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Review

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A Practical Diagnostic View to Primary Hyperaldosteronism for Nephrology Practice

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SUMMARY

Primary hyperaldosteronism (PH) is the excessive and uncontrolled production of aldosterone from the adrenal glands. Until now, the disease was frequently discussed among the endocrine causes of secondary hypertension, and patients with particularly resistant hypertension were included in the risk group. However, the data that emerged over the years have changed this perspective. Currently, the incidence of PH among hypertensive patients is more than 20% and it is clear that it affects a much larger population than previously thought. We consider that PH is an important public health problem and should be considered by all physicians dealing with the hypertensive population. In this article, we aim to create a practical approach to the diagnosis of PH from our clinical viewpoint and in the light of the contemporary literature.

Keywords: Primary hyperaldosteronism, nephrology practice, practical approach

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INTRODUCTION

Primary hyperaldosteronism (PH) is the result of excessive and uncontrolled production of aldosterone by the adrenal glands. A clear definition of the disease was made by American scientist JW Conn in 1955.[1] By convention, PH is discussed among the endocrine causes of secondary hypertension and is considered among the differential diagnosis of resistant hypertension. However, the current data have changed this perspective. In some series, the incidence among hypertensive patients has been reported to be more than 20%. It has been suggested that not only patients with resistant hypertension but also patients with relatively low blood pressure are also at risk.[2-4] In addition, it has been determined that cardiovascular, cerebrovascular, renal, and metabolic abnormalities develop in affected patients independent of blood pressure values.[4-9] All these data show that the incidence and clinical significance of PH are far beyond the current concept and might be an important public health problem. However, the number of patients diagnosed with PH in internal medicine and nephrology clinics referring to a large hypertensive population is quite low. We consider that the low awareness among physicians and the complexity of the diagnostic stages are the most important reasons for this underestimation.

The purpose of this article is to provide faster and more easier diagnostic ways to the clinicians for the evaluation of PH.

Physiology of aldosterone

Aldosterone is a mineralocorticoid hormone responsible for regulating the extracellular volume and potassium homeostasis. It is controlled by the renin-angiotensin aldosterone system (RAAS), adrenocorticotropic hormone (ACTH), and serum potassium concentration itself.[10-12] However, its main regulator is RAAS. The renin

secreted from the macula densa region of the renal tubules converts the angiotensinogen to angiotensin (ang)-I. Ang-I is converted to ang-II by the angiotensin-converting enzyme. Ang-II stimulates aldosterone synthesis through the aldosterone synthase enzyme in the zona glomerulosa layer of the adrenal glands.[10,11] Salt and fluid loss, sudden blood pressure decline due to vasodilation or bleeding, decreased renal perfusion due to stenosis of renal arteries, activation of the sympathetic nervous system due to posture or stress activate RAAS. Volume and sodium overload, sympathetic activity blockade, renal failure, and increased ang-II can suppress renin and aldosterone production.[10,11]

Aldosterone is a lipophilic hormone that passes freely through cell membranes and binds to cytoplasmic mineralocorticoid receptors. It has a wide potential of action through mineralocorticoid receptors on various cells, such as epithelial cells, endothelial cells, vascular smooth muscle cells, macrophages, adipocytes, cardiomyocytes, and central nervous system cells.[10,12-14] Mineralocorticoid receptors activated by aldosterone in the cortical collecting tubules of the kidneys increase the expression of epithelial sodium channels located on the apical surfaces of the chief cells. Sodium enters the cell and passes through the basolateral *Na-K-ATPase* pump to the interstitial space. The electrochemical gradient that occurs in the tubular lumen causes potassium to be secreted into the tubular lumen via the apical potassium channels. Aldosterone also increases hydrogen secretion into the tubular lumen via the *H-ATPase* pump in intercalated cells. As a result, aldosterone increases sodium reabsorption and intravascular volume, leading to potassium and hydrogen excretion.[10-12,15,16]

Primary hyperaldosteronism

Primary hyperaldosteronism is a clinical condition caused by excessive aldosterone release from the adrenal glands. Aldosterone production is out of control of RAAS, which is the dominant control mechanism in normal physiology. However, the effects of weaker regulators, such as ACTH and serum potassium concentration, may be partially continued.[10,12] The potential effects of these regulators may cause some confusion during the PH diagnostic stages.

Causes of autonomic aldosterone secretion may be bilateral hyperplasia of the adrenal glands (idiopathic hyperaldosteronism, 60%), unilateral adenoma (Conns' syndrome, 35%), familial hyperaldosteronism (5%), unilateral hyperplasia (2%), and adrenocortical carcinoma (<2%).[11]

Excessive amounts of aldosterone can impair glucose regulation and vascular remodeling. It may cause endothelial dysfunction, arterial stiffness, and inflammation.[10,17,18] It causes water and salt retention. Simultaneous sympathetic activation, direct stimulation of smooth muscles, and endothelial cells also increase blood pressure.[4] Nephropathy may develop in a significant number of patients with two-staged pathogenesis. Increased sodium and fluid absorption increases renal perfusion pressure, causes glomerular hyperfiltration and suppresses RAAS. These initial functional adaptation mechanisms result in the development of structural damage in the kidney over time, increase in protein excretion, and decrease in glomerular filtration rate.[19,20]

Increased blood pressure, headache, weakness, visual disturbances, paresthesia, muscle weakness and cramps, nocturia, increased urination, and thirst may be observed in affected patients.[20,21] Approximately 20% of the diagnosed patients have impaired kidney functions.[19,20] Independent of blood pressure values, left ventricular hypertrophy, heart failure, arrhythmia (especially atrial fibrillation), myocardial infarction, and stroke may develop.[5-8,10,20-25]

Increased aldosterone often causes hypertension. Until recently, patients with resistant hypertension (blood pressure > 140/90 mmHg despite 3 antihypertensive drugs) were included in the PH risk category. However, the contemporary data revealed that patients with relatively mild increases in blood pressure should also be screened in terms of PH.[4] Accordingly, a significant number of patients defined as having early-stage hypertension according to the guidelines are at risk for PH. However, PH screening is generally not performed in these patients, as the relationship of PH with mild blood pressure increase is not clearly known and the presence of hypokalemia is considered as a *sine qua non* for screening. It is clear that hypertensive patients with spontaneous or diuretic-induced hypokalemia should be screened with a pre-diagnosis of PH. However, it should be kept in mind that the frequency of hypokalemia in PH patients is only 9-37% and a significant number of patients do not have hypokalemia.[4] Hypertensive patients with a history of obstructive sleep apnea or cerebrovascular events, family history of early-onset hypertension (<40 years), or PH are also at risk for PH.[4]

Diagnosis of primary hyperaldosteronism

The most difficult part of PH management is the diagnosis phase, as there is not any definitive and rapid diagnostic method defined. The proposed algorithmic steps are difficult to implement in a standardized way. For this reason, adequate interest and success for the diagnosis of PH cannot be achieved. Unfortunately, an only a small number of PH cases are diagnosed in nephrology outpatient clinics dealing with a large number of hypertensive patients.[26,27] Its prevalence among patients with chronic kidney disease is also unknown. The need for high clinical suspicion and non-specific findings make the diagnosis almost impossible in cases with comorbidities. According to the 2016 International Endocrine Society guidelines, PH is diagnosed in 3 stages consisting of identification, validation, and typing steps.[4] We would like to list our practical suggestions for some equivocal points during the diagnosis phase, in line with this guideline (Figure 1).

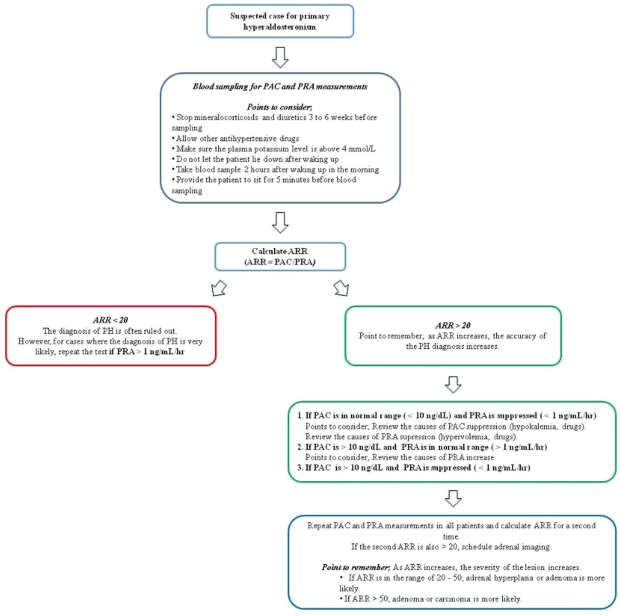

Figure 1. Diagnostic algorithm for primary hyperaldosteronism. PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone to renin ratio.

Identification

In this step, plasma renin and aldosterone concentrations are evaluated in suspected cases. In PH, an increase in plasma aldosterone concentration (PAC) and suppression of renin by the negative feedback mechanism are expected. Although not in all patients, exaggerated aldosterone effect may result in hypokalemia and mild metabolic alkalosis.[4,10,12]

Renin release can be evaluated directly by measuring plasma renin concentration (*direct renin concentration: DRC in mU/L*). However, plasma renin activity (*PRA, in ng/mL/hr*), reflecting the amount of ang-I converted from angiotensinogen per unit time, gives relatively sensitive results. Both can be converted into each other (*PRA/DRC = 12*).[28] When evaluating the results, the degree of renin suppression should definitely be evaluated.[4,28,29] Because, even when PAC is in normal ranges, severe renin suppression may lead to positive ARR results.[29] In the presence of ARR above the threshold value, the probability of PH is considered as positive. It should be known that the threshold values may change according to the unit differences. When PAC is measured in ng/dL and PRA is measured in ng/mL/h, the positive ARR threshold is > 20. It should be kept in mind that, when PRA is severely suppressed (< 1 ng/mL/h), PAC must be > 10 ng/dL to evaluate ARR as positive.[3,30,31]

Verification

Second-line analyzes should be performed in cases with positive ARR results. The goal in this step is to control the suppressibility of aldosterone production. Each of the tests recommended for this purpose requires very rigorous and difficult applications in practice (saline infusion, captopril test, etc.). Repeated tests may cause loss of concentration, and the diagnosis may be overlooked.[32-34]

If identification and verification steps can be evaluated with a single test, the diagnostic algorithm can be simplified.[29,33-35] The results of the AQUARR study support that progressively increasing ARR values are significant and more valuable for the diagnosis of PH, and ARR can be used for both screening and validation steps.[33] The initial 2 steps can be unified with ARR especially in some patient groups[4,29,33,35]:

a. the ones with hypokalemia,
b. patients having PAC > 20 ng/dL, and
c. patients having markedly suppressed renin activity (<0.6 ng/mL/h).

We consider that if renin and aldosterone measurements are made and evaluated under stringent and standard conditions, both steps can be combined in most of the patients. This approach may provide easier, faster, and more effective results for the diagnosis of PH.[28,33,35]

Typing

In this step, the localization and lateralization of adrenal pathology are tried to be determined in patients diagnosed with PH. For this purpose; ARR, adrenal computed tomography (CT), and adrenal venous blood sampling can be used. The results obtained at the end of this step will determine the patient's treatment plan.

a. *ARR:* The AQUARR study shows that ARR also provides information during the typing step. While mild increases in ARR are detected in cases of adrenal hyperplasia, higher values (≥50) are found in cases of adrenal adenoma or carcinoma.[33]
b. *Adrenal CT:* High-resolution CT is very successful in showing and typing adrenal lesions; however, it does not comment on the activity of the lesions.[1,33] If there is a lesion in a single adrenal gland in CT, it can be evaluated as unilateral disease without further examination.[4,33,35] The size and some phenotypic features of the lesion can provide important information. For example, homogeneous lesions of 1-2 cm are usually adenomas; lesions larger than 4 cm are likely to be carcinoma.[1,37]
c. *Adrenal venous blood sampling:* When the lateralization of the pathology cannot be clarified with the examinations performed up to this point, adrenal venous sampling can be performed. This test is an invasive procedure that requires a high level of experience.[38] Although it is defined as more reliable than CT, no significant differences were found in terms of both typing and treatment success in the only controlled study focusing on this issue.[36]

Diagnosis of Primary Hyperaldosteronism in Kidney Disease Patients

Some special points should be taken into account when defining PH in patients with chronic kidney disease[38-40];

- Resistant hypertension in euvolemic patients may be a clinical clue.
- Decrease in renal potassium excretion may prevent the development of hypokalemia.
- Predisposition to metabolic acidosis may mask the development of metabolic alkalosis.
- Validation tests may be avoided due to concerns that they could cause water and sodium overload. Therefore, ARR results are extremely valuable.[38-40]
- In severely suspected cases, diagnosis can be made through treatment. Blood pressure control and elimination of renin suppression provided after mineralocorticoid receptor blocker therapy support the diagnosis.

RECOMMENDATIONS FOR ALDOSTERONE AND RENIN MEASUREMENTS

In patients with suspected PH, PRA, and ARR are evaluated together in the first step.[4,28,29] Since some factors affecting renin and aldosterone levels may cause significant variability, some confirmation tests are recommended for most of the patients whose first-line test results are considered as positive for PH.[29,34,41] These tests are the most tiring and difficult part of the diagnosis of PH, and check the suppression of aldosterone. At this point, it should be remembered that there are some exceptional groups that do not require verification tests.[29,34,35] Among these patients, we would like to draw attention to the ones with a *PAC > 20 ng/dL and significantly suppressed PRA.* We consider that test variability can be reduced if renin and aldosterone measurements are made and evaluated under stringent standard conditions. So, more patients can skip the verification step by entering this exceptional group. With this approach, faster and more effective results can be obtained.

In the light of our experience and the current data, we suggest a three-step approach to reduce the variability of PAC and PRA measurements[4,29,34,41,42];

a. Repeat the tests at least twice on 2 separate days.
b. Perform the tests under standard conditions and pay attention to check points.
c. Examine the factors that can affect the blood test results and their possible mechanisms of action.

Check points

a. *Check the patient's diet and do not allow salt restriction or salt overload:* Salt consumption of <2 g/day or >6 g/day can lead to RAAS activation (effect on renin secretion greater than aldosterone) and false-negative results. To avoid both, the patient may be referred to a dietitian prior to the test.
b. *Check serum potassium concentration and do not allow hypokalemia:* In hypokalemic patients, potassium concentration should be increased to above 4 mmol/L before measurements. Aldosterone production in PH is beyond the control of RAAS. However, the effect of ACTH and potassium level may continue, albeit partially. Hypokalemia may cause false-negative results by suppressing aldosterone release.[10,12]
c. *Check the time and posture before sampling:* Blood sample should be taken 2 h after the patient wakes up in the morning. The patient's posture during this period does not affect the tests unless he is in the lying position.
d. *Check the posture during sampling:* Before the blood sample is taken, the patient must be seated and rested for at least 5 min. Blood accumulation in the lower extremities while standing causes a decrease in renal perfusion and an increase in aldosterone release. Decreased hepatic perfusion may contribute to increasing aldosterone concentration by decreasing aldosterone clearance. Acute ACTH increase and sympathetic activation during stress may increase aldosterone release. All these reasons can result in false positivity.
e. *Check the antihypertensive medications:* Most of the patients investigated with a pre-diagnosis of PH are under antihypertensive treatment. Generally, these drugs are planned to be discontinued due to their possible effects on PAC and PRA. At this point, important problems arise in practical application. Due to fluctuations in blood pressure and difficulties in patient compliance, discontinuation of drug therapy is not possible in every hypertensive patient, and some clinicians give up PH screening in patients taking antihypertensive agents. In fact, the effects of many antihypertensive drugs on renin and aldosterone are negligible. In most patients, tests can be done safely without changing or stopping treatment. The exceptional group of drugs here is minocorticoid receptor blockers and diuretics. These drugs should be discontinued 3-6 weeks before measurements due to their strong effects. Drugs that have the least effect on ARR (such as verapamil, hydralazine, prazosin, doxazosin) may be preferred in patients who are newly starting or changing antihypertensive drugs. After the definitive diagnosis is made, revision can be made in the treatment if necessary.

Factors that can affect the blood test results

a. *Age:* Decreasing nephron count with advanced age may cause a decrease in renin and aldosterone release. This situation becomes evident especially after the age of 60 and is more pronounced on the renin.
b. *Gender:* Estrogen can suppress renin release. Therefore, it is more appropriate to evaluate ARR in women while they are in the follicular phase of the menstrual cycle.
c. *Time of measurement:* Increasing ACTH level in the morning hours has a strong stimulating effect on aldosterone release. Hence, it is recommended that the tests be performed in the morning hours.

d. *Kidney functions:* Impaired kidney function can result in both nephron loss and reduced renin release through water/salt retention. This effect is particularly pronounced when the patient loses 50% of GFR.
e. *Medications:* As we emphasized before, the drugs that should be discontinued before the tests are mineralocorticoid receptor blockers and diuretics. Other antihypertensive agents have no significant effect on ARR. However, knowing the possible effects of drugs on renin and aldosterone helps to interpret the results more accurately and professionally. For example, detection of suppressed renin levels despite drug intake that increases renin release is very important for the diagnosis of PH.
   - Angiotensin-converting enzyme inhibitors increase renin and decrease aldosterone. They block aldosterone synthesis via inhibition of angiotensin-converting enzyme. The reduction of angiotensin II also reduces the release of noradrenaline and peripheral vascular resistance. Decreased peripheral vascular resistance, and the elimination of feedback inhibition caused by angiotensin II increases renin release.
   - Angiotensin type I receptor blockers increase renin and decrease aldosterone. They block AT I receptors, decrease aldosterone synthesis and increase renin release.
   - Calcium channel blockers increase renin. They block flow-dependent calcium channels in vascular smooth muscle and myocardium. In particular, dihydropyridine-type calcium channel antagonists can increase renin release by sympathetic activation, natriuretic effects, and direct stimulation.
   - Sympathetic system blockers decrease renin. Beta-blockers prevent the binding of endogenous catecholamines to adrenergic receptors and central alpha-2 agonists (clonidine, alpha-methyldopa) reduce sympathetic activation.

Evaluation of false positive results according to different clinical scenarios

1. PAC is within normal limits, PRA suppressed, and ARR > 20. In such a case, the ARR result that exceeds the threshold value can be considered positive. However, this result may be false positive for 2 reasons:
   - Suppressed PRA: Although PAC was within normal limits, over-suppressed PRA may have caused the ARR to exceed the threshold. At this point, possible causes that may suppress the patient's renin should be reviewed. For example, hypervolemia can suppress renin release via RAAS. In such a case, the tests should be repeated after reaching the volume balance.
   - Suppressed PAC: Causes that could even suppress autonomous aldosterone release may have masked the increase in PAC. Hypokalemia is an example. After serum potassium has been increased to above 4 mmol/L, the PAC measurement should be performed again.
2. PAC increased, PRA is within normal limits, and ARR > 20. In such a case, ARR exceeding the threshold value can be considered positive. However, it should be kept in mind that the factors that trigger renin release may also cause this result. RAAS blockers and Ca channel blockers rarely lead to this condition (in fact, PRA usually remains suppressed). In such a case, if the PAC is > 10 ng/dL (reference: 1-21 ng/dL), suspicious drugs should be replaced and the tests should be repeated within 2 weeks.
3. PAC increased, PRA suppressed, and ARR > 20. If this patient is using a RAS blocker, these results strongly suggest the diagnosis of PH. Because, despite a drug that stimulates renin release, suppressed PRA supports a strong autonomous increase in aldosterone.

CONCLUSION

It is clear that primary hyperaldosteronism affects a much larger population than previously thought. This important public health issue should be identified by all clinicians dealing with the hypertensive population. In this article, a practical approach for the diagnosis of PH is aimed in the light of the literature. In patients with positive ARR results, some confirmatory tests should be performed to check the suppression of aldosterone production. Although these tests are absolutely necessary to confirm the diagnosis, clinical applications are extremely difficult. These tests may be skipped in some patients, such as patients with PAC > 20 ng/dL or PRA < 0.6 ng/mL/h. Faster and more effective results can be obtained in these patients. If clinicians can ensure that plasma renin and aldosterone measurements are made under optimal conditions, more patients can achieve these specific conditions.

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REFERENCES

1. Dick SM, Queiroz M, Bernardi BL, et al. Update in diagnosis and management of primary aldosteronism. *Clin Chem Lab Med*. 2018;56(3):360-372. [CrossRef]
2. Ganguly A. Primary aldosteronism. *N Engl J Med*. 1998;339(25):1828-1834. [CrossRef]
3. Byrd JB, Turcu AF, Auchus RJ. Primary aldosteronism: a practical approach to diagnosis and management. *Circulation*. 2018;138(8):823-835. [CrossRef]

4. Funder JW, Carey RM, Mantero F, et al. The management of primary aldosteronism: case detection, diagnosis, and treatment: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2016;101(5):1889-1916. [CrossRef]
5. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. *Lancet Diabetes Endocrinol*. 2018;6(1):51-59. [CrossRef]
6. Mulatero P, Monticone S, Bertello C, et al. Longterm cardio and cerebrovascular events in patients with primary aldosteronism. *J Clin Endocrinol Metab*. 2013;98:4826-4833.
7. Catena C, Colussi G, Nadalini E, et al. Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med*. 2008;168(1):80-85. [CrossRef]
8. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2018;6(1):41-50. [CrossRef]
9. Williams TA, Reincke M. Management of Endocrine Disease: Diagnosis and management of primary aldosteronism: the Endocrine Society guideline 2016 revisited. *Eur J Endocrinol*. 2018;179:R19-R29.
10. Myśliwiec J, Górska M. Primary aldosteronism: a common and important problem. A practical guide to the diagnosis and treatment. *Endokrynol Pol*. 2012;63(4):324-336.
11. Farrugia FA, Zavras N, Martikos G, et al. A short review of primary aldosteronism in a question and answer fashion. *Endocr Regul*. 2018;52(1):27-40.
12. Stowasser M, Gordon RD. Primary aldosteronism: changing definitions and new concepts of physiology and pathophysiology both ınside and outside the kidney. *Physiol Rev*. 2016;96(4):1327-1384. [CrossRef]
13. Oki K, Gomez-Sanchez EP, Gomez-Sanchez CE. Role of mineralocorticoid action in the brain in salt-sensitive hypertension. *Clin Exp Pharmacol Physiol*. 2012;39(1):90-95. [CrossRef]
14. Tarjus A, Amador C, Michea L, Jaisser F. Vascular mineralocorticoid receptor and blood pressure regulation. *Curr Opin Pharmacol*. 2015;21:138-144. [CrossRef]
15. Oliver WJ, Cohen EL, Neel JV. Blood pressure, sodium intake, and sodium related hormones in the Yanomamo Indians, a "no-salt" culture. *Circulation*. 1975;52(1):146-151. [CrossRef]
16. Young DB, Smith Jr. MJ, Jackson TE, Scott RE. Multiplicative interaction between angiotensin and K concentration in stimulation of aldosterone. *Am J Physiol*. 1984;247(3 Pt 1):E328-E335. [CrossRef]
17. Burrello J, Monticone S, Buffolo F, et al. Issues in the diagnosis and treatment of primary aldosteronism. *High Blood Press Cardiovasc Prev*. 2016;23(2):73-82. [CrossRef]
18. Luther JM. Aldosterone in vascular and metabolic dysfunction. *Curr Opin Nephrol Hypertens*. 2016;25(1):16-21. [CrossRef]
19. Catena C, Colussi G, Sechi LA. Aldosterone, organ damage and dietary salt. *Clin Exp Pharmacol Physiol*. 2013;40(12):922-928. [CrossRef]
20. Kawashima A, Sone M, Inagaki N, et al. Renal impairment is closely associated with plasma aldosterone concentration in patients with primary aldosteronism. *Eur J Endocrinol*. 2019;181(3):339-350. [CrossRef]
21. Sechi LA, Colussi G, Di Fabio A, Catena C. Cardiovascular and renal damage in primary aldosteronism: outcomes after treatment. *Am J Hypertens*. 2010;23(12):1253-1260. [CrossRef]
22. Watanabe D, Morimoto S, Takano N, et al. Complete remission of hypertension in a hemodialysis patient after adrenalectomy for primary aldosteronism and renal transplantation. *CEN Case Rep*. 2018;7(1):77-82. [CrossRef]
23. Burrello J, Monticone S, Buffolo F, et al. Issues in the diagnosis and treatment of primary aldosteronism. *High Blood Press Cardiovasc Prev*. 2016;23(2):73-82. [CrossRef]
24. Luther JM. Aldosterone in vascular and metabolic dysfunction. *Curr Opin Nephrol Hypertens*. 2016;25(1):16-21. [CrossRef]
25. Hundemer GL. Primary aldosteronism: cardiovascular outcomes pre-and post-treatment. *Curr Cardiol Rep*. 2019;21(9):93. [CrossRef]
26. Mulatero P, Monticone S, Burrello J, et al. Guidelines for primary aldosteronism: uptake by primary care physicians in Europe. *J Hypertens*. 2016;34(11):2253-2257. [CrossRef]
27. Rossi E, Perazzoli F, Negro A, Magnani A. Diagnostic rate of primary aldosteronism in Emilia-Romagna, Northern Italy, during 16 years (2000-2015). *J Hypertens*. 2017;35(8):1691-1697. [CrossRef]
28. Vilela LAP, Almeida MQ. Diagnosis and management of primary aldosteronism. *Arch Endocrinol Metab*. 2017;61(3):305-312. [CrossRef]
29. Schilbach K, Junnila RK, Bidlingmaier M. Aldosterone to renin ratio as screening tool in primary aldosteronism. *Exp Clin Endocrinol Diabetes*. 2019;127(2-3):84-92. [CrossRef]
30. Nishizaka MK, Pratt-Ubunama M, Zaman MA, Cofield S, Calhoun DA. Validity of plasma aldosterone-to-renin activity ratio in African American and white subjects with resistant hypertension. *Am J Hypertens*. 2005;18(6):805-812. [CrossRef]
31. Montori VM, Schwartz GL, Chapman AB, Boerwinkle E, Turner ST. Validity of the aldosterone-renin ratio used to screen for primary aldosteronism. *Mayo Clin Proc*. 2001;76(9):877-882. [CrossRef]
32. Buffolo F, Monticone S, Burrello J, et al. Is primary aldosteronism still largely unrecognized? *Horm Metab Res*. 2017;49(12):908-914. [CrossRef]
33. Maiolino G, Rossitto G, Bisogni V, et al. Quantitative value of aldosterone-renin ratio for detection of aldosterone-producing adenoma: the aldosterone-renin ratio for primary aldosteronism (AQUARR) study. *J Am Heart Assoc*. 2017;6(5):e005574. [CrossRef]
34. Rossi GP, Seccia TM, Pessina AC. A diagnostic algorithm the Holy Grail of primary aldosteronism. *Nat Rev Endocrinol*. 2011;7(12):697-699. [CrossRef]
35. Pilz S, Keppel MH, Trummer C, et al. Diagnostic accuracy of the aldosterone-to-active renin ratio for detecting primary aldosteronism. *J Endocr Soc*. 2019;3(9):1748-1758. [CrossRef]
36. Dekkers T, Prejbisz A, Kool LJS, et al. Adrenal vein sampling versus CT scan to determine treatment in primary aldosteronism: an outcome-based randomised diagnostic trial. *Lancet Diabetes Endocrinol*. 2016;4(9):739-746. [CrossRef]
37. Patel SM, Lingam RK, Beaconsfield TI, Tran TL, Brown B. Role of radiology in the management of primary aldosteronism. *RadioGraphics*. 2007;27(4):1145-1157. [CrossRef]
38. Young WF, Stanson AW. What are the keys to successful adrenal venous sampling (AVS) in patients with primary aldosteronism? *Clin Endocrinol*. 2009;70(1):14-17. [CrossRef]
39. Chand R, Tandukar S, Asmil S, Chico M. Primary hyperaldosteronism in end-stage renal disease: diagnostic challenges and treatment considerations. *Cureus*. 2020;12(8):e9599. [CrossRef]
40. Kazory A, Weiner ID. Primary hyperaldosteronism in a patient with end-stage renal disease. *Nephrol Dial Transplant*. 2007;22(3):917-919. [CrossRef]

41. O'Shea PM, Griffin TP, Denieffe S, Fitzgibbon MC. The aldosterone to renin ratio (ARR) in the diagnosis of primary aldosteronism (PA): promises and challenges. *Int J Clin Pract*. 2019;73(7):e13353. [CrossRef]

42. Tomaschitz A, Pilz S. Aldosterone to renin ratio a reliable screening tool for primary aldosteronism? *Horm Metab Res*. 2010;42(6):382-391. [CrossRef]