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Review Article

Hyperaldosteronism Etiology and Diagnosis

Rasha Khaled Sendy[1]*, Waleed Alsalhi[2], Salma Mubarak Buhelaiga[3], Khulud Mohammed Alkhars[4], Khalid Jamal Alzayer[5], Haytham Nabil Alhazmi[6], Ghiad Fahd Alquthami[7], Hussam Abdulaziz Alghamdi[8], Abdullah Jamal Alzayer[9], Khalid Abdullah Aljlayl[10], Mohammed Abdullah Bohaligah[11] and Reham Ahmed Alghamdi[12]

[1]King Fahad General Hospital, Jeddah, Saudi Arabia

[2]Majmaah University, Al-Majmaah, Saudi Arabia

[3]Alaziziyah Health Center, Dammam, Saudi Arabia

[4]Arabian Gulf University, Bahrain

[5]Dammam Medical Complex, Dammam, Saudi Arabia

[6]King Fahad Hospital, Medina, Saudi Arabia

[7]King Abdulaziz Specialist Hospital, Taif, Saudi Arabia

[8]Dar Al Uloom University, Riyadh, Saudi Arabia

[9]Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

[10]Imam Mohammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

[11]Khafji General Hospital, Khafji, Saudi Arabia

[12]King Abdullah Medical Complex, Jeddah, Saudi Arabia

***Corresponding Author:** Rasha Khaled Sendy, Medical Registrar, King Fahad General Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: The exterior layer of the Adrenal cortex is called the zona glomerulosa, which secretes the mineralocorticoid hormone. As the name suggests, the increase in the secretion of aldosterone from zona glomerulosa is referred to as hyperaldosteronism. The chief role of aldosterone is the maintenance of volume circulation and metabolic activities. Irregularities in the level of aldosterone may cause extracellular volumetric changes. Aldosterone also has some potent effects on cardiovascular tissues like the endothelium and myocardium. The management of PA depends on the etiological factors behind the disease. The aim of complete treatment of PA is the reduction of the effects produced by excess aldosterone in the system like myocardial infarction, heart failure, stroke, etc. and increasing the levels of potassium, controlling the blood pressure levels.

Aim of the Study: This review aims at overviewing Hyperaldosteronism, etiological factors behind it, and the management techniques.

Methodology: This review is a comprehensive research of PUBMED and Google Scholar from the year 1990 to 2021.

Conclusion: The excess of aldosterone in the system is termed Hyperaldosteronism. Hyperaldosteronism is different from other hormonal excess states in the body as the effects of HA are mainly related to the cardiovascular tissues leading to an increased risk of fatality. The recent technological advances have enabled us to diagnose the condition more effectively, which further helps in better treatment planning for the condition. Understanding the etiological factors is of utmost importance as it dominates the management technique to be used. Radiofrequency ablation and Laparoscopic surgeries to manage HA have shown increased patient compliance

Keywords: *Hyperaldosteronism; Aldosterone; Bilateral Adrenal Hyperplasia; Renin-Angiotensin System; Radiofrequency Ablation*

Introduction

The external layer of the Adrenal cortex is called the zona glomerulosa, which secretes the mineralocorticoid hormone. As the name suggests, the increase in the secretion of aldosterone from zona glomerulosa is referred to as Hyperaldosteronism. The chief role of aldosterone is the maintenance of volume circulation and metabolic activities. Irregularities in the level of aldosterone may cause extracellular volumetric changes. It helps in the urinary excretion of potassium and hydrogen and reabsorption of sodium which further helps in the absorption of water and expansion of intravascular volume. Aldosterone also has some potent effects on cardiovascular tissues like the endothelium and myocardium [1,2].

The production of aldosterone is exclusive to the zona glomerulosa layer of the adrenal cortex as the aldosterone synthase (CYP11B2) is present specifically in this layer. Various factors like an adrenocorticotropic hormone, angiotensin II, potassium, and estrogen are

responsible for the secretion of aldosterone. An increased expression of CYP11B2 and phosphorylation of StAR protein increases the production of Aldosterone [3]. Aldosterone production is also regulated by the renin-angiotensin system. The action resulting in the production of aldosterone is explained in the following figure (Figure 1) [4].

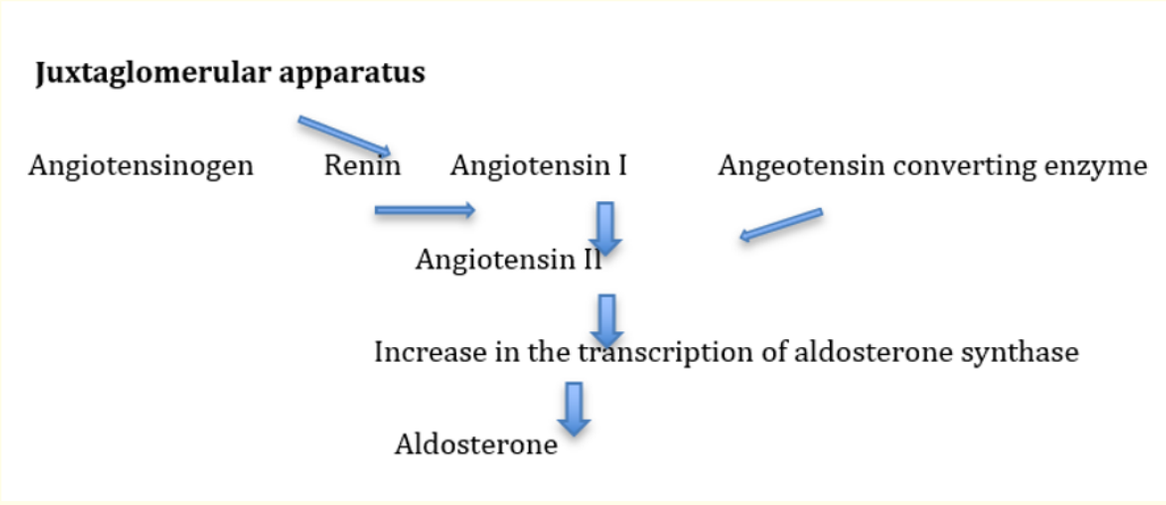

Figure 1: *Role of renin-angiotensin system in the production of aldosterone [4].*

Increased expression of serum potassium also regulates the production of aldosterone as it affects the production of aldosterone synthase. ACTH is also accountable for the production of Aldosterone. In a study conducted by Markou., *et al*. they studied the relationship of increased aldosterone syntheses in patients suffering from hypertension and concluded that the cells of zona glomerulosa were primed by increased stress which increased the production of aldosterone. The primary symptom of Hyperaldosteronism is a mild to moderate case of hypertension. Hyperaldosteronism can be further branched into two categories are primary and secondary, which present with almost similar symptoms but have different biochemical readings. The management of Hyperaldosteronism is case-specific and depends on the etiological factors and presenting symptoms [5].

Etiology

Hyperaldosteronism can be caused by multiple factors depending on whether it's of the primary or secondary form [4].

Primary hyperaldosteronism

The main reason behind primary aldosteronism is the increased production of aldosterone from the adrenal glands. The primary reason behind this increased production is decreased plasma renin activity and increased plasma aldosterone to renin activity ratio. It can be seen as Conn syndrome, which is a primary tumor in the gland or unilateral Adrenal Hyperplasia. There are various, less common subtypes of primary hyperaldosteronism (PA) (Table 1).

Subtypes of Primary Hyperaldosteronism
1. Aldosterone-producing adenoma (APA)
2. Bilateral adrenal hyperplasia (BAH)
3. Unilateral adrenal hyperplasia (UAH)
4. Glucocorticoid-remediable aldosteronism (GRA)
5. Adrenocortical carcinoma (rarest form)
6. Familial Hyperaldosteronism type 1

Table 1: *Subtypes of primary aldosteronism [4].*

Bilateral adrenal hyperplasia is the most common form of HA, accounting for approximately 60% of the cases, followed by APA and UAH, which constitute the remaining 40% [6]. In order to thorough management, understanding the etiology and coming to a conclusive diagnosis is of utmost importance as the management primarily involves treatment of the etiological factors. APA and UAH share many biochemical factors with minute differences. APAs generally present as small tumors measuring up to 2 cms. Cells of both glomerulosa and fasciculata are seen in APA's histopathology. The differentiating factor between the diagnosis of UAH and APA is the absence of a radiographic mass in the former. The management technique for both APA and UAH is unilateral adrenalectomy [6]. As compared to APA, BAH presents with milder symptoms of hypertension and hypokalemia. Adrenal carcinomas are larger, measuring up to 4cms, and secrete numerous adrenal cortical hormones like cortisol and aldosterone, but their contribution to PA has been minimal [4].

Secondary hyperaldosteronism

Increased activity of the Renin-angiotensin system leads to the production of excessive aldosterone, which accounts for Secondary Hyperaldosteronism (SH). Subtypes of SH can be divided based on etiological factors causing hypertension and those not causing them.

Normotensive	Hypertensive
1. Bartter's syndrome	1. Renal Artery Stenosis
2. Gittleman's Syndrome	2. Aortic Coarctation
	3. Reninoma

Table 2: *Subtypes of secondary hyperaldosteronism [4].*

The most prevalent reason for SH is an illness like Congestive Heart Failure and nephrotic syndrome, which tend to reduce the circulating blood volume. Treatment following these diseases leads to reversal of RAS. Consumption of diuretics also leads to SH as it reduces the extracellular and intravascular volume resulting in increased renin leading to excess aldosterone. Other reasons for SH are the presence of renin-producing tumors, pregnancy, cirrhosis [7].

Patient history and diagnosis of hyperaldosteronism

The diagnosis of HA can be a dilemma as the symptoms could be overlapping with other hypertensive disorders, which leads to decreased sensitivity of the diagnostic tests. Patients that present with hypertension should always be considered as potential cases of HA. A mild to severe case of Hypertension in patients has a higher chance of underlying increased aldosterone. The endocrine society has laid down a certain set of screening factors to decide which patients should be considered as candidates for possible HA (Table 3) [8].

1.	Patients who have a persistent reading of BP > 150/100 mm Hg on different days
2.	Patients who are resistant to 3 hypertensive drugs and require more medication
3.	Patients with sleep apnea and hypertension
4.	A case of adrenal adenoma with hypertension
5.	Patients who have had a family history of early Hypertension
6.	A case of hypokalemia with hypertension
7.	Patient with a family history of Primary Aldosteronism presenting with Hypertension

Table 3: *Criteria for screening of patients for PA as per the endocrine society [8].*

A fluctuating blood pressure reading can be suggestive of HA. It can range from normal to severe hypertension, depending on the subtype of HA. A high blood pressure reading is seen in patients with Renal artery stenosis and coarctation of the aorta which presents as headache, eyesight issues, dizziness, pain in the chest, and breathing difficulties. Patients presenting with heart failure, cirrhosis, or nephrotic syndrome have a decreased blood volume. A decreased blood pressure reading is seen in patients with Gliterman's syndrome and Bartter's syndrome. A reduction in potassium levels in the body can present with neuromuscular issues like weakness, tiredness, muscle cramps, weakening of muscles, irregular heart rhythm [7].

Diagnostic tests for HA

The diagnostic reading for Hyperaldosteronism is similar to those of Hypokalemia, hypernatremia, and decreased magnesium reading [3,9]. The first test performed in patients with HA is the plasma renin activity (PRA) and plasma aldosterone concentration (PAC). Changes in PRA or PAC value are negligible in the case of PA as the aldosterone is secreted in excess by the glomerulosa. In the case of SH, the reading of PAC and PRA are high. The best results are seen when the tests are done in the morning after two hours of the patient waking up, but the patient should be seated for 5 - 10 minutes before the test is performed. The PAC to PRA ratio has proven to be a confirmatory diagnostic test for PA with a specificity and sensitivity greater than 90% [10]. In a study conducted by Vilela., *et al*. they concluded that the value of PAC/PRA ratio higher than 20 and PAC value higher than 15 ng/dL is sufficient to confirm the diagnosis for Hyperaldosteronism. The value of PRA and PAC is increased in the case of secondary Hyperaldosteronism, but PAC/PRA ratio is less than PA [11].

The value of Aldosterone should be decreased in the system to come to a final diagnosis. Aldosterone value can be reduced by increasing the sodium levels in the body either through oral or intravenous loading. In oral loading, patients are made to consume around 5000 mg sodium through diet or a 90 mEq for three days. A PAC value of more than 12 ng/dL is consistent with hyperaldosteronism. Cases where there is a time crunch or any other form of urgency, can opt for intravenous sodium loading where two ltr of isotonic saline solution is infused over 4 hours, and the resulting aldosterone concentration is higher than 10 ng/dL [12].

Adrenal vein sampling (AVS) is considered a gold standard to differentiate a unilateral and bilateral diseases. The sample is taken from the left and right adrenal veins as well as the inferior vena cava and measured for aldosterone and cortisol concentration. [13] An incompatible reading in the left and right suggests unilateral pathology where the adenoma is present on the side of the elevated value, and a compatible reading suggests bilateral pathology. Patients that are contraindicated for AVS sampling are younger individuals (< 35) with potassium deficiency, increased reading of aldosterone concentration, and signs of adrenal carcinoma on radiographic imaging. An increased pH value of the tissue is also associated with hyperaldosteronism [12].

Radiographic imaging in PA

Computed tomography (CT) scans are the best radiographic approach for the diagnosis of PA. Adrenocortical carcinomas present as masses greater than 4 cms in size and must be ruled out through CT scans. Adrenal nodule presenting solitarily with a size smaller than 2 cm suggests APA. Few studies have established that CT scans cannot differentiate adenoma from bilateral adrenal Hyperplasia and the radiographical interpretation is often not associated with a functional equivalent [14].

Management of hyperaldosteronism

The management of PA depends on the etiological factors behind the disease. The aim of complete treatment of PA is the reduction of the effects produced by excess aldosterone in the system like myocardial infarction, heart failure, stroke, etc., and increasing the levels of potassium, controlling the blood pressure levels [15].

The commonest mode of treatment is surgery which is done through a laparoscope. Using a laparoscopy technique increases patients' comfort by reducing the recovery time and duration of hospital stay. Complete or partial removal of the adrenal glands (Adrenalectomy) is

suggested to reduce the aldosterone levels in the body; complete removal of adrenal glands has proven to give better results than partial removal as there are lesser chances of recurrence and better reduction in symptoms [16]. A novel approach to surgical treatment is radiofrequency ablation which is done in unilateral APAs. Radiofrequency ablation requires an image-guided placement of a needle followed by ablation. Although radiofrequency ablation has various advantages like reduced healing time, non-surgical management, and more patient comfort, it has its own set of drawbacks like the destruction of the pathological tissue leading to the inability of the clinician to do a histopathological test; patients have also experienced hypertensive episodes, pain in the abdomen, abscess formation in the adrenals, inflammation of the pancreas to name a few [17].

Abscission and removal of adrenal glands tend to reduce hypertension and reverse hypokalemia. A wide range of success rates ranging from 30 - 70% is seen for unilateral adrenalectomy, with unsuccessful cases mainly being either case of existing family history [18]. Cautions should be taken preoperatively and postoperatively to ensure successful management. Preoperatively, the blood pressure and potassium levels should be controlled well by adding a mineralocorticoid receptor antagonist (MRA) [12]. Post operatively, some patients may suffer from an increased state of potassium, wasting of salt, dehydration, and hypotension as a result of decreased secretion of aldosterone from the contralateral gland. To avoid such complications, administration of MRAs and Potassium are ceased. The overall improvement in hypertension and other symptoms takes about one to six months postoperatively [19].

Patients who opt for a Non-surgical treatment approach, Bilateral Hyperplasia, or cases where surgery cannot be performed are treated using MRAs. The most commonly used drug is Spironolactone or eplerenone. The endocrine Society guidelines in 2016 stated that spironolactone dosage starts with 50 to 400 mg per day taken once daily and can be slowly increased up to two weeks depending on the decrease or increase in clinical symptoms. The disadvantages associated with spironolactone in men and women are different. In men, gynecomastia and erectile dysfunction have been seen, and women have generally presented with menstrual dysfunction. The dosage of Eplerenone starts with 25 mg twice a day and goes up to 100 mg per day varying on the patient's needs [20]. Other drugs like amiloride and calcium channel antagonists have also been shown to reduce hypertension and are generally used in addition to spironolactone. Lifestyle changes like alcohol cessation, avoidance of smoking, regular physical workouts, reducing sodium consumption, and maintaining body weight also aid in the treatment [21].

Treatment of secondary Hyperaldosteronism generally aims at improving renal function, controlling blood pressure and cardiovascular diseases. Medical therapy in combination with revascularization techniques can be used as a treatment modality for secondary hyperaldosteronism. Cases of fibromuscular dysplasia in the renal artery are managed with primary angioplasty, but a stent with angioplasty is required in cases of atherosclerotic renovascular disease. Drugs like ACE inhibitors and ARBs are generally the preferred choice of medical therapy as they help to reduce blood pressure while protecting renal functions.

The major complications associated with Hyperaldosteronism are cardiovascular emergencies like myocardial infarction, left ventricular hypertrophy, atrial fibrillation, and stroke [22].

Conclusion

The excess of aldosterone in the system is termed Hyperaldosteronism. Hyperaldosteronism is different from other hormonal excess states in the body as the effects of HA are mainly related to the cardiovascular tissues leading to an increased risk of fatality. The recent technological advances have enabled us to diagnose the condition more effectively, which further helps in better treatment planning for the condition. Understanding the etiological factors is of utmost importance as it dominates the management technique to be used. Radiofrequency ablation and Laparoscopic surgeries to manage HA have shown increased patient compliance enabling a better prognosis of the disease.

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