 45.9% among men which worsened with increasing age [15]. In the Cologne study, the prevalence of erectile dysfunction was 19% with a sharp increase from 2.3% to 53.4% associated with aging [16]. Age undoubtedly proves to be a strong risk factor for erectile dysfunction. The pathogenesis of erectile dysfunction with aging has been associated with uncoupling of endothelial nitric oxide synthase (eNOS) from tetrahydrobiopterin (BH_4) [17]. Angiotensin-II has been found to reduce BH_4 leading to oxidative stress and erectile dysfunction [17]. The uncoupling of eNOS from BH_4 diverts the enzymatic action of eNOS from nitric oxide to superoxide production [18]. A vicious cycle occurs as superoxide mediates further uncoupling of nitric oxide (NO) from eNOS.

Arginase is an enzyme which acts on L-arginine and converts it into urea and ornithine. L-arginine is a substrate for eNOS and highly essential in the anabolism of nitric oxide [19]. Nitric oxide synthase competes with arginase for the substrate L-arginine leading an eventual reduction in nitric oxide and hence erectile dysfunction [20]. The substrate, ornithine has been associated with neurovascular diseases such as atherosclerosis and erectile dysfunction [21]. A trial where long-term administration of arginase inhibitor (2-S-amino-6-boronohexanoic acid) improved erectile dysfunction in aged rats [22].

A Clinical study in patients unresponsive to sildenafil, found high levels of plasma arginase. Erectile function was enhanced in patients who received arginase inhibitors compared to placebo [23]. These findings support the effects of disturbed enzymatic pathways on erectile dysfunction. Further studies are required to determine the possibility of drugs modulating arginase in managing erectile dysfunction in humans.

3. Prevalence of Sexual Dysfunction Among Hypertensives

Hypertension is a disorder with high mortality and morbidity associated with its progression especially if poorly managed [24]. The issue of erectile dysfunction cannot be segregated from hypertension which has raised several concerns most especially in deciphering where the etiology lies. Regardless of this conundrum, multiple studies have confirmed the direct link between the pathogenesis of erectile dysfunction and hypertension. The prevalence of systolic hypertension linearizes with increasing age [25].

Diastolic blood pressure, however, decreases with increasing age [26] as compared to systolic blood pressure. Sexual dysfunction is now considered a sign of systemic vasculopathy [27].

A retrospective study done on patients without atherosclerotic disease prior to the manifestation of erectile dysfunction were sampled. It was realized that a significant number of patients developed atherosclerotic plaques after the manifestation of erectile dysfunction [28]. Several published studies are advocating for erectile dysfunction to be considered a premonitory sign to adverse cardiovascular events such as ischemic heart disease, heart failure and sudden cardiac death [29]. Erectile dysfunction has been found to be the highest independent risk factor for cardiovascular diseases [30].

Experimental follow-up studies found out that cavernous arteries were susceptible to hypertensive vasculopathy compared to coronary arteries [31]. This explains why erectile dysfunction predates angina in coronary artery disease and the need for total cardiovascular evaluation in hypertensive patients presenting with erectile dysfunction.

The *Treatment of Mild Hypertension Study* (TOMHS) reported a prevalence of erectile dysfunction as 12% of study participants which was quite low. TOMHS was one of the big pioneer trials to investigate on erectile dysfunction [32]. In contrast to these findings, an incidental observation was made at the end of TOMHS where erectile dysfunction among male hypertensive patients was associated with polytherapy and increased systolic blood pressure [33]. A study found out that the presence of vasculogenic erectile dysfunction among hypertensive men was associated with subclinical

atherosclerosis, impaired arterial function as well as endothelial and systemic inflammation [34].

A study done in hypertensive women of 60 to 80 years found a significant relationship between antihypertensive medications and the prevalence of sexual dysfunction. The antihypertensive drugs implicated were enalapril, atenolol or isradipine [35]. There were no reference control groups to compare with but this finding galvanized further studies to start investigating hypertensive women on treatment for possible sexual dysfunction.

However, a prospective study by *Monowar and colleagues* found out that erectile dysfunction among Blacks was (7.9%), Hispanics (6.3%) and Caucasians (4.7%) had the least prevalence. In the study, it was realized that age was the only significant factor that influenced sexual dysfunction among the various races [36]. This was supported by the Boston Area Community Health (BACH) study where no significant relationship was found between race and erectile dysfunction [37].

4. Pathophysiology of Sexual Dysfunction Among Hypertensives

Hypertension and its related disorders have an impact on various end-organs such as kidney, brain as well as the vasculature. Hypertension causes erectile dysfunction in men via endothelial dysfunction and subsequently impairing the function of nitric oxide [21] Experimental studies have revealed anatomical aberrations within the penile blood vessels [38]. Longstanding hypertension leads to oxidative stress, endothelial injury and subsequently arteries, arterioles and sinusoids of corpus cavernosum fail to relax [39].

Several studies on the effect of hypertension on ED have found vasculopathy and higher levels of serum inflammatory mediators to be a implicated [34]. Nitric oxide is the main vasodilator involved in the erectile pathway mediated by cyclic-guanosine monophosphate (C-GMP) although bradykinin's effect on activation bradykinin type 2 receptors from current studies has been implicated [35]. The Enos activity in several experimental studies have been found to play a crucial role in the erectile pathway. The intact endothelium responds adequately to NO and hence any impairment in endothelium will result in minimal or no response [18]. Angiotensin-II has been recently been implicated in erectile dysfunction [36]. Angiotensin-II is found in both plasma and tissues with variable levels of concentration with corporal cavernosum containing angiotensin-II of about 200-fold compared to plasma [37-38]. Angiotensin-converting enzyme inhibitors (ACEIs) reduce the level of angiotensin-II but less efficacious compared to Angiotensin-II receptor type-I blockers (ARBs) [39]. Chymase is usually up-regulated with long-term use of ACEIs [40]. Angiotensin-II receptor type-1 blockers halt the progression of erectile dysfunction [41]. Bradykinin has been implicated as a vasodilator involved in erection whose levels increase with the use of ACEIs [42]. The predominant bradykinin receptor type in the penile tissues and blood vessels needs to be investigated upon as bradykinin type-II receptor activation favors erectile function while type-I activation inhibits erection. ACEIs' inferiority to ARBs in improving erectile function might be from the prevalence of bradykinin-type-1 receptor in penile tissues.

In a pre-clinical study, Chymase to angiotensin converting enzyme concentration in the penile tissues was found to be 160-fold to 30-fold respectively [43].

5. Antihypertensive Medications and Erectile Dysfunction

The role of antihypertensive medications in the management of hypertension and its related disorders cannot be understated. Antihypertensive medications from different classes target specific pathways making combination therapy an essential aspect of management [43 - 44]. Antihypertensive drugs can affect the central nervous system by reducing libido and inducing depression while peripherally by reducing vasodilators and reducing receptor sensitivity [45]. Although an advantage of combination therapy is to reduce the incidence of side effects by reducing dosages while maintaining efficacy. The older generation of drugs in the classes of beta-blockers, diuretics and centrally acting agents have been greatly implicated [32] while newer agents have neutral (ACEIs and calcium channel blockers, CCBs) or improved effect (ARBS and Nebivolol) on erectile function [46]. Most of these drugs has side effects which are unbearable in patients [5]. Antithetical to this, some antihypertensive drugs are able to improve erectile function by donating nitric oxide [47] blocking or reducing angiotensin-II [46] and aiding in alternate pathways mediating erection. Nitric oxide is found in the chemical structure of some antihypertensive drugs [48] but only the modified type is physiologically active.

5.1. Beta-Blockers (BB)

Beta blockers have been implicated in erectile dysfunction [49] but this effect has been found to be drug-specific other than class effect [50]. Decreased sympathetic outflow coupled with depression and loss of libido (reduced level of testosterone) are implicated in the pathophysiology of erectile dysfunction among hypertensive individuals on beta-blockers [49]. A recent survey, where 199 patients were followed-up after coronary artery bypass graft. These patients were on two different beta-blockers, nebivolol and metoprolol. An increased incidence of erectile dysfunction was observed with metoprolol and nebivolol but a reduced risk was associated with nebivolol use [47]. The findings in this study were in line with several studies which clearly implicated erectile dysfunction among certain drugs in this class (beta-blockers).

A prospective study in 44 patients on beta-blockers who presented with erectile dysfunction after initiation of treatment had nebivolol replacing the other beta-blockers. After 3 months of therapy, 68% had an appreciable

improvement of erectile function [51].

On a large cross-sectional study, hypertensive patients who reported with erectile dysfunction while on beta-blockers were recruited. Metoprolol and carvedilol were associated with the highest prevalence of erectile dysfunction, while atenolol and bisoprolol had a moderate impact on erectile dysfunction and nebivolol was associated with the lowest prevalence of erectile dysfunction [52]. The essential information is drawn from the fact that various beta blockers have variable effects on erectile function. Nebivolol has a good profile with less erectile dysfunction which can be ascribed to the nitric oxide moiety [53].

Beta-blockers (Nebivolol, bisoprolol, atenolol, and carvedilol) were given for 12 weeks. At the end of the study, there was a statistically significant wane in the arterial flow velocities in participants who were on carvedilol, atenolol, and bisoprolol while nebivolol had no impact on flow velocity [54]. Nebivolol is the only beta-blocker shown to have a favorable impact on erectile function [51]. Boydak and colleagues in a randomized double-blind study assessed the influence of beta-blockers (nebivolol and atenolol) and a diuretic (chlorthalidone) on erectile dysfunction. After a 3-month period of follow-up, it was realized that erectile dysfunction worsened with atenolol use and this select was exaggerated when chlorthalidone was added. In contrast to this, nebivolol did not affect sexual function in these study subjects [55]. Nebivolol is peno-protective effect compared to other beta-blockers and its choice is appropriate in patients requiring beta-blockers as well as maintenance of erectile function.

In contrast to the aforementioned evidence on beta-blockers, some studies have implicated the knowledge of side effects of beta-blockers as the primary psychogenic factors mediating erectile dysfunction in some hypertensive men [56 - 57].

The findings on the psychogenic etiology implies that fear of side effects can aggravate the erectile dysfunction caused by the medications.

5.2. Calcium Channel Blockers (CCBs)

CCBs are essential in the management of hypertension and its role cannot be underemphasized in black populations and the aged [58]. Some calcium channel blockers have been implicated in erectile dysfunction [33]. Calcium channel blockers are known to have a neutral effect on erectile function although some reports have been made concerning its association with erectile dysfunction [59]. The occurrence of erectile dysfunction with calcium channel blockers can be possibly ascribed to reduced blood flow especially in patients with atherosclerotic arteries who have a reduced mean arterial pressure while on CCBs [60]. Further research will be required in this area to determine the effect of blood pressure reduction and erectile dysfunction in patients on CCBs. In a study, patients taking verapamil developed hyperprolactinemia which was associated with gynecomastia and erectile dysfunction as a result of reduced testosterone [61]. In another study, the dihydropyridine and benzothiazepines were not involved in serum prolactin increment while verapamil was still implicated [62]. In another study involving 134 patients on calcium channel blockers (diltiazem, verapamil, and nifedipine), angiotensin-converting enzyme inhibitors (lisinopril) and diuretics (frusemide and hydrochlorothiazide). Diltiazem and nifedipine were shown to improve erectile function, while verapamil, frusemide, and lisinopril exhibited neutral effects. Hydrochlorothiazide use was associated with reduced libido and poor erectile function [63]. In contrast to this, a prior pre-clinical study found out that, the use of amlodipine was associated with a decline in testosterone levels which was ascribed to increased prolactin secretion and subsequently leading to reduced libido and erectile function. Amlodipine's effect on ED was dependent on dose and duration [64]. The evidence so far on calcium channel blockers is inconclusive but a possibility of erectile dysfunction might result from specific agents increasing serum prolactin. Serum prolactin should be monitored in suspected patients on calcium channel blockers exhibiting anti-androgenic symptoms. Further studies are required in this area to elucidate possible hormonal imbalances with the use of calcium channel blockers.

5.3. Diuretics (Ds)

Diuretics have been the most implicated antihypertensive drugs causing erectile dysfunction [65] followed by centrally acting agents and beta-blockers. Thiazide mediates the antihypertensive action through a reduction in effective plasma volume and vasodilation caused by the release of a nitric oxide moiety in its chemical architecture [66]. In the Trial of Antihypertensive Interventions and Management (TAIM) study, erectile function was assessed among patients taking atenolol, chlorthalidone, and placebo. At the end of the study, erectile dysfunction was highest among the group on chlorthalidone (28%), atenolol (11%) and placebo (3%). Of note, weight reduction among patients who received chlorthalidone had an improved sexual Function [67]. Chlorthalidone and hydrochlorothiazide were associated with worsened erectile dysfunction in a study assessing the impact of diuretic therapy on erectile function [68]. Hormonal disturbances are common with spironolactone which causes loss of libido and gynecomastia leading to erectile dysfunction [69].

5.4. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Angiotensin-converting enzyme inhibitors (ACEIs) have a neutral effect on erectile function similar to calcium channel blockers. With the recent implication of angiotensin-II in affecting erectile dysfunction negatively, much focus was placed on ACEIs [70]. ACEIs play a neutral role or enhances erectile function but inferior to angiotensin-II receptor-type-I blockers [39] due ~~owing~~ to the fact that alternate enzymes such as Chymase mediates conversion of angiotensin-I to angiotensin-II [72].

5.5. Angiotensin Receptor Type-I Blockers (ARBs)

ARBs have an excellent impact on halting progression or

reversal of erectile dysfunction. Intracavernosal injection of angiotensin-II led to reduced erectile function and detumescence in the erected penis but the injection of losartan had an antithetical effect [73]. In a robust study by Della and colleagues, valsartan use was associated with an improved sexual function among 2202 hypertensive individuals recruited. In several pre-clinical trials, intracavernous injection of angiotensin-II led to reduced intracavernosal pressure and prevented erection as well as aborted erection already in place [74].

Blockade of angiotensin-II with losartan a led to an increase in intracavernosal pressure and hence erection [75]. Clinical trials have affirmed the experimental studies where an improvement with the use of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors were associated with an improved erectile function [38].

5.6. Centrally-Acting Agents (CA)

Centrally-acting agents, methyldopa, and clonidine have been implicated in erectile dysfunction although the latter drug has been withdrawn due to multiple side effects. Of note, no new drugs have been recently produced from this class as a result of the presence of other effective and beneficial drug-classes. In the era of clonidine prescription, a pre-clinical study was set out to determine its effects together with other medications on erectile function. Propranolol and clonidine were associated with poor sexual performance in males whereas captopril was without erectile dysfunction [76]. Multiple studies have shown methyldopa to aggravate or cause erectile dysfunction in hypertensive males [77], [78]. This class has all agents entirely involved in erectile dysfunction.

6. Conclusion

Erectile dysfunction is a challenge to both the physician and the hypertensive patient as the progression of the disease, aging, co-morbidities, and medications all affect sexual function or combination of these factors. Erectile dysfunction is currently being advocated for as a risk factor in cardiovascular diseases as evidence shows its occurrence prior to asymptomatic cardiovascular diseases. Spurious associations linking erectile dysfunction and antihypertensive medications, or hypertension can be obviated by assessing the state of erectile function prior to the commencement of antihypertensive therapy. The natural progression of hypertension can invariably lead to erectile dysfunction through endothelial dysfunction or disturbances in vasodilation. Undoubtedly, multiple studies on antihypertensive drugs have proven to have an impact on erectile function by negatively or positively affecting it. The diuretics and centrally acting drugs are the class-specific drugs implicated in erectile dysfunction while the other classes (beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers) are drug-specific in causing erectile dysfunction. Erectile dysfunction among patients with hypertension needs to be critically evaluated by all physicians treating patients with hypertension and its related disorders.

References

[1] Burchardt, M., Burchardt, T., Anastasiadis, A. G., Kiss, A. J., Shabsigh, A., De La Taille, A., Shabsigh, R. (2001). Erectile dysfunction is a marker for cardiovascular complications and psychological functioning in men with hypertension. *International Journal of Impotence Research*, *13* (5), 276-281.

[2] Fisher, W. A., Rosen, R. C., Mollen, M., Brock, G., Karlin, G., Pommerville, P., Sand, M (2005). Improving the Sexual Quality of Life of Couples Affected by Erectile Dysfunction: A Double-Blind, Randomized, Placebo-Controlled Trial of Vardenafil. *The Journal of SexualMedicine*, *2* (5), 699-708.

[3] NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. (1993). *The Journal of the Ameri can Medical Association*, *270* (1), 83-90.

[4] Bachmann, G. A., and Avci, D. (2004). Evaluation and Management of Female Sexual Dysfunction. *The Endocrinologist*, *14* (6), 337-345.

[5] Viigimaa, M., Doumas, M., Vlachopoulos, C., Anyfanti, P., Wolf, J., Narkiewicz, K., & Mancia, G. (2011). Hypertension and sexual dysfunction: time to act. *Journal of Hypertension*, *29* (2), 403-407.

[6] Fogari, R. (2002). Different effect of valsartan and lisinopril on sildenafil use in hypertensivemen with erectile dysfunction. *American Journal of Hypertension*, *15* (4), A37.

[7] Jackson, G., Rosen, R. C., Kloner, R. A., and Kostis, J. B. (2006). REPORT: The Second Princeton Consensus on Sexual Dysfunction and Cardiac Risk: New Guidelinesfor SexualMedicine. *The Journal of Sexual Medicine*, *3* (1), 28-36.

[8] Montorsi, P., Montorsi, F., and Schulman, C. C. (2003). Is Erectile Dysfunction the "Tip of the Iceberg" of a Systemic Vascular Disorder? *European Urology*, *44* (3), 352-354.

[9] Virag, R., Bouilly, P., & Frydman, D. (1985). About arterial risk factors and impotence. *The Lancet*, *325* (8437), 1109-1110.

[10] Bocchio, m., Desideri, g., Scarpelli, p., Necozione, s., Properzi, g., Spartera, c., Francavilla, s. (2004). Endothelial cell activation in men with erectile dysfunction without cardiovascular risk factors and overt vascular damage. *The Journal of Urology*, *171* (4), 1601-1604.

[11] Albersen, M., Shindel, A., and Lue, T. (2009). Sexual dysfunction in the older man. *Reviews in Clinical Gerontology*, *19* (04), 237.

[12] Dean, J., De Boer, B., Graziottin, A., Hatzichristou, D., Heaton, J., and Tailor, A. (2006). The Role of Erection Hardness in Determining Erectile Dysfunction (ED) Treatment Outcome. *European Urology Supplements*, *5* (13), 767-772.

[13] Lewis, R. W., Fugl-Meyer, K. S., Corona, G., Hayes, R. D., Laumann, E. O., Moreira, E. D., Segraves, T. (2010). Definitions/Epidemiology/Risk Factors for Sexual Dysfunction. *The Journal of Sexual Medicine*, *7* (4), 1598-1607.

[14] Feldman, H. A., Goldstein, I., Hatzichristou, D. G., Krane, R. J., and McKinlay, J. B. (1994). Impotence and Its Medical and Psychosocial Correlates: Results of the Massachusetts Male Aging Study. *The Journal of Urology*, *151* (1), 54-61.

[15] Moreira Júnior, E. D., Bestane, W. J., Bartolo, E. B., and Fittipaldi, J. A. (2002). Prevalence and determinants of erectile dysfunction in Santos, southeastern Brazil. *Sao Paulo Medical Journal*, *120* (2), 49-54.

[16] Braun, M., Wassmer, G., Klotz, T., Reifenrath, B., Mathers, M., and Engelmann, U. (2000). Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *International Journal of Impotence Research*, *12* (6), 305-311.

[17] Chalupsky, K., and Cai, H. (2005). Endothelial dihydrofolate reductase: Critical for nitric oxide bioavailability and role in angiotensin II uncoupling of endothelial nitric oxidesynthase. *Proceedings of the National Academy of Sciences*, *102* (25), 9056-9061.

[18] Johnson, J. M., Bivalacqua, T. J., Lagoda, G. A., Burnett, A. L., and Musicki, B. (2011). eNOS-uncoupling in age-related erectile dysfunction. *International Journal of Impotence Research*, *23* (2), 43-48.

[19] Durante, W., Johnson, F. K., & Johnson, R. A. (2007). Arginase: a critical regulator of nitric oxide synthesis and vascular function. *Clinical and Experimental Pharmacology and Physiology*, *34* (9), 906-911.

[20] Yang, J., Gonon, A. T., Sjoquist, P., Lundberg, J. O., & Pernow, J. (2013). Arginase regulates red blood cell nitric oxide synthase and export of cardioprotective nitric oxide bioactivity. *Proceedings of the National Academy of Sciences*, *110* (37), 15049-15054.

[21] Caldwell, R. B., Toque, H. A., Narayanan, S. P., & Caldwell, R. W. (2015). Arginase: an old enzyme with new tricks. *Trends in Pharmacological Sciences*, *36* (6), 395-405.

[22] Segal, R., Hannan, J. L., Liu, X., Kutlu, O., Burnett, A. L., Champion, H. C., Bivalacqua, T. J. (2012). Chronic Oral Administration of the Arginase Inhibitor 2 (S)-amino-6-boronohexanoic Acid (ABH) Improves Erectile Function in Aged Rats. *Journal of Andrology*, *33* (6), 1169-1175.

[23] Lacchini, R., Muniz, J. J., Nobre, Y. T., Cologna, A. J., Martins, A. C., and Tanus-Santos, J. E. (2017). Influence of arginase polymorphisms and arginase levels/activity on the response to erectile dysfunction therapy with sildenafil. *The Pharmacogenomics Journal*.

[24] Zanchetti, A. (2014). Predictive, mechanistic, and therapeutic studies on hypertension and cardiovascular morbidity and mortality. Journal of Hypertension, 32 (8), 1549-1550.

[25] Paneni, F., Diaz Cañestro, C., Libby, P., Lüscher, T. F., & Camici, G. G. (2017). The Aging Cardiovascular System. *Journal of the American College of Cardiology*, *69* (15), 1952-1967.

[26] Scuteri, A., Morrell, C. H., Orru, M., Strait, J. B., Tarasov, K. V., Ferreli, L. A., Lakatta, E. G. (2014). Longitudinal Perspective on the Conundrum of Central Arterial Stiffness, Blood Pressure, and AgingNovelty and Significance. *Hypertension*, *64* (6), 1219-1227.

[27] Labbate, L. (2010). Faculty of 1000 evaluation for Erectile dysfunction predicts cardiovascular events in high-risk patients receiving telmisartan, ramipril, or both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. *F1000 - Post-publication peer review of the biomedical literature*.

[28] Chew, K., Finn, J., Stuckey, B., Gibson, N., Sanfilippo, F., Bremner, A., Jamrozik, K. (2010). Erectile Dysfunction as a Predictor for Subsequent Atherosclerotic Cardiovascular Events: Findings from a Linked-Data Study. *The Journal of Sexual Medicine*, *7* (1), 192-202.

[29] Bohm, M., Baumhakel, M., Teo, K., Sleight, P., Probstfield, J., & Gao, P. (2010). Erectile Dysfunction Predicts Cardiovascular Events in High-Risk Patients Receiving Telmisartan, Ramipril, or Both: The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (ONTARGET/TRANSCEND) Trials. *Circulation*, *121* (12), 1439-1446.

[30] Thompson, I. M., Tangen, C. M., Goodman, P. J., Probstfield, J. L., Moinpour, C. M., and Coltman, C. A. (2006). Erectile Dysfunction and Incidence of Cardiovascular Disease—Reply. *JAMA*, *295* (17), 1998.

[31] Kaiser, D. R., Billups, K., Mason, C., Wetterling, R., Lundberg, J. L., and Bank, A. J. (2004). Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. *Journal of the American College of Cardiology*, *43* (2), 179-184.

[32] Grimm, R. H., Grandits, G. A., Prineas, R. J., McDonald, R. H., Lewis, C. E., Flack, J. M., Stamler, J. (1997). Long-term Effects on Sexual Function of Five Antihypertensive Drugs and Nutritional Hygienic Treatment in Hypertensive Men and Women: Treatment of Mild Hypertension Study (TOMHS). *Hypertension*, *29* (1), 8-14.

[33] Javaroni, V., and Neves, M. F. (2012). Erectile Dysfunction and Hypertension: Impact on Cardiovascular Risk and Treatment. *International Journal of Hypertension*, *2012*, 1-11.

[34] Vlachopoulos, C., Aznaouridis, K., Ioakeimidis, N., Rokkas, K., Tsekoura, D., Vasiliadou, C., Stefanadis, C. (2008). Arterial function and intima-media thickness in hypertensive patients with erectile dysfunction. *Journal of Hypertension*, *26* (9), 1829-1836.

[35] Perry, H., Hall, W., Benz, J. R., Bartels, D. W., Kostis, J. B., Townsend, R. R., Sirgo, M. (1994). Efficacy and safety of atenolol, enalapril, and isradipine in elderly hypertensive women. The American Journal of Medicine, 96 (1), 77-86.

[36] Hosain, G. M., Latini, D. M., Kauth, M. R., Goltz, H. H., and Helmer, D. A. (2013). Racial Differences in Sexual Dysfunction Among Postdeployed Iraq and Afghanistan Veterans. *American Journal of Men's Health*, *7* (5), 374-381.

[37] Kupelian, V., Link, C. L., Rosen, R. C., and McKinlay, J. B. (2008). Socioeconomic Status, Not Race/Ethnicity, Contributes to Variation in the Prevalence of Erectile Dysfunction: Results from the Boston Area Community Health (BACH) Survey. *The Journal of Sexual Medicine*, *5* (6), 1325-1333.

[38] Park, J. K., Kim, S. Z., Kim, S. H., Park, Y. K., and Cho, K. W. (1997). Renin Angiotensin System in Rabbit Corpus Cavernosum. *The Journal of Urology*, 653-658.

[39] Weber, M. A. (2003). Review: Angiotensin II receptor blockers and cardiovascular outcomes: what does the future hold? *Journal of the Renin-Angiotensin-Aldosterone System*, *4* (2), 62-73.

[40] Zablocki, D., and Sadoshima, J. (2010). The one-two punch: knocking out angiotensin II in the heart. *Journal of Clinical Investigation*, *120* (4), 1028-1031.

[41] Pedrosa, K., & Clinton, R. (2012). Mechanisms in Erectile Function and Dysfunction: An Overview. *Erectile Dysfunction - Disease-Associated Mechanisms and Novel Insights into Therapy*.

[42] Izzo Jr, J. L., and Weir, M. R. (2011). Angiotensin-Converting Enzyme Inhibitors. *The Journal of Clinical Hypertension*, *13* (9), 667-675.

[43] Takai, S., and Miyazaki, M. (2002). The role of chymase in vascular proliferation. *Drug News and Perspectives*, *15* (5), 278.

[44] Seftel, A. D., Sun, P., and Swindle R. (2004). The prevalence of hypertension, hyperlipidemia, diabetes mellitus and depression in men with erectile dysfunction. *The Journal of Urology*, *171* (6), 2341-2345.

[45] Stadler, T., Bader, M., Uckert, S., Staehler, M., Becker, A., and Stief, C. G. (2006). Adverse effects of drug therapies on male and female sexual function. *World Journal of Urology*, *24* (6), 623-629.

[46] Baumhäkel, M., Schlimmer, N., Kratz, M., Hacket, G., Jackson, G., and Böhm, M. (2011). Cardiovascular risk, drugs and erectile function - A systematic analysis. *International Journal of Clinical Practice*, *65* (3), 289-298.

[47] Gür, Ö., Gurkan, S., Yumun, G., and Turker, P. (2017). The Comparison of the Effects of Nebivolol and Metoprolol on Erectile Dysfunction in the Cases with Coronary Artery Bypass Surgery. *Annals of Thoracic and Cardiovascular Surgery*, *23* (2), 91-95.

[48] Tzemos, N., Lim, P. O., and MacDonald, T. M. (2001). Nebivolol Reverses Endothelial Dysfunction in Essential Hypertension: A Randomized, Double-Blind, Crossover Study. *Circulation*, *104* (5), 511-514.

[49] Manolis, A., & Doumas, M. (2016). Erectile Function in Cardiovascular Disease and Hypertension: the Role of Nebivolol. *Journal of Hypertension: Open Access*, *05* (02).

[50] Sharp, R. P., and Gales, B. J. (2017). Nebivolol versus other beta blockers in patients with hypertension and erectile dysfunction. *Therapeutic Advances in Urology*, *9* (2), 59-63.

[51] Doumas, M. (2006). Factors Affecting the Increased Prevalence of Erectile Dysfunction in Greek Hypertensive Compared With Normotensive Subjects. *Journal of Andrology*, *27* (3), 469-477.

[52] Cordero, A., Bertomeu-Martanez, V., Mazan, P., Facila, L., Bertomeu-Gonzalez, V., Conthe, P., & Gonzalez-Juanatey, J. R. (2010). Erectile Dysfunction in High-Risk Hypertensive Patients Treated with Beta-Blockade Agents. *Cardiovascular Therapeutics*, *28* (1), 15-22.

[53] Brixius, K., Middeke, M., Lichtenthal, A., Jahn, E., and Schwinger, R. H. (2007). Nitric oxide, erectile dysfunction and beta-blocker treatment (MR NOED STUDY): Benefits ofnebivolol versus metoprolol in hypertensive men. *Clinical and Experimental Pharmacology and Physiology*, *34* (4), 327-331.

[54] Botros, S. M., Mohamed Hussein, A., and Elserafy, A. S. (2015). Effect of different beta-blockers on penile vascular velocities in hypertensive males. *The Egyptian Journal of Radiology and Nuclear Medicine*, *46* (3), 749-754.

[55] Boydak, B., Nalbantgil, S., Fici, F., Nalbantgil, I., Zoghi, M., Ozerkan, F., Onder, R. (2005). A Randomised Comparison of the Effects of Nebivolol and Atenolol with and without Chlorthalidone on? the Sexual Function of Hypertensive Men. *Clinical Drug Investigation*, *25* (6), 409-416.

[56] Silvestri, A. (2003). Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. *European Heart Journal*, *24* (21), 1928-1932.

[57] Cocco, G. (2009). Erectile Dysfunction after Therapy with Metoprolol: The Hawthorne Effect. *Cardiology*, *112* (3), 174-177.

[58] Ubaidi, B. A. (2015). Putting Evidence Based JNC 8 Guideline into Primary Care Practice. *Journal of Hypertension: Open Access*, *04* (01).

[59] Omvik P, Thaulow E, Herland OB, et al. Double-blind, parallel, comparative study on quality of life during treatment with amlodipine or enalapril in mild or moderate hypertensive patients: a multicentre study. Journal of Hypertension. 1993; 11 (1): 103–13.

[60] M. Bocchio, P. Scarpelli, S. Necozione. (2006). "Penile duplex pharmaco-ultrasonography of cavernous arteries in men with erectile dysfunction and generalized atherosclerosis," *International Journal of Andrology*, vol. 29, no. 4, pp. 496–501.

[61] Bowman, J. D., Kim, H., & Bustamante, J. J. (2012). Drug-Induced Gynecomastia. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *32* (12), 1123-1140.

[62] Knoepfelmacher, M., Villares, S., Nicolau, W., Germek, O., Lerario, A., Wajchenberg, B., and Liberman, B. (1994). Calcium and Prolactin Secretion in Humans: Effects of the Channel Blocker, Verapamil, in the Spontaneous and Drug-Induced Hyperprolactinemia. *Hormone and Metabolic Research*, *26* (10), 481-485.

[63] Kloner, R. A., and Henderson, L. (2013). Sexual Function in Patients With Chronic Angina Pectoris. *The American Journal of Cardiology*, *111* (11), 1671-1676.

[64] Onwuka, F. C., Iwuanyanwu, P., Nnodu, C., and Erhabor, O. (2015). Effect of amlodipine, a calcium channel antagonist, on gonadal steroid of male wistar albino rats. *Maturitas*, *81* (1), 208.

[65] Dusing, R. (2005). Sexual Dysfunction in Male Patients with Hypertension. *Drugs*, *65* (6), 773-786.

[66] Grossman, E., Verdecchia, P., Shamiss, A., Angeli, F., and Reboldi, G. (2011). Diuretic Treatment of Hypertension. *Diabetes Care*, *34* (Supplement_2), S313-S319.

[67] Wassertheil-Smoller, S., Oberman, A., Blaufox, M. D., Davis, B., & Langford, H. (1992). The Trial of Antihypertensive Interventions and Management (TAIM) Study: Final Results With Regard to Blood Pressure, Cardiovascular Risk, and Quality of Life. *American Journal of Hypertension*, *5* (1), 37-44.

[68] Chang, S. W. (1991). The impact of diuretic therapy on reported sexual function. *Archives of Internal Medicine*, *151* (12), 2402-2408.

[69] Lue, T. F. (2000). Erectile Dysfunction. *New England Journal of Medicine*, *342* (24), 1802-1813.

[70] Fogari, R., & Zoppi, A. (2004). Effect of Antihypertensive Agents on Quality of Life in the Elderly. *Drugs & Aging*, *21* (6), 377-393.

[71] Dorrance, A. M., Lewis, R. W., & Mills, T. M. (2002). Captopril treatment reverses erectile dysfunction in male Stroke Prone Spontaneously Hypertensive Rats. *International Journal of Impotence Research*, *14* (6), 494-497.

[72] Ahmad, S., Simmons, T., Varagic, J., Moniwa, N., Chappell, M. C., and Ferrario, C. M. (2011). Chymase-Dependent Generation of Angiotensin II from Angiotensin-(1-12) in Human Atrial Tissue. *PLoS ONE*, *6* (12), e28501.

[73] Chiesa, A. D., Pfiffner, D., Meier, B. and Hess, O. M. (2003). Sexual activity in hypertensive men. *Journal of Human Hypertension*, *17* (8), 515-521.

[74] SHIMIZU, S., TSOUNAPI, P., HONDA, M., DIMITRIADIS, F., TANIUCHI, K., SHIMIZU, T., SAITO, M. (2014). Effect of an angiotensin II receptor blocker and a calcium channel blocker on hypertension associated penile dysfunction in a rat model. *Biomedical Research*, *35* (3), 215-221.

[75] Srilatha, B., Adaikan, P. G., Arulkumaran, S., and Ng, S. C. (1999). Sexual dysfunction related to antihypertensive agents: results from the animal model. *International Journal of Impotence Research*, *11* (2), 107-113.

[76] Lovic, D. (2014). Pathophysiology of Erectile Dysfunction. *Erectile Dysfunction in Hypertension and Cardiovascular Disease*, 19-28.

[77] Ferrario, C. M. and Levy, P. (2002). Sexual Dysfunction in Patients With Hypertension: Implications for Therapy. *The Journal of Clinical Hypertension*, *4* (6), 424-432.