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HYPERTENSION CAN INCREASE RISK OF ERECTILE DYSFUNCTION (ED) HOWEVER; ANTIHYPERTENSIVE DRUGS ALSO CAN CONTRIBUTE TO THE PROBLEM

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Abstract

Hypertension (HTN) is a medical condition that persistently raises blood pressure in the arteries. HTN is an asymptomatic disease; in the early stage people experience a few symptoms like light-heartedness, vertigo, altered vision, etc. It is a silent risk factor for end-organ diseases such as cardiovascular and chronic kidney diseases, erectile dysfunction (ED) and so on. ED has a high prevalence in hypertensive people because of the condition, and different clinical types of medications alter the blood flow for penis & endothelial functioning. Different therapeutic classes of antihypertensive drugs are causing ED with different incidence & severity. Diuretics and beta-blockers are having a high incidence, vasodilators and calcium channel blockers and angiotensin-converting enzyme inhibitors having the medium incidence, angiotensin II receptor blockers have a rare incidence to cause ED. This review mainly focuses on 1) Various antihypertensive drugs associated occurrence of ED, 2) Toassess differences between antihypertensive drug categories regarding their effects on erectile function, 3) Does switching from one to another class affect erectile function. Lifestyle is an important part of your blood pressure care. You can prevent, postpone or minimize the need for medication if your blood pressure is successfully managed through a healthy lifestyle.

Introduction

Hypertension (HTN) is a long-term medical condition in which the blood pressure in the arteries is persistently elevated (1). According to the recently published observational studies, an estimated 26% of the world's population has HTN, and the prevalence is expected to increase to 29% by 2025. Blood pressure tends to rise with age (2). Six to eight percent of people aged 60-69 years, and about 12-16% of those aged 70-79 years, around 7.5 million deaths worldwide occur due to HTN (3).

Hypertension is an asymptomatic condition and in the early stages, people may experience a few symptoms like vertigo, altered vision, or fainting. Hypertension is a silent risk factor for end-organ diseases like cardiovascular diseases and chronic kidney diseases, retinal problems, brain strokes, erectile dysfunction (ED), metabolic disorders by blocking or damaging the blood vessels in end organs (4).

There are several therapeutic groups of drugs are available to treat HTN, it includes diuretics, beta-blockers (BB's), calcium channel blockers (CCB's), angiotensin-converting enzyme inhibitors (ACEI's), angiotensinII receptor blockers (ARB's),alpha-receptor blockers, direct renin inhibitors. The principle therapeutic mechanism involved in the treatment of HTN is decreasing of body fluid volume, a fraction of ejection of blood from heart, vasodilation of blood vessels, which may also have several side effects. This includes heart palpitations, swollen feet & ankles, bradycardia, ED (5).

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In this paper, we have mainly focused on HTN and antihypertensive drugs induced ED. Erectile dysfunction is a form of sexual dysfunction known as impotence that is characterized by the inability to create or retain penile erection during sexual intercourse (6). According to earlier research studies, ED has a high prevalence among hypertensive men comparing with non-hypertensive men.

The pathology of ED involved in hypertensive patients is the blood pressure that can damage the endothelium of arteries by causing them to become thicker, or even to burst. This can restrict blood flow to the penis, then which may cause ED. On the other hand, ED is an intermittent side-effect of some of the groups of antihypertensive drugs like diuretics and CCB's, ARB's, ACEI's, alpha-receptor blockers, vasodilators. Each therapeutic class of antihypertensive drugs has shown to cause ED with different pathological mechanisms. The severity of ED depends on the dose and frequency of use of antihypertensive drugs in hypertensive men. This may cause different levels of side effects, adverse effects (7).

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Table: -1Various pharmacological classes of antihypertensive drugs & its side effects (7).

Therapeutic class	Examples	Adverse Events	Contraindications
Diuretics	Chlorothiazide, Hydrochlorothiazide, Furosemide, Spironolactone, Amiloride, Acetazolamide.	Hyponatremia, hypokalaemia, acid-base changes, hyperuricemia, erectile dysfunction.	Gout, diabetic patients, pancreatitis, systemic lupus erythematosus, kidney diseases.
Calcium Channel Blockers	Amlodipine, Verapamil, Diltiazem, Nifedipine.	Swollen feet &ankles, flushing, tiredness, and heart palpitations.	Kidney and liver diseases, hypotension, congestive heart failure, depression.
Vasodilators	Sodium nitroprusside, Hydralazine.	Heart palpitations, headaches, swelling around the eyes.	Cerebrovascular disease, cardiovascular diseases, diabetes.
Beta-Blockers	Atenolol, Carvedilol, Metoprolol, Esmolol, Pindolol.	Bradycardia, swelling of hands and legs, hypotension, erectile dysfunction.	Asthma, hyperthyroidism, chronic pulmonary disease, cardiovascular disease.
Alpha-Receptor Blockers	Prazosin, Terazosin.	Rapid heart rate, ED, loss of bladder control, sleep disturbances.	Cardiovascular diseases, narcolepsy patients.
Angiotensin Converting Enzyme Inhibitors	Captopril, Enalaprill, Ramiprill, Lisinoprill, Benzaprill, Quinapril.	Loss of taste, dry cough, hypotension erectile dysfunction.	Diabetes, cardiovascular diseases, chronic kidney disease.
Angiotensin II Receptor Blockers	Losartan, Telmisartan, Valsartan.	Joint Pain, sore throat, cough, diarrhoea, ED.	Diabetes, severe congestive heart failure.
Centrally Acting Antihypertensive Drugs	Carbidopa, Methyldopa.	Feeling faint or weak when standing slow heart rate, drowsiness lethargy.	Cardiovascular disease, kidney or liver diseases, parkinsonism disease, depression.

The major symptom of antihypertensive medications in ED is worsening blood supply to the penis, with structural / functional changes in the penile arteries leads to dysfunction (8). Treatment of ED in HTN patients is however difficult and should take into account. There are various levels of severity in erectile dysfunction by antihypertensive drug groups. The main thrust for the treatment of patients with untreated HTN should be lifestyle changes. In diagnosed hypertensive patients switching antihypertension medication should be considered.

The ED is an early sign of cardiovascular disease. Nevertheless, the relationship between HTN and ED has several clinically meaningful concerns (9). Whether ED is beneficial or detrimental to blood pressure control? Are the effects of ED associated with antihypertensive medications? Are there any variations in their efficacy on ED between the groups of antihypertensive drugs? Does it influence ED by switching from one drug class to another?

There are four major bioactive components are involved in regulating the blood pressure in healthy people, including angiotensin II (Ang-II), endothelin-1(ET-1), nitric oxide (NO), and hydrogen sulfide (H_2S). Both components help maintain systemic blood pressure, by modifying kidney, lung, and blood vessel function and morphology. Ang-II and ET-1act as vasoconstrictors, while the NO & H_2Sact as vasodilators. An increase of Ang-II & ET-1 levels in the circulatory system may cause the contraction in the vascular muscle and sodium retention that leads to HTN (10)(11). Decreasing the levels of NO& H_2S leads to HTN. According to earlier studies, the imbalance

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between bioactive vasoconstrictors and vasodilators may lead to HTN. Hence this imbalance may indirectly contribute to the ED in hypertensive patients by reducing the blood flow to the penis.

The goal of this analysis is to assess (1) ED-related antihypertensive drugs, 2) To treat the ED isthe beneficial or harmful hypertensive condition, 3) Differences in their effect on erectility in the categorizing of antihypertensive medicines, 4) do they move from drug to drug class?

We also collected findings from the review of various articles reviewed by peers. The main focus of this research was the assessment of the efficacy of sexual activity in hypertensive men of antihypertensive drugs.

Results & Discussion

According to the WHO, hypertension is a condition in which blood vessels have constantly increased pressure. The primary treatment outcome of HTN is that normal blood pressure is preserved. The treatment outcome of HTN is related to the prevention of damage to the end organ (chronic kidney disease) and prevents the adverse effects, including ED, hypotension, etc. (12) (13). ED usually occurs as a result of multiple physical, psychological and pharmacological causes. ED's risk is ex-aggregated with changes in lifestyle such as alcohol abuse and cigarettes and co-morbidity conditions.

Table:-2 Causes of erectile dysfunction(14).

Cause	Examples
Psychological conditions	Anxiety, stress, relationship problems, depression. personal sexual fears, etc.
Physiological conditions	Hypertension, diabetes mellitus, prostate cancer, spinal cord injury, multiple sclerosis, parkinson's disease, lumber disc diseases, etc.
Pharmacological compounds	Antihypertensive, antihistamines, opiates, tricyclic antidepressants, antipsychotics, benzodiazepines, etc.

Erectile dysfunction is often a side effect of many common drugs. In fact, 25% of all EDs are reported to be due to medication. The antihypertensive treatment has been discussed in table 1 (7). In a European Heart Journal, one of the study is Harvard Special Health Report Erectile Dysfunction confirmed that in the early stage of cardiovascular disease patients there was no erectile dysfunction persist, after starting the treatment with antihypertensive drugs the researchers are noticed the erectile dysfunction. In this study initially, the researchers began beta-blocker atenolol therapy. Some study participants were advised that the blood pressure drug had sexual side effects, while almost one-third registered the ED. Blood pressure may raise if you do not take anti-hypertensive medications, and high blood pressure may also be a symptom of ED. Nevertheless, men with ED are approximately 38% more likely than men without ED to experience HTN, according to a study that analysed medical records for more than 1.9 million men (15).

I) Correlation between Erectile Dysfunction and Hypertension: -

There is a complex relationship between HTN and ED that is explained by the multifactorial pathophysiological process that takes place in both conditions. The main pathology involved in HTN is damaging of endothelial cells in the penile artery which leads to decreasing of Nitrous Oxide levels from endothelial cells. This Nitrous oxide is

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responsible for vasoconstriction and vasodilation of blood penile artery. Hence endothelial dysfunction is directly related to ED (16).

II) Correlation between Erectile Dysfunction and Anti-Hypertensive drugs: -

ED is the occasional side effect of anti-hypertensive medicaments such as thiazide diuretics, loop diuretics, and vasodilators, according to previous studies. This may reduce the flow of blood into the penis and make an erection difficult. Nevertheless, EDs are rarely formed by other antihypertensive medicines, including alpha-blockers, ACEI's and ARB's (17)(18).

A) High prevalence of therapeutic group:-

1) Diuretics: - Diuretics are primarily used in the treatment of HTN with alteration of the body fluid volume and their composition. It involves thiazide, loop, potassium-sparing diuretics, which include the reduction in penile blood flow and depletion of zinc levels in the body and are two triggering mechanisms involved. For testosterone synthesis, zinc and some other minerals are essential (19).

2) Beta-blockers:- Beta-blockers can generally lead to ED by reducing the flow of penile blood into the penile artery during sexual intercourse and which will cause mood destabilization, such as anxiety and depression (20).

B) Medium prevalence of therapeutic group:-

1) Calcium channel blockers: - These CCB's like amlodipine, verapamil, and other drugs prevent calcium from entering into the cells of the heart and blood vessel walls, resulting in lower blood pressure. Excessive and Prolongusage of these drugs can lead to depletion in forceful blood supply for erection, Hence, this condition may results as ED (21).

2) Angiotensin-converting enzyme inhibitors: - In generally ACEI's produce vasodilation by inhibiting the formation of angiotensin II, which leads to low blood flow into penis results in ED (22).

3) Vasodilators:-Vasodilators are reduced the penile blood flow by dilating the blood vessels. The mechanism involved in vasodilators is preventing the muscles from tightening and the walls from narrowing (23) (24).

4) Rarely prevalence causing therapeutic group:-

1) Angiotensin II receptor blockers: - Angiotensin II receptor blockers are drugs that stop angiotensin II bindings to receptors of angiotensin II. As a result, decreases the fraction of ejection blood flow from the heart. It leads to reduced blood flow to the penis for erection (25).

Table 3:- Key findings from different studies

SN	Authors	Clinical trial	Subjects (n)	Ages	Study design	Key findings
1.	Chang SW, et al. (17). (1991)	The impact of diuretic therapy on reported sexual function.	176 Males.	35 to 70 years.	A randomized placebo-controlled trial.	Diuretic use is associated with male sexual dysfunction but does not appear to adversely affect other aspects of quality of life.

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2.	Silvestri A, et al. (2003). (26)	Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo.	96 Males, (Divided into 3 groups, as 33 subjects in each group).	52+/-7 years.	A randomized cohort study. Group A (Blinded), Group B (Known about the drug), Group C(Known about drug & side effects).	After 3 months the incidence of erectile dysfunction was 3.1% in group A, 15.6% in group B and 31.2% in group C (P<0.01).
3.	Shiri R, et al. (2007). (27).	Cardiovascular drug use and the incidence of erectile dysfunction.	1665 males.	55 to 75 years.	Community based survey by mail questionnaires.	The risk of ED was higher in men using calcium channel inhibitor (adjusted relative risk (RR)=1.6, 95% confidence interval (CI) 1.0-2.4).
4.	WABlumentals, et al. (2003). (28).	Antihypertensive treatment and erectile dysfunction in a cohort of type II diabetes patients	634 Males	54.5 years mean age.	Randomized observational studies.	Increased risk of ED was observed among patients taking the following antihypertensive: ACE inhibitors (OR=1.47, 95% CI=1.21, 1.80) and alpha-blockers (OR=1.54, 95% CI=1.11, 2.12).
5.	Elisabet Ekman, et al. (29).	Antihypertensive drugs and erectile dysfunction as seen in spontaneous reports, with a focus on angiotensin II type 1 receptor blockers.	225 Subjects case reports.	Not mentioned.	Observational studies.	Compared with all other drugs in the database. Positive dechallenge was reported in 43 cases (72%).
6.	Khalid A. J. Al Khaja et al. (2016). (30).	Antihypertensive drugs and Male sexual dysfunction: A Review of Adult Hypertension Guideline Recommendations.	_____	_____ _	Reviewed by 2000 research articles.	There is no clarity on β-blockers and thiazide-class diuretics because one-third of the guidelines are vague about individual β-blockers and diuretics, and there is no statement on third-generation β-blockers and thiazide-like diuretics that can improve erectile function.

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III) Treatment of Erectile dysfunction in HTNmen-

A) Pharmacological therapy:-While the treatment of ED can be difficult in previously untreated hypertensive patients because the severity of the disease and certain antihypertensive medications cause ED risks. There is always a cloud over the doctors ' mind in such situations. Based on the length and frequency of the HTN, there is a severity of ED. As a result, the most frequently reported sexual dysfunctions in patients long-term (> 5-6 years) and serious HTN may occur.

It's tricky to manage ED in HTN patients. Changing the lifestyle (weight loss, stop smoking) or turning off other anti-hypertensive medication therapy classes that are less prone to triggering ED may be the main treatment options (23). If still, sexual dysfunction persists more active treatments should be chosen to help phosphodiesterase-5 inhibitors (PDE5 Inhibitors). Nowadays, sildenafil, tadalafil, vardenafil, and avanafil are commonly used PDE5 inhibitors. The mechanism of PDE5 inhibitors involves causing smooth muscle relaxation in the blood vessels that supply the corpus cavernosum, resulting in increased blood flow and erection (31). These drugs are available in different dosage forms like a suppository, transdermal creams. However, this medication class is contraindicated (32). Therefore,PDE5 inhibitors are contraindicated in cardiac origin HTN. Therefore physicians should be more careful about the drug choice, dosage and intensity when treating ED in hypertensive people.

***B) Non-Pharmacological* therapy** includes vacuum erector devices, penile implants & modifications in lifestyle (33). Lifestyle is an important part of your blood pressure care. You can prevent, postpone or minimize the need for medication if your blood pressure is successfully managed through a healthy lifestyle.

Conclusion

In this study, we observed that both the Hypertension & anti-hypertensive drugs affect the blood flow into the penis resulting in erectile dysfunction may occur. Erectile dysfunction has a negative physical and psychological effect on the patient's quality of life. However, healthy food, regular exercises, cutting sodium intake, reducing stress, limiting alcohol intake and quitting smoking may help in controlling hypertension. Lifestyle is an important part of your blood pressure care. You can prevent, postpone or minimize the need for medication if your blood pressure is successfully managed through a healthy lifestyle.

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