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Review Article

Hypertension beyond Lifestyle: The Underrecognized Impact of Drugs and Medical Procedures

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ABSTRACT

Hypertension is a leading global health concern, with lifestyle factors often emphasized as primary contributors. However, drug-induced and iatrogenic hypertension remains under-recognized yet significant cause of elevated blood pressure, complicating disease management. Various pharmacological agents, including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral contraceptives, decongestants, psychotropic drugs, and chemotherapeutic agents, can induce hypertension through mechanisms such as fluid retention, increased sympathetic activity, and endothelial dysfunction. The widespread use of polypharmacy, especially in elderly and comorbid patients, further exacerbates the risk of iatrogenic hypertension. Accurate diagnosis is often challenging, as medication-induced hypertension can mimic primary hypertension, leading to inappropriate treatment strategies. Advances in pharmacogenomics provide an opportunity to predict hypertensive responses to medications, allowing for personalized therapeutic approaches. Management strategies should focus on identifying high-risk patients, adjusting or substituting medications, and implementing non-pharmacological interventions. Increased pharmacovigilance studies are essential to understand drug-related hypertensive risks better and develop safer therapeutic alternatives. Moreover, patient education and clinician awareness play a crucial role in minimizing the burden of iatrogenic hypertension. Future research should explore the long-term cardiovascular effects of drug-induced hypertension and optimize treatment algorithms to reduce its prevalence. Addressing this overlooked aspect of hypertension management can lead to improved cardiovascular outcomes and better patient care.

Keywords: Drug-related hypertensive risks, Hypertension, Pharmacogenomics

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INTRODUCTION

Hypertension, a major risk factor for cardiovascular diseases (CVDs), continues to be a growing global health challenge. While lifestyle modifications have been the cornerstone of prevention and treatment, drug-induced hypertension (DIH) is increasingly recognized as a significant contributor to elevated blood pressure. Pharmacological agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, oral contraceptives, and psychotropic medications, can lead to or exacerbate hypertension, thus complicating the management of patients with pre-existing conditions.[1,2] The rise of polypharmacy, particularly among elderly individuals, further increases the risk of iatrogenic hypertension.[3] Accurate diagnosis, patient education, and tailored treatment strategies are essential to mitigate these risks. Moreover, advances in pharmacogenomics offer promising avenues for personalized medicine, which could improve treatment outcomes and reduce adverse drug reactions.[4] As hypertension treatment continues to evolve, there is a critical need for more pharmacovigilance studies and the development of safer therapeutic alternatives. This review aims to explore the impact of drugs and medical interventions in the pathogenesis of hypertension and highlight future research directions.

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Pathophysiology of Non-Lifestyle-Related Hypertension

Non-lifestyle-related hypertension, encompassing drug-induced and iatrogenic hypertension, arises from various pharmacological agents and medical interventions that disrupt normal blood pressure regulation. The pathophysiology involves multiple mechanisms, including increased sodium and water retention, heightened sympathetic nervous system activity, and alterations in vascular tone. Certain medications, such as NSAIDs, corticosteroids, and oral

contraceptives, can induce hypertension by promoting renal sodium retention, leading to expanded extracellular fluid volume and elevated blood pressure. Additionally, some drugs may activate the renin-angiotensin-aldosterone system (RAAS), further contributing to increased vascular resistance and hypertension.[5]

Iatrogenic hypertension can result from medical procedures or interventions that inadvertently affect blood pressure control. For instance, certain surgical procedures or use of specific medical devices may lead to sympathetic nervous system activation or vascular endothelial dysfunction, culminating in elevated blood pressure.[6] A bioinformatic analysis identified numerous human genes related to blood pressure regulation, highlighting the complex interplay between various drug targets and hypertensive responses. This complexity underscores the importance of understanding individual patient susceptibilities when prescribing medications known to influence blood pressure.[7]

In summary, non-lifestyle-related hypertension is a multifaceted condition resulting from diverse pharmacological and iatrogenic factors. A comprehensive understanding of the underlying pathophysiological mechanisms is essential for healthcare providers to prevent, identify, and effectively manage this form of hypertension.

Drug-Induced Hypertension: A Silent Culprit

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are widely used for their analgesic and anti-inflammatory properties. However, their impact on blood pressure regulation is a significant concern. NSAIDs inhibit cyclooxygenase enzymes, leading to reduced prostaglandin synthesis. Prostaglandins play a crucial role in vasodilation and sodium excretion; thus, their inhibition can result in sodium retention and increased vascular resistance, contributing to elevated blood pressure. Clinical studies have demonstrated that NSAID use can disrupt blood pressure control in hypertensive patients, increasing the risk of cardiovascular events. A retrospective cohort study observed that incident NSAID use was associated with significant increases in systolic blood pressure among patients with hypertension. Given these findings, healthcare providers must monitor blood pressure in patients prescribed NSAIDs, especially those with pre-existing hypertension or cardiovascular risk factors. Alternative pain management strategies should be considered to mitigate potential adverse effects on blood pressure.[8-10]

Corticosteroids and Immuno-suppressants

Corticosteroids, such as prednisone, are potent anti-inflammatory and immunosuppressive agents widely used in managing various inflammatory and autoimmune conditions. However, their use is associated with several metabolic side effects, including the development of hypertension. The hypertensive effect of corticosteroids is primarily due to sodium retention and increased systemic vascular resistance.[11] A population-based cohort study analyzing electronic health records from 389 practices in England during 1998–2017 found that oral glucocorticoid use was associated with an increased incidence of hypertension in adults with chronic inflammatory diseases. Additionally, long-term corticosteroid therapy can lead to other metabolic complications such as osteoporosis, dyslipidemia, and insulin resistance. Given these risks, healthcare providers must monitor blood pressure and other metabolic parameters in patients receiving corticosteroid therapy, especially those with pre-existing cardiovascular risk factors.[12,13]

Oral Contraceptives and Hormonal Therapies

Oral contraceptives (OCs), particularly those containing estrogen, have been associated with elevated blood pressure. The estrogen component is believed to activate the renin-angiotensin-aldosterone system, leading to an increased sodium retention and vascular resistance, thereby raising blood pressure. A study reported that even low-dose estrogen in OCs can induce hypertension through this mechanism. Additionally, early epidemiologic studies using high-dose estrogen found mean elevations in blood pressure of 3 to 6 mmHg systolic and 2 to 5 mmHg diastolic, with approximately 5% of women developing new hypertension. Given these risks, healthcare providers must monitor blood pressure in women using OCs, especially those with pre-existing hypertension or other cardiovascular risk factors.[14,15]

Decongestants and Sympathomimetics

Decongestants, such as pseudoephedrine and phenylephrine, are commonly used to alleviate nasal congestion by constricting blood vessels in the nasal passages. However, their sympathomimetic properties can lead to increased blood pressure, posing risks for individuals with hypertension.[16] A meta-analysis indicated that pseudoephedrine at recommended doses had a minimal effect on systolic and diastolic blood pressure in healthy individuals and those with controlled hypertension. However, higher doses and immediate-release formulations were associated with more pronounced cardiovascular effects. Given these potential effects, healthcare providers should exercise caution when recommending decongestants to patients with hypertension. Alternative treatments, such as saline nasal sprays or antihistamines without decongestant properties, may be preferable to mitigate cardiovascular risks.[17,18]

Antidepressants and Psychotropic Medications

Antidepressants and psychotropic medications can influence blood pressure through various mechanisms. Selective serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, have been associated with dose-dependent increases in blood pressure, particularly at higher doses. A meta-analysis indicated that venlafaxine at doses ≥300 mg/day was linked to significant systolic and diastolic blood pressure elevations.[19,20]

Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) can also elevate blood pressure, primarily due to their anticholinergic effects and potential to cause orthostatic hypotension. Additionally, certain antipsychotic medications may contribute to hypertension through metabolic pathways, including weight gain and insulin resistance. Given these potential effects, healthcare providers should monitor blood pressure in patients prescribed these medications, especially those with preexisting hypertension or cardiovascular risk factors. Adjusting the medication regimen or implementing lifestyle modifications may be necessary to mitigate cardiovascular risks.[21,22]

Chemotherapeutic and Targeted Cancer Drugs

Chemotherapeutic agents, particularly angiogenesis inhibitors, are associated with hypertension. These agents, including bevacizumab

and tyrosine kinase inhibitors like sunitinib, can elevate blood pressure by inhibiting vascular endothelial growth factor (VEGF), leading to endothelial dysfunction and increased vascular resistance. A systematic review highlighted that hypertension is a common side effect of these therapies, with varying incidence rates depending on the specific agent used. The pathogenesis involves VEGF inhibition, resulting in endothelial cell apoptosis, reduced nitric oxide production, and increased endothelin-1 levels, all contributing to vasoconstriction and elevated blood pressure. Additionally, hypertension in cancer patients undergoing targeted therapy has been linked to improved treatment outcomes, suggesting a potential pharmaco-dynamic biomarker for therapy efficacy.

Given these associations, it is crucial for healthcare providers to monitor blood pressure in patients receiving chemotherapeutic and targeted cancer drugs. Early detection and management of hypertension can help mitigate cardiovascular risks and optimize cancer treatment outcomes.[23,24]

Mechanisms of Drug-Induced Hypertension

Drug-induced hypertension arises from various mechanisms, including sodium and fluid retention, activation of the RAAS, and alterations in vascular tone. Medications such as corticosteroids can cause sodium retention, leading to fluid retention and increased blood pressure. Other drugs may activate the RAAS, resulting in vasoconstriction and elevated blood pressure. Additionally, certain medications can directly affect vascular tone, contributing to hypertension. Recognizing these mechanisms is crucial for identifying and managing drug-induced hypertension.[25,26]

Iatrogenic Hypertension: Medical Interventions as a Risk Factor

Iatrogenic hypertension refers to the elevated blood pressure resulting from medical treatments, such as medications or procedures. Several drug classes contribute to iatrogenic hypertension, including corticosteroids, NSAIDs, and decongestants, which induce sodium retention and increased vascular resistance.[27] Angiotensin-converting enzyme inhibitors and certain chemotherapeutic agents can also elevate blood pressure through mechanisms such as vascular dysfunction and fluid retention. In addition to pharmacological factors, medical procedures, such as renal biopsies and other invasive treatments, can lead to hypertension by causing renal compression or activating the renin-angiotensin-aldosterone system. It is crucial to monitor blood pressure regularly in patients undergoing these interventions, as unmanaged hypertension can significantly increase the risk of cardiovascular events.[28-30]

Special Populations at Risk

Certain populations are at higher risk for developing hypertension due to genetic, environmental, and socioeconomic factors. African Americans, for example, have a higher prevalence of hypertension compared to other racial groups, with a greater tendency for more severe disease and complications, such as stroke and heart failure. Older adults are particularly susceptible due to age-related changes like arterial stiffness and increased vascular resistance.[1,2] Obesity is another significant risk factor, contributing to higher blood pressure through mechanisms such as increased cardiac output and resistance. Pregnant women can also develop hypertension, particularly preeclampsia, which poses risks to both mother and child.[31,32] Children and adolescents, particularly those who are overweight, are increasingly diagnosed with hypertension, often linked to lifestyle factors such as poor diet and lack of exercise. Early detection and tailored interventions are key to reducing hypertension risks in these special populations.[33]

Diagnostic Challenges and Clinical Implications

Hypertension remains a complex condition to diagnose due to its often asymptomatic nature, particularly in its early stages. The clinical challenge lies in the accurate measurement of blood pressure, as factors like white coat syndrome and masked hypertension can lead to misdiagnosis. Furthermore, there is a lack of consensus on the optimal frequency and methods for screening, especially in high-risk populations such as those with diabetes, obesity, and a family history of hypertension.[34] Ambulatory blood pressure monitoring (ABPM) has emerged as a more reliable diagnostic tool for detecting hypertension, allowing for 24-hour monitoring and better identification of variations in blood pressure throughout the day. Additionally, understanding the underlying mechanisms, such as genetic predisposition, metabolic syndrome, and endothelial dysfunction, is crucial for proper management. Failure to adequately diagnose and treat hypertension increases the risk of cardiovascular events, renal disease, and stroke.[35-38]

Management Strategies and Preventive Approaches

Effective management of hypertension includes adjusting or substituting medications when side effects or ineffectiveness arise. In cases of drug-induced hypertension, alternative medications such as calcium channel blockers or beta-blockers may be considered. Pharmacogenomics plays a crucial role in predicting individual responses to antihypertensive drugs, enabling personalized treatment plans for better efficacy and fewer adverse effects.[2,4] Non-pharmacological interventions, such as dietary changes, exercise, and stress reduction techniques, are integral in managing iatrogenic hypertension, especially in elderly patients. Additionally, patient education and awareness are vital for improving medication adherence and promoting lifestyle changes, ultimately reducing the long-term cardiovascular risk associated with hypertension.[39,40]

Future Directions and Research Gaps

Future research in hypertension management should focus on pharmacovigilance to better understand adverse drug reactions and identify safer therapeutic options. While current medications are effective, their long-term side effects and interactions remain a concern, highlighting the need for more comprehensive safety studies. Developing safer therapeutic alternatives is essential, particularly for patients with comorbidities or drug-induced hypertension.[41-43] Research into novel drug classes and the role of natural compounds in hypertension management could offer promising solutions. Additionally, personalized medicine approaches, including the use of pharmacogenomics, hold great potential in tailoring treatment plans based on genetic predisposition, improving efficacy and reducing adverse effects.

CONCLUSION

In conclusion, drug-induced and iatrogenic hypertension poses significant challenges in the management of hypertensive patients, complicating diagnosis and treatment. A comprehensive approach that includes accurate diagnosis, patient education, and personalized treatment strategies is crucial to mitigate these risks. Advancements in pharmacogenomics offer promising opportunities for optimizing antihypertensive therapy, reducing adverse drug reactions, and improving patient outcomes. Additionally, there is an urgent need for more pharmacovigilance studies to better understand the safety profiles of commonly prescribed medications. Future research should focus on safer therapeutic alternatives and tailored management plans to address the evolving landscape of hypertension treatment.

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