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Review
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Low renin hypertension – an endocrine perspective

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Abstract

Approximately 30% of hypertensive patients have low renin concentrations. Measurement of renin and aldosterone is the key to diagnosing low-renin hypertension and confirming the phenotype. It occurs because of inherited genetic syndromes, acquired somatic mutations and endogenous and exogenous factors. Therapy depends on the subtype of low-renin hypertension. Primary aldosteronism is the leading cause of secondary hypertension worldwide and is the main form of low-renin hypertension. Its harmful effects outstrip those due to blood pressure elevation alone. Surgical intervention may sometimes result in a complete cure, obviating the need for lifelong antihypertensive treatment. This review will discuss the main factors responsible for an accurate differential diagnosis of low-renin hypertension.

Keywords: renin, low renin, aldosterone, aldosterone renin ratio, hypertension, resistant hypertension.

Introduction

Hypertension is a common disorder and one of the leading causes of overall morbidity and mortality related to its impact on the cardiovascular and renal systems [1, 2].

Up to 10% of the total cases of hypertension in adults have secondary hypertension, indicating an underlying and potentially reversible cause [3]. The prevalence of secondary hypertension varies with age and is most prevalent in younger persons accounting for 30% of cases of hypertension in those 18 to 40 years of age. The secondary causes of hypertension include but are not limited to renal causes, such as renal parenchymal or renovascular disease, vascular abnormalities, certain medications or drugs, states of high cardiac output and endocrine disorders. Hyperaldosteronism represents the most common endocrine disorder causing secondary hypertension, responsible for up to 5% of the hypertensive population in primary care [4].

The renin-angiotensin-aldosterone system (RAAS) is a critical regulator of volume, sodium and potassium homeostasis. Based on renin level, hypertensive patients can be classified as low-, normal- or high-renin hypertension [5].

Low renin hypertension comprises 30% of the total hypertensive patient, with essential hypertension, primary aldosteronism and Liddle syndrome being the most common causes [6].

Renin secretion, stimulated by renal hypofiltration or activation of the sympathetic nervous system, generates angiotensin II, a potent vascular pressor, and regulates aldosterone production in adrenal zona-glomerulosa [7, 8]. When renal hypofiltration is sensed, this hormonal system is activated via the secretion of renin, responsible for generating angiotensin I, which is subsequently modified to

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generate angiotensin II. Angiotensin II controls aldosterone secretion by acting on the key enzyme of his synthesis, CYP11B2 (aldosterone synthase). Angiotensin-independent molecular mechanisms for aldosterone secretion are potassium and, to a lesser extent, adrenocorticotropic hormone (ACTH), which is also known to stimulate the release of aldosterone. When evaluating low-renin hypertension, aldosterone measurement is the cornerstone for the differential diagnostic workup, with primary aldosteronism (PA) being the most prevalent cause of low-renin hypertension [2, 5, 8, 9].

Low renin-high plasma aldosterone hypertension

Autonomous aldosterone secretion from the glomerulosa zone, either of one or both adrenals, independent of its main regulators, angiotensin II and high potassium levels that is not suppressible by sodium loading defines the primary aldosteronism (PA) [10, 11]. Aldosterone binds mineralocorticoid receptors (MR) in the kidneys, the primary target organ. Endogenous glucocorticoids can also activate MR. The specificity of the aldosterone effect on the MR is offered mainly by the 11-β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which inactivates the mineralocorticoid action of circulating cortisol.

Aldosterone binding to his receptor increases the expression of epithelial sodium channels (ENaC) in the luminal membrane of the principal cells in the collecting tubules and, to a lesser extent, the expression of the thiazide-sensitive Na-Cl symporter in the distal convoluted tubule. Overall, these renal actions of aldosterone promote sodium reabsorption and potassium elimination, with compensatory suppression of renin and angiotensin II [12].

Primary aldosteronism has a prevalence of 5% to 30%, depending on the severity of the hypertensive group where it is reported [13, 14]. In most cases, PA is sporadic, with the underlying cause represented either by bilateral adrenal hyperplasia (BAH) in 60% of the subjects or an aldosterone-producing adenoma (APA) in 30% of the cases [15–17]. Rare causes of primary hyperaldosteronism (below 1%) include adrenal carcinoma and familial hyperaldosteronism (type I-IV), genetic disorders typically diagnosed at less than 20 years of age.

The treatment goal in patients with primary aldosteronism is to prevent the morbidity and fatality associated with hypertension, hypokalemia, nephrotoxicity and cardiovascular damage [12]. A large meta-analysis found excessive morbidity, including stroke (odds ratio [OR] 2·58), coronary artery disease (OR 1·77), heart failure (OR 2·05), and atrial fibrillation (OR 3·52), when compared patients with primary aldosteronism, independent of the subtype, with matched patients with essential hypertension and similar risk profile as a control group [18, 19].

There is a continuum of renin-independent aldosterone production that parallels the severity of hypertension with biochemical demonstrated PA described in normotensive patients [4]. Current guidelines indicate screening for PA among populations where the prevalence has been reported to be the highest (Table 1) [8, 20–25]. The normalization of blood pressure should not be the only goal of treatment; the normalization of circulating aldosterone or mineralocorticoid receptor blockade should be part of the management plan for all patients with primary aldosteronism.

As a case-detection test, the plasma aldosterone to renin ratio (ARR) is the most recommended screening test for primary hyperaldosteronism. It was initially described as a ratio of aldosterone concentration (AC) and plasma renin activity (PRA) measured by radioimmunoassay (RIA).

The traditional enzymatic RIA for plasma renin activity (PRA) quantifies angiotensin I generated as a function of time [26]. Whilst PRA has high analytical sensitivity at small renin concentrations, it has the disadvantage of being manual, time-consuming and producing radioactive waste. It has been progressively replaced with direct plasma renin concentration (DRC) measurement using chemiluminescent methods (CLIA) or liquid chromatography with tandem mass spectrometry detection (LC-MS). The newer methods are a reliable alternative giving comparable results [27, 28]. The conversion factor of PRA (1 ng/mL/h) to DRC (mU/liter) is assay dependent, and an acceptable value stated in the guideline is 8.2 (range 8.2–12) [29].

Reliable diagnosis of PA, including case-finding, case-confirmation and subtype differentiation tests, depends on the accuracy and reproducibility of hormonal assays.

The potentially confounding factors for the measurements of ARR should be considered when the results of ARR are interpreted [8, 30].

As a screening test, sensitivity is essential, so ARR should be done in a setting that lowers the rate of false negative results. Pharmacological factors (Table 2) and pathologic or physiologic conditions are interactive factors for the ARR that can modify the test performance when a specific cutoff is used.

Agents that markedly affect ARR and a four weeks-washout period are recommended:

- Mineralocorticoid receptor antagonists (spironolactone, eplerenone);
- Potassium-sparing (amiloride) and wasting diuretics;
- Liquorice ingestion – due to glycyrrhizin acid that inhibits the action of 11β HSD2 to inactivate mineralocorticoid action of cortisol (grapefruit, sweetener, chewing tobacco, cough mixtures and some herbal medicines).

Table 1. Patient groups in whom screening for primary aldosteronism (PA) is recommended.

Patient group	Remarks
Blood pressure greater than 150/100 mmHg during three consecutive measurements, on different days.	Prevalence of PA increases as the stage of hypertension increases; the reported prevalence of PA is 15.7%, 21.6% and 29.1%, corresponding for stages 1, 2, and resistant hypertension, respectively [4, 14, 20–23].
Patients resistant to conventional antihypertensive medication defined as BP >140/100 mmHg despite the use of three agents, including a diuretic.	
Controlled blood pressure despite using 4 or more antihypertensive medications.	
Hypertension associated with spontaneous or diuretic-induced hypokalaemia (potassium <3.5 mmol/L, regardless of thiazide use).	Low potassium is present in 10–40% [8].
Hypertension and adrenal incidentaloma.	Screening for primary hyperaldosteronism in hypertensive patients with incidental found adrenal mass is 2% (range, 1.1–10%).
First-degree relative of a patient with primary aldosteronism and hypertension.	Familial hyperaldosteronism (FH): FH type I-glucocorticoid- remediable; FH II-IV- germline mutations.
Hypertension and family history of hypertension or stroke at a young age (before 40).	
Hypertension and sleep apnea.	34% have obstructive sleep apnea [24, 25].

Posture and time of the day: blood sample collection is recommended morning after patients have been out of bed for 2h, usually after they have been seated for 5–15 minutes; samples collection after overnight recumbency can increase ARR by 50% due to lower renin levels and the circadian aldosterone ACTH-dependency.

Low dietary salt intake increases the renin concentration, so patients are encouraged to have an unrestricted sodium diet quantifiable as a urinary excretion for sodium more than 150 mmol/L.

The presence of hypokalemia induced a decrease in aldosterone concentration, and corrected plasma potassium with supplements to 4 mmol/L is urged. The demonstration of inappropriate kaliuresis, defined as urinary potassium above 30 mmol/L in the presence of low serum potassium, is expected in hyperaldosteronism.

Pregnancy, renovascular hypertension and malignant hypertension are other conditions that can lead to false negative results. At the same time, renal impairment, advancing age and the luteal phase of the menstrual cycle can produce false positive results.

The suppression of renin defined as PRA below 0.65 to 1 ng/mL/h (equivalent when measured as

Table 2. Medication that should be considered when interpreting test results for ARR.

Medication with net effect – an increase of the false positive results	
β-blockers central α2 agonists (clonidine, α methyldopa) α1-blockers NSAIDs and COX2 inhibitors Renin-inhibitors unfractionated heparin	To exclude FP results for ARR retest after two weeks of washout; lowering renin by β-blockers also lower angiotensin II and aldosterone, and thus FP due to β-blockers alone is uncommon; α1-blockers are considered to have a low impact on ARR and, therefore, are acceptable to use as an antihypertensive agent.
Medication with net effect – an increase of the false negative results by reducing the ARR	
ACE ARBs Calcium blockers	A washout period of 2 weeks is recommended because this medication can raise renin levels; when renin is suppressed, the test is valid; calcium blockers have a low impact on the renin level and are acceptable antihypertensive medication.

ARR – aldosterone: renin ratio; FP – false positive; FN – false negative; NSAIDs – Non-steroidal anti-inflammatory drugs; COX2 – cyclooxygenase-2; ACE – Angiotensin-converting-enzyme; ARBs – Angiotensin II receptor blockers.

DRC) is a biochemical requisite to support autonomous aldosterone secretion [31]. As the elevation of the aldosterone to renin ratio is highly dependent on renin level as a denominator factor, the most common culprit antihypertensive medication are those that raise the renin and lower ARR, affecting the sensibility as a screening test [8, 31–34].

In many cases, the patients are tested under antihypertensive medication with an effect on renin or aldosterone levels – that should be accounted for when the screening test results are interpreted [29, 35, 36].

ARR screening test for primary hyperaldosteronism gives a probability for the disease depending on ratio cutoffs. The optimal value to define a positive test for ARR is debated. The most widely used cutoff for ARR is at least 3.7 ng/dL per mU/L with an aldosterone level above 15 ng/dL (and less frequently 10 ng/dL). The higher values used for the ARR cutoff provide a higher probability for detecting an APA as the cause of PA and, thus, the possibility of surgical cure of the disease. Alternatively, more permissive screening criteria with suppressed renin in the context of non-suppressed aldosterone (6–9 ng/dL) and an ARR>2.4 ng/dL per mU/L are proposed to recognize milder forms of PA with earlier case detection. This will increase the proportion of false negative results and subsequent cost and invasiveness of the medical testing [8, 37, 38].

Confirmatory tests showing failure of aldosterone suppression by sodium/volume overload should follow a positive screening test.

Between 30 to 50% of patients with a positive screening test usually achieve suppressed aldosterone levels after a confirmatory test [39–41].

Further confirmatory tests are unnecessary for spontaneous hypokalemia, undetectable renin, plus a plasma aldosterone concentration above 15–20 ng/dL (550 pmol/litre). Suppressed plasma renin in patients receiving mineralocorticoid receptor antagonists should be a strong indicator of primary aldosteronism in these patients. When confirmatory testing is needed, a salt-loading test, either via oral salt in an outpatient setting or saline infusion in a hospital setting, should be performed. Alternative confirmatory tests that should be considered are the fludrocortisone suppression test, done with many adverse effects in a hypokalemic, hypertensive patient and the captopril challenge test, with equivocal results and a high frequency of false-negative results [2].

Once the diagnosis of AP is confirmed, an additional step is to locate and lateralize the source of excess aldosterone; subtyping the disease as a unilateral APA or bilateral adrenal hyperplasia has implications for therapeutic management.

Computed tomography (CT) scan has been proven to have similar results to magnetic resonance imaging (MRI) in identifying more than 5 mm adrenal nodules and is the first choice to eliminate the possibility of an adrenal carcinoma. The incidence of adrenal nodules rises from 2% at 40 years to 10% at 70 years, usually non-functional adrenal nodules[42, 43]. As a result, non-functional imaging cannot provide information about the source of hyperaldosteronism and additional detailed attempts at localization are need it for the surgical candidates.

Adrenal vein sampling (AVS) is considered the most reliable method to determine whether aldosterone production is unilateral or bilateral. AVS is only offered at a limited number of referral centers, making it relatively inaccessible. Moreover, the inability to obtain a good sample while trying to canulate the right adrenal vein of small size and difficulty to locate is a main limitation of the technic. Missed opportunities for adrenalectomy or non -AVS guided adrenalectomy often occur. Catheterization of the adrenal veins may not be necessary if there is a unilateral mass above 10 mm, with normal contralateral adrenal in a young patient with hypokalemia and high aldosterone levels [2, 43–45].

Low renin hypertension – low plasma aldosterone hypertension

Low renin and low aldosterone hypertension can be acquired or genetically determined. Several conditions should be considered in the differential diagnosis of the acquired forms.

The most common cause of low-renin low-aldosterone hypertension is represented by a high-sodium diet and drugs that reduce RAAS activation (β-blockers, centrally acting agents, nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors). The mechanism implicated in her development is volume expansion.

Licorice or carbenoxolone ingestion acts by inhibiting the 11β HSD type II, the enzyme that protects the MR from cortisol agonism by inactivating it to cortisone.

A reduction in nephrons with reduced sodium excretion and increased volume expansion (diabetic nephropathy, glomerulonephritis and aging) may also induce a low-renin and low aldosterone status [5, 6, 9, 33, 36, 46]. Hypertensive patients with suppressed renin levels are more likely to have sodium-volume-dependent hypertension. It has been suggested that they respond better to a low-sodium diet and drugs having a natriuretic effect [6, 47].

A rare form of acquired low- renin low aldosterone hypertension is Cushing's syndrome resulting in excess cortisol secretion. The autonomous cortisol secretion is driven by adrenocorticotropin hormone (ACTH) excess, usually a pituitary source and rarely an ectopic source in the context of a paraneoplastic syndrome or from an adrenal source, an adrenal adenoma and less common adrenal carci-

noma. Symptoms are dependent on the age and sex of the patient and are usually progressive and may present for several years before the diagnosis. Severe myopathy, easy bruising, mood disturbance, menstrual irregularities in women and, low libido and impotence in males, arrested growth in children are among the more specific clinical features. The mortality is six times greater than the general population due to the increased incidence of venous thromboembolism and infections [48–50].

Hypercortisolemia is associated with hypertension in 50% to 80% of adult cases and half of the children [51, 52]. Low renin hypertension is more likely in patients with ectopic Cushing syndrome, characterized by high cortisol excess. The 24-hour ambulatory blood pressure monitoring in autonomous cortisol secretion shows a non-dipping pattern by attenuation of the normal nocturnal decline correspondent to the loss of circadian nadir of cortisol at bedtime [53, 54].

There are several mechanisms of blood pressure elevation in Cushing's syndrome. Extremely high cortisol levels saturate the renal 11 beta-hydroxysteroid -dehydrogenase type-2 (11-beta HSD2), so it cannot convert all cortisol to cortisone. In healthy individuals, tissue-specific inactivation occurs, a mechanism that protects the mineralocorticoid receptor from activation by circulating cortisol, which carries the same affinity but much higher levels than aldosterone [49, 55]. This mechanism also explains the hypokalemia that is seen in patients with cortisol levels more than five times above the average range, usually in the context of ectopic Cushing Syndrome [56, 57].

At the vascular smooth muscle cells existence of 11 beta-hydroxysteroid -dehydrogenase type-1 (11-beta HSD1) converts inactive cortisone to cortisol with local effect enhanced sensitivity to vasoconstrictors as angiotensin II, renin and catecholamines, despite their physiologic levels. Decreased levels of endothelial vasodilators, including nitric oxide, prostacyclin and prostaglandin E2, are also involved in the pathogenesis of hypertension.

Some genetic disorders can be the culprit in low-renin low-aldosterone levels hypertension. Liddle syndrome is an autosomal dominant condition with variable penetrance caused by mutations in genes encoding epithelial sodium channel subunits (ENaC). This leads to constitutive activation of sodium transport independent of the mineralocorticoid effect in the distal nephron. It is responsible for 1% to 6% of the cases of low renin hypertension and responds to ENaC blockers (Amiloride, Triamterene) and a low sodium diet [58].

Congenital adrenal hyperplasia is caused by a mutation in genes involved in cortisol biosynthesis enzymes 21-hydroxylase deficiency is responsible for more than 90% of the disease. Atypical forms of congenital adrenal hyperplasia due to 11β-hydroxylase deficiency and 17α-hydroxylase deficiency can have the phenotype of low-renin hypertension. The reduced enzymatic activity for steroid 11β-hydroxylase responsible for the final step of cortisol synthesis in the adrenal zona fasciculata overproduces deoxycorticosterone (DOC) under increased ACTH stimulation due to the lack of negative cortisol feedback. DOC is a steroid with mineralocorticoid activity. The primary treatment is glucocorticoid replacement [59].

Glucocorticoid resistance syndrome is a familial disease caused by inactivating mutations of the glucocorticoid receptor gene (NR3C1). The classic phenotype accompanies the biochemical pattern of increased ACTH and cortisol with low renin hypertension, hypokalemia, and clinical androgen excess in addition to chronic fatigue and malaise in the context of a relative glucocorticoid deficiency [60].

The syndrome of apparent mineralocorticoid excess (AME) is an autosomal recessive condition due to loss of function mutations in 11β HSD2. The treatment is low-dose Dexamethasone to suppress endogenous cortisol production, MR antagonist and, in extreme cases, renal transplantation. Milder phenotypes of AME due to mutations responsible for partial 11βHSD2 activity have been described in recent years as responsible for a proportion of low renin hypertension [12, 61, 62].

Conclusion

Plasma renin level can be used to classify hypertension. A phenotype of low renin hypertension encompasses a broad spectrum of disorders with low or undetectable renin concentration. Identifying a subtype of the condition is of practical interest, as it may carry important clinical prognostic and therapeutic implications. Low renin essential hypertension and primary aldosteronism are the most common subtype, but monogenic forms of hypertension with specific treatments can be uncovered with the proper use of the algorithm.

Conflict of interest

The authors declare no conflict of interest.

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