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REVIEW ARTICLE

Interaction between primary hyperaldosteronism and blood pressure regulation

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ABSTRACT

Introduction: Primary hyperaldosteronism (PA) is the most common endocrine cause of secondary hypertension, with significant implications for cardiovascular and renal risk.
Objective: To evaluate the interaction between primary hyperaldosteronism and blood pressure regulation.
Methods: A documentary review was conducted using meta-search engines such as Epistemonikos and Tripdatabase, as well as databases including Medline, Scopus, and Cochrane. MeSH terms related to hyperaldosteronism, hypertension, and pathophysiology were applied. Studies published between 2018 and 2023 were included, prioritizing systematic reviews, clinical guidelines, and meta-analyses. Outdated or scientifically unsound works were excluded. Analysis was performed through critical synthesis of diagnostic algorithms and therapeutic strategies.
Development: Primary hyperaldosteronism is characterized by autonomous aldosterone secretion, renin suppression, and sodium retention. Its prevalence ranges from 5 % to 20 % among hypertensive patients, and is higher in resistant cases. Main subtypes include aldosterone-producing adenoma and bilateral adrenal hyperplasia. Diagnosis relies on the aldosterone-to-renin ratio (ARR), confirmatory tests, and imaging or adrenal venous sampling. Treatment includes laparoscopic adrenalectomy for unilateral forms and mineralocorticoid receptor antagonists for bilateral cases. Evidence shows that timely intervention reduces cardiovascular, metabolic, and renal complications.
Conclusions: Primary hyperaldosteronism is a curable but underdiagnosed cause of hypertension. Early detection and subtype differentiation are essential to guide effective therapies. Appropriate management improves blood pressure control and reduces cardiovascular and metabolic risks, providing a solid foundation to optimize clinical practice and patient quality of life.

Keywords: CARDIOVASCULAR DISEASES; HYPERALDOSTERONISM; HYPERTENSION.

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INTRODUCTION

Primary hyperaldosteronism (PA) is a disorder characterized by inappropriate elevation of aldosterone relative to serum sodium levels, autonomous aldosterone production independent of the renin-angiotensin-aldosterone system (RAAS), and failure of aldosterone suppression in response to sodium loading. This inappropriate elevation causes hypertension, cardiovascular damage, sodium retention, renin suppression, and increased potassium excretion, which—if persistent—can lead to hypokalemia.[1]

In 1953, American endocrinologist Jerome W. Conn described a young patient who presented with intermittent muscle spasms, weakness, and paralysis lasting approximately seven years. Suspecting that the symptoms resulted from hypersecretion of a salt-retaining corticosteroid (aldosterone), Dr. Conn performed urine analyses that revealed extremely high aldosterone levels, supporting his diagnosis. The patient underwent surgical exploration of the adrenal glands, revealing a unilateral adrenal tumor. Following tumor removal, her symptoms resolved and metabolic abnormalities normalized—a phenomenon that led to the characterization of a new clinical entity known as "Conn's syndrome," now recognized as primary hyperaldosteronism (PA).[2]

Identifying this condition is critically important, as PA remains a frequent yet curable form of hypertension affecting millions worldwide—and yet it is an overlooked disease with low diagnostic rates. When unrecognized, it leads to cardiovascular and renal complications through mechanisms independent of those mediated by hypertension alone. Clinicians often consider PA only when no other explanation exists for a patient's elevated, refractory blood pressure, resulting in increased morbidity and mortality due to heightened cardiovascular risk compared to hypertensive patients without PA. Given these considerations, this review was conducted to evaluate the interaction between PA and blood pressure regulation.

METHODS

A descriptive systematic review was carried out to evaluate diagnostic algorithms and management strategies for PA. The search period was limited to 2018–2023.

Meta-search engines such as Epistemonikos and Tripdatabase were consulted, along with high-impact biomedical databases: Medline, ScienceDirect, Scopus, Cochrane Library, Web of Science, and Google Scholar. Grey literature (clinical guidelines and case reports) was also included. The PICO framework and MeSH terms were applied: "primary hyperaldosteronism," "Conn syndrome," "secondary hypertension," "diagnosis," "treatment," using Boolean operators (AND, OR) to develop the search algorithm.

Inclusion and exclusion criteria

Studies published in the last five years with verifiable and clinically relevant information were included. Works prior to 2018, non-scientific publications, and documents from blogs or unvalidated sources were excluded. Articles in English, Spanish, and Portuguese were considered.

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Selection process
The initial search yielded 50 records. After applying exclusion criteria (n=32), 18 articles were selected for final analysis. The process was represented using a PRISMA diagram illustrating identification, screening, eligibility, and inclusion phases. Variables extracted included author, year, cohort type, PA prevalence, clinical characteristics, and diagnostic outcomes. A qualitative synthesis was performed, and prevalences were compared using descriptive tables.

DEVELOPMENT

PA, also known as Conn's syndrome, is a common, curable form of arterial hypertension characterized by low plasma renin and high plasma aldosterone levels.[3] Three cardinal pathophysiological features define PA:[4]

- Suppression of basal renin secretion: PA involves extracellular fluid volume expansion (effective arterial blood volume expansion), leading to renin suppression and consequently reduced angiotensin II generation.
- Inability to normally stimulate renin secretion: The degree of renin suppression due to volume expansion from excess mineralocorticoid activity can be quantified by an inadequate renin increase in response to physiological stimuli—including upright posture, sodium/volume contraction via diuresis or dietary sodium restriction, or angiotensin-converting enzyme inhibition. PA patients show only a moderate renin rise under these stimuli.
- Inappropriate and non-suppressible aldosterone production: Aldosterone production in PA is renin-independent and remains unsuppressed despite volume expansion, angiotensin II inhibition, and hypokalemia.

The true prevalence of PA remains unclear. It has been estimated at 1 % among hypertensive populations when potassium measurement is used for screening; however, only 30 % of PA patients present with hypokalemia, implying many cases occur with normokalemia—thus underestimating prevalence. Studies report PA prevalence of 10 % in hypertensive patients and 20 % in those with pharmacotherapy-resistant hypertension.[3,5]

The introduction of the aldosterone-to-renin ratio (ARR) as a screening test and its application to increasingly broad hypertensive populations has led to a notable rise in PA detection. Variability in prevalence rates stems from differences in diagnostic methods, cutoff values, and the variable selectivity of examined cohorts (Table 1).[6]

Table 1. PA prevalence across patient cohorts.

Patient cohort	PA prevalence
Hypertensives in primary care	3,2-12,7 % (median: 5,9 %)
Hypertensives referred to tertiary centers	0,7-21,9 % (median: 7,2 %)
Stage 1 hypertension	3,9-15,7 %
Stage 2 hypertension	9,7-21,6 %
Stage 3 hypertension	11,8-19 %
Resistant hypertension	20,5-22 %
Hypertension with hypokalemia	28,1 %
Adrenal incidentaloma	1,6-4,3 %
Hypertension with atrial fibrillation	42,5 %
Hypertension with diabetes mellitus	11,3-19,1 %

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The most common etiologies are:[7,8]
• Aldosterone-producing adenoma (APA): ~30 % of cases
• Idiopathic bilateral adrenal hyperplasia (IHA): ~60 %
• Unilateral primary adrenal hyperplasia: ~2 %
• Adrenocortical carcinoma: <1 %
• Familial hyperaldosteronism (FH)
• Ectopic aldosterone-producing adenoma: <0,1 %

Familial hyperaldosteronism is typically diagnosed when PA is discovered before age 20 or when multiple family members are affected. Four familial forms exist (Table 2).[7]

Table 2. Types of familial PA.

Type	Alternate name	Germline mutation
FH type 1	Glucocorticoid-remediable aldosteronism	Chimeric CYP11B1/CYP11B2 gene; ACTH—not angiotensin II—becomes the main regulator of aldosterone secretion
FH type 2	Non-glucocorticoid-suppressible hyperaldosteronism	CLCN2 chloride channel mutation; autosomal dominant
FH type 3		KCNJ5 gene mutation; patients often present with refractory hypertension before age 7 and massive bilateral hyperplasia, requiring bilateral adrenalectomy
FH type 4		CACNA1H gene mutation; autosomal dominant inheritance

The adrenal glands are organs composed of two structures: the adrenal cortex and the adrenal medulla. The adrenal cortex is further subdivided into three zones: the zona glomerulosa, responsible for the production of mineralocorticoids (aldosterone); the zona fasciculata, which produces glucocorticoids (cortisol, corticosterone, and cortisone); and the zona reticularis, which produces gonadocorticoids (androgens and estrogens).[9]

PA results from unregulated, autonomous aldosterone production by the adrenal cortex. Normally, aldosterone is regulated by the RAAS: in response to reduced renal perfusion, the kidney releases renin, which—via hepatic angiotensinogen—leads to angiotensin II formation. Angiotensin II indirectly increases effective circulating volume by stimulating adrenal aldosterone production, which promotes renal sodium and water reabsorption.[2]

In PA, excess aldosterone is autonomously produced due to APA or IHA and is not regulated by RAAS. Although the exact causes are unknown, several mutations in aldosterone-regulating genes (KCNJ5, CACNA1D, ATP1A1, ATP2B3, CTNNB1) increase susceptibility. These genetic alterations affect zona glomerulosa cells, promoting overexpression of CYP11B2—the gene encoding aldosterone synthase, a key enzyme in aldosterone biosynthesis. While IHA pathophysiology is less understood than APA, a recent study of adrenal specimens from IHA patients suggests that clusters of aldosterone-producing cells with CACNA1D mutations may precede IHA development.[10]

Autonomous, non-suppressible, renin-independent aldosterone secretion is an underdiagnosed cause of treatment-resistant hypertension. The classic PA triad includes: refractory hypertension despite optimal therapy, hypokalemia, and metabolic alkalosis. Current evidence indicates only 37 % of patients present with hypokalemia. The most common—and sometimes sole—clinical

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manifestation is pharmacologically resistant hypertension, defined as blood pressure >140/90 mmHg uncontrolled by three antihypertensives (including a diuretic). If hypokalemia is present, accompanying symptoms include fatigue, muscle weakness, paralytic ileus, and cramps. With potassium <2 mEq/L, patients may exhibit ascending flaccid facial paralysis and respiratory difficulty—though this presentation is rare.[11]

It is important to note that hypertension and hypokalemia are not fundamental features of PA but rather dependent manifestations that occur when intra-arterial volume expansion exceeds vascular capacity to maintain normal blood pressure and/or when distal nephron sodium delivery accelerates sodium-potassium exchange and kaliuresis beyond potassium intake thresholds. Thus, the more severe and prolonged the exposure to renin-independent aldosterone production and sodium retention, the greater the risk of severe hypertension and hypokalemia.[4]

PA is frequently overlooked because clinicians seek other medical explanations first. By the time PA is investigated, patients are typically aged 30–60 and present with marked hypokalemia, muscle cramps, and other manifestations. Given its prevalence and cardiovascular morbidity impact, early PA detection is crucial. The following patient groups should be screened for PA:[5,7]

- Hypertension diagnosed before age 40
- Severe hypertension at any age
- Hypertension uncontrolled with ≥3 medications
- Hypertension with hypokalemia
- Hypertension with adrenal incidentaloma
- First-degree hypertensive relatives of PA patients
- Hypertension with family history of early-onset hypertension or stroke before age 40
- Atrial fibrillation
- Obstructive sleep apnea (OSA), metabolic syndrome, or obesity

According to Endocrine Society guidelines, PA diagnosis should follow a three-step approach in most cases:[12]
- Screening (ARR)
- Confirmatory/exclusion testing
- Subtype diagnosis to distinguish unilateral from bilateral disease

PA diagnosis is based on demonstrating low/undetectable renin and inappropriately high aldosterone. Current guidelines recommend screening for PA via ARR in patients with severe hypertension or hypertension accompanied by hypokalemia, sleep apnea, or adrenal mass. A positive ARR warrants definitive confirmation through dynamic reference tests.[13,14]

The ARR is the mathematical ratio of plasma aldosterone concentration to plasma renin activity. The characteristic alteration is elevated aldosterone with low/suppressed renin. Cutoff values for a positive ARR range from 20–40 ng/dL per ng/mL/h, with 30 being most commonly used. However, the Argentine Society of Endocrinology and Metabolism established a cutoff of 36 ng/mL/h.[5]

Due to the ARR's low specificity, confirmatory testing is necessary. The Endocrine Society recommends four procedures: fludrocortisone suppression test (FST), oral sodium loading test (SLT), saline infusion test (SIT), and captopril challenge test (CCT). No sufficient evidence currently favors one procedure over another.[12]

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Subtype diagnosis to distinguish unilateral from bilateral disease
These tests are performed after PA confirmation to differentiate between bilateral adrenal hyperplasia and aldosterone-producing adenoma. Abdominal computed tomography (CT) provides adrenal anatomical information to detect adenomas or thickening (hyperplasia). Adrenal venous sampling (AVS) is the most effective method for PA subtyping.[5]

Treatment
Surgical adrenalectomy or mineralocorticoid receptor antagonist (MRA) therapy are recommended for PA. Therapeutic goals include blood pressure normalization and hypokalemia correction. However, recent studies show PA patients have higher risks of cardiovascular complications (stroke, coronary artery disease, atrial fibrillation, heart failure, type 2 diabetes, left ventricular hypertrophy). Thus, treatment must not only control blood pressure but also reduce aldosterone production or effectively block mineralocorticoid receptors.[15]

Unilateral laparoscopic adrenalectomy
For unilateral PA, adrenalectomy is the recommended treatment, as it eliminates the source of autonomous aldosterone excess. Adrenalectomy is now typically performed laparoscopically—rather than open—resulting in lower perioperative complication rates and shorter hospital stays. Clinical benefits include cure or significant improvement of hypertension, reduced cardiovascular and renal disease risk, lower diabetes incidence, decreased mortality, and improved quality of life.[16]

Mineralocorticoid receptor antagonists (MRAs)
MRAs are first-line for bilateral PA. Spironolactone is the initial drug of choice, effective for blood pressure control and end-organ protection. Its natriuretic effect persists for days after discontinuation; thus, it should be withheld for at least six weeks in patients requiring blood pressure reassessment. Dosing starts at 12,5–25 mg/day, up to 400 mg/day. Taking it with a high-fat meal significantly improves oral bioavailability. Side effects are primarily feminizing (due to androgen and progesterone receptor blockade); adding a low-dose thiazide diuretic can mitigate them.[1,15,17]

Eplerenone is a second option, with fewer anti-androgenic effects as it minimally antagonizes androgen and progesterone receptors. It is 25 % less potent than spironolactone and has a shorter half-life (6–8 hours), requiring twice-daily dosing versus once-daily for spironolactone.[1]

A recent meta-analysis of 31 studies (3,838 PA patients vs. 9,284 with essential hypertension) found APA and IHA patients had higher risks of stroke, coronary artery disease, atrial fibrillation, and heart failure. PA diagnosis also increased risks of diabetes, metabolic syndrome, and left ventricular hypertrophy—indicating aldosterone-specific cardiovascular toxicity beyond hypertension.[8]

A 2020 case-control study followed PA patients matched by age, sex, and hypertension severity. PA patients had 6,5× higher risk of non-fatal myocardial infarction, 12,1× higher risk of atrial fibrillation, 4,2× higher stroke risk, and 3,7× higher type 2 diabetes risk compared to essential hypertension subjects.[18]

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CONCLUSIONS

PA is considered the leading cause of secondary arterial hypertension, yet it remains underdiagnosed due to limited awareness—leading many hypertensive patients to exhibit resistance to standard treatment and increased cardiovascular, metabolic, renal, and cerebrovascular risk. Therefore, screening hypertensive patients, timely PA detection, and lateralization are crucial to guide appropriate pharmacological or surgical treatment—ensuring blood pressure control, reduced cardiovascular and renal risk, prevention of diabetes mellitus, and improved patient quality of life.

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