



OVERVIEW OF HYPERALDOSTERONISM

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Abstract:

The zona glomerulosa, an outer layer of the Adrenal cortex, is designated as such due to its function of secreting the mineralocorticoid hormone. When there is an elevation in aldosterone secretion from the zona glomerulosa, it is identified as hyperaldosteronism, a condition with significant physiological implications. The primary responsibility of aldosterone lies in regulating the volume of circulation and metabolic processes within the body, showcasing its critical role in maintaining homeostasis. Deviations in the aldosterone levels can lead to alterations in extracellular volume, potentially disrupting the delicate balance of bodily fluids. Moreover, aldosterone influences cardiovascular tissues such as the endothelium and myocardium, highlighting its multifaceted impact on physiological functions beyond fluid balance. The effective management of Primary Aldosteronism (PA) hinges on identifying and addressing the underlying causes of the disorder, emphasizing the importance of a comprehensive approach to treatment. The overarching goal of treating PA comprehensively involves mitigating the adverse effects stemming from excessive aldosterone levels, which can manifest as severe conditions like myocardial infarction, heart failure, and stroke, underscoring the urgency of intervention. Furthermore, interventions aim to restore potassium levels, regulate blood pressure, and restore the body's equilibrium. The intricate interplay between aldosterone, fluid balance, and cardiovascular health underscores the complexity of PA management, necessitating a tailored and holistic treatment strategy to optimize patient outcomes.

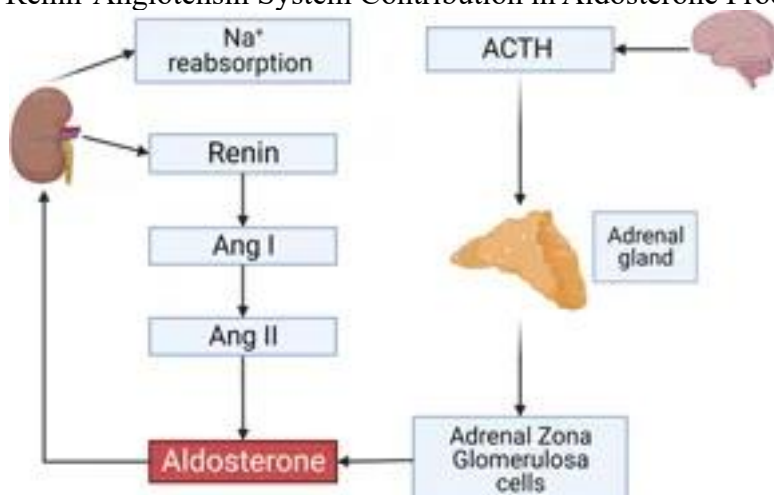
Introduction:

The outermost layer of the adrenal cortex is known as the zona glomerulosa, which is responsible for secreting the mineralocorticoid hormone. Hyperaldosteronism is the term used to describe the increased secretion of aldosterone from the zona glomerulosa. Aldosterone plays a crucial role in

maintaining the circulation volume and various metabolic activities within the body. Any disturbances in the aldosterone levels can lead to alterations in extracellular volume. This hormone facilitates the elimination of potassium and hydrogen ions through urine while promoting sodium reabsorption, aiding in water retention and intravascular volume expansion. Also, aldosterone significantly affects cardiovascular tissues, such as the endothelium and myocardium. [1,2].

The exclusive aldosterone production occurs solely within the zona glomerulosa layer of the adrenal cortex due to the presence of aldosterone synthase (CYP11B2) in this particular layer. Several factors, such as adrenocorticotrophic hormone, angiotensin II, potassium, and estrogen, play crucial roles in aldosterone secretion. The increased expression of CYP11B2 and the phosphorylation of the StAR protein are key mechanisms leading to enhanced aldosterone production. Besides, the regulation of aldosterone production is also influenced by the renin-angiotensin system, which adds another layer of complexity to the process. The intricate interplay between various factors and regulatory pathways ultimately controls the synthesis and secretion of aldosterone. This complex regulatory network ensures that aldosterone levels are finely tuned to meet the body's physiological needs [3]. A detailed explanation of the actions involved in aldosterone production can be observed in the schematic diagram (Figure 1). This visual representation aids in understanding the sequential events and molecular processes that culminate in the synthesis of aldosterone within the adrenal cortex [4].

Figure 1: Renin-Angiotensin System Contribution in Aldosterone Production [5].



Increased expression of serum potassium also plays a crucial role in regulating aldosterone production due to its impact on aldosterone synthase production. The activity of ACTH is another factor that contributes to the stimulation of aldosterone production. Markou et al. conducted a study focusing on the correlation between elevated aldosterone synthesis and hypertension in patients, determining that heightened stress levels primed the zona glomerulosa cells, increasing aldosterone production. The main clinical manifestation of Hyperaldosteronism typically manifests as a mild to moderate form of hypertension. This medical condition can be categorized into primary and secondary Hyperaldosteronism, which exhibit similar clinical presentations but differ in their biochemical profiles. The management of Hyperaldosteronism necessitates a tailored approach that considers the individual's underlying causes and specific symptoms. The treatment strategy for each case of Hyperaldosteronism should be carefully customized based on the etiology and the clinical manifestations observed in the patient. [6].

Etiology:

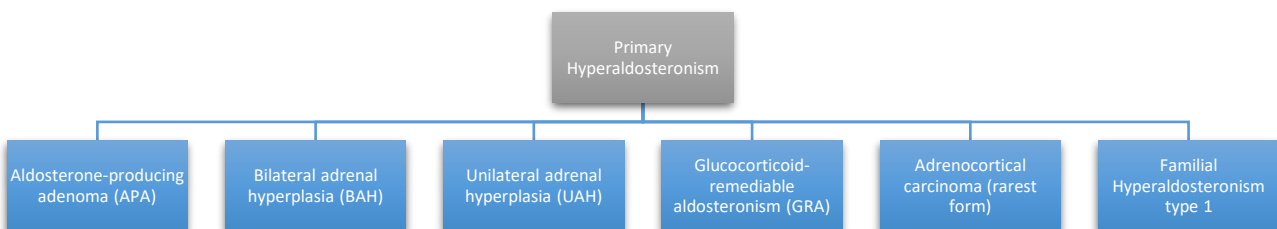
Hyperaldosteronism, whether in its primary or secondary form, can arise due to a variety of factors that differ depending on the specific subtype being considered [4].

Primary Hyperaldosteronism:

The primary cause of aldosteronism is the heightened synthesis of aldosterone originating from the adrenal glands. This overproduction of aldosterone is primarily attributed to a reduction in plasma renin activity and an escalation in the ratio of plasma aldosterone to renin activity. Primary aldosteronism can manifest as Conn syndrome, characterized by a primary tumor within the gland or unilateral Adrenal Hyperplasia. Additionally, there exist several less prevalent subcategories of primary hyperaldosteronism (PA). These subtypes may vary in clinical presentation and underlying mechanisms, necessitating a comprehensive understanding for accurate diagnosis and management. The complexity of primary aldosteronism underscores the importance of thorough evaluation and tailored treatment strategies to address the diverse manifestations and potential complications associated with this endocrine disorder.

The various subtypes of Primary Hyperaldosteronism are as follows (Figure 2): Aldosterone-producing adenoma (APA), Bilateral adrenal hyperplasia (BAH), Unilateral adrenal hyperplasia (UAH), Glucocorticoid-remediable aldosteronism (GRA), Adrenocortical carcinoma (considered the rarest form), and Familial Hyperaldosteronism type 1. Aldosterone-producing adenoma (APA) refers to a benign tumor in the adrenal gland that autonomously produces aldosterone. Bilateral adrenal hyperplasia (BAH) involves the enlargement of both adrenal glands, leading to excessive aldosterone production. Unilateral adrenal hyperplasia (UAH) is characterized by the overgrowth of one adrenal gland, resulting in increased aldosterone secretion. Glucocorticoid-remediable aldosteronism (GRA) is a genetic disorder where aldosterone production is regulated by adrenocorticotrophic hormone. Adrenocortical carcinoma is an exceedingly rare malignant tumor of the adrenal cortex associated with excess aldosterone release. Familial Hyperaldosteronism type 1 is an inherited condition marked by early-onset hypertension due to overactive adrenal glands. [4].

Figure (2): Primary Hyperaldosteronism subtypes



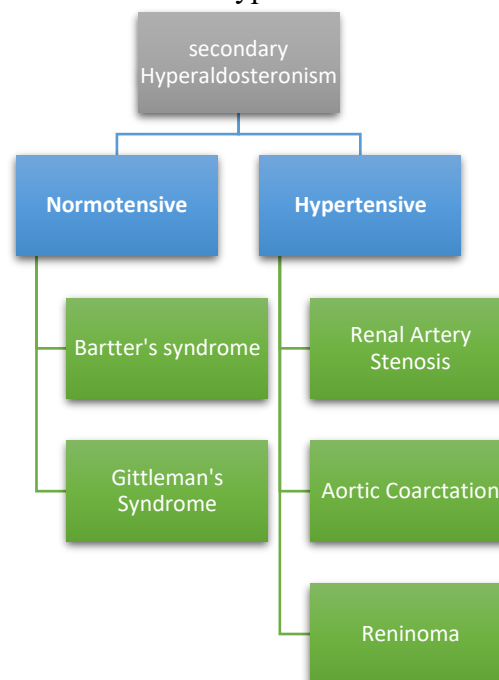
Bilateral adrenal hyperplasia, which accounts for about 60% of cases of hyperaldosteronism, is the most prevalent form of this condition, followed by aldosterone-producing adenomas (APAs) and unilateral adrenal hyperplasia (UAH), which together make up the remaining 40% of cases. Thorough management of hyperaldosteronism necessitates a comprehensive understanding of its etiology and the attainment of a definitive diagnosis, as treatment primarily revolves around addressing the underlying causes. Despite some subtle differences, APAs and UAH share many biochemical aspects. APAs typically manifest as small tumors, usually measuring no more than 2 centimeters, with histopathological features displaying cells from both the glomerulosa and fasciculata. The key distinguishing factor between diagnosing UAH and APA lies in the former's absence of a detectable radiographic mass. The recommended approach for managing both APAs and UAH is through unilateral adrenalectomy. In comparison to APAs, bilateral adrenal hyperplasia typically presents with less severe symptoms of hypertension and hypokalemia. Adrenal carcinomas, on the other hand, are characterized by larger tumor sizes, reaching up to 4 centimeters, and the secretion of a variety of

adrenal cortical hormones such as cortisol and aldosterone, although their involvement in primary aldosteronism has been minimal. [4,7].

Secondary Hyperaldosteronism:

Increased activity of the Renin-angiotensin system results in the overproduction of aldosterone, leading to the development of Secondary Hyperaldosteronism (SH). SH can be categorized into different subtypes based on the underlying factors that contribute to hypertension and those that do not. When considering normotensive SH, disorders like Bartter's syndrome and Gitelman's syndrome are commonly observed, each with distinct pathophysiological mechanisms. On the other hand, hypertensive SH may be associated with conditions such as Renal Artery Stenosis or Aortic Coarctation, which directly impact blood pressure regulation. Furthermore, specific rare causes like Reninoma can also lead to the manifestation of Secondary Hyperaldosteronism, highlighting the complexity and diversity of this endocrine disorder in clinical practice [8].

Figure (3): secondary Hyperaldosteronism subtypes



Diagnosis of Hyperaldosteronism:

The diagnosis of hypertensive aldosteronism (HA) can often pose a significant challenge due to the potential overlap of symptoms with various other hypertensive disorders, ultimately resulting in a reduced sensitivity of the diagnostic tests employed in clinical settings. Healthcare professionals must exercise caution and thorough evaluation when encountering patients presenting with hypertension, as they should consistently entertain the possibility of HA as an underlying condition. In cases ranging from mild to severe hypertension among patients, there exists a notably heightened probability of an associated increase in aldosterone levels, further underscoring the need for targeted screening and diagnostic measures. The esteemed Endocrine Society has meticulously outlined specific screening criteria to guide clinicians in determining the appropriate candidates for further assessment and potential diagnosis of HA, as delineated in their comprehensive guidelines and recommendations. These guidelines encompass various crucial factors and indicators that necessitate consideration, such as persistent blood pressure readings exceeding 150/100mm Hg on multiple occasions, resistance to three or more hypertensive medications leading to escalating treatment requirements, the coexistence of sleep apnea alongside hypertension, the presence of adrenal adenoma in conjunction with hypertension, a documented family history of early-onset hypertension, instances of hypokalemia concurrently with hypertension, and lastly, individuals with familial predisposition to primary

aldosteronism who manifest with symptoms of hypertension. By adhering to these established screening parameters and criteria, healthcare providers can enhance the accuracy and efficiency of their diagnostic processes, thereby facilitating the timely identification and management of hypertensive aldosteronism in affected individuals [9].

A fluctuating blood pressure measurement may indicate the presence of a hypertensive crisis, which can vary from being within the normal range to reaching severe levels, depending on the specific subtype of the hypertensive crisis being experienced. Individuals affected by Renal artery stenosis and coarctation of the aorta often exhibit elevated blood pressure readings, accompanied by symptoms such as headaches, visual disturbances, vertigo, chest pain, and respiratory distress. Conversely, patients diagnosed with conditions like heart failure, cirrhosis, or nephrotic syndrome may show a reduction in blood volume, leading to lower blood pressure levels. Conditions such as Glitterman's and Bartter's syndrome are associated with decreased blood pressure readings in affected individuals. Furthermore, a deficiency in potassium levels within the body can manifest as various neuromuscular symptoms, including muscle weakness, fatigue, muscle cramps, muscle deterioration, and irregularities in heart rhythm. [8].

Diagnostic tests for HA.

The diagnostic assessment for Hyperaldosteronism presents similarities with those observed in conditions such as Hypokalemia, hyponatremia, and decreased magnesium levels. When evaluating patients with HA, the initial examination typically involves measuring plasma renin activity (PRA) and plasma aldosterone concentration (PAC). In Primary Aldosteronism (PA) cases, any fluctuations in PRA or PAC levels tend to be insignificant due to the excessive secretion of aldosterone by the glomerulosa. Conversely, in Secondary Hyperaldosteronism (SH), elevated readings of PAC and PRA are commonly observed. Optimal test outcomes are usually obtained when conducting the assessments in the morning, approximately two hours post-patient awakening. The patient should remain seated for 5-10 minutes before the commencement of the test. The PAC to PRA ratio has emerged as a reliable confirmatory diagnostic tool for PA, exhibiting a specificity and sensitivity exceeding 90%. A research study by Vilela and colleagues deduced that a PAC/PRA ratio exceeding 20 and a PAC value surpassing 15 ng/dL is indicative enough to substantiate a diagnosis of Hyperaldosteronism. Notably, in secondary Hyperaldosteronism, PRA, and PAC values are elevated, yet the PAC/PRA ratio remains lower than PA [3,10-12].

The final diagnosis can be reached by decreasing the presence of Aldosterone in the system. This reduction in aldosterone levels can be achieved by elevating sodium levels in the body, which oral or intravenous methods can do. In the case of oral loading, patients are instructed to incorporate approximately 5000mg of sodium into their diet or take a 90mEq tablet over three days to reduce Aldosterone values. Hyperaldosteronism is typically indicated by a PAC value exceeding 12ng/dL, highlighting the importance of monitoring Aldosterone levels. Individuals may choose intravenous sodium loading when time constraints or emergencies are a concern. This process involves the infusion of two liters of isotonic saline solution over 4 hours. Following this procedure, if the resultant aldosterone concentration surpasses 10ng/dL, it may suggest the presence of underlying health issues that need further investigation. [13].

Adrenal vein sampling (AVS) is widely recognized as the benchmark method for distinguishing between unilateral and bilateral diseases. The AVS procedure involves the extraction of samples from both the left and right adrenal veins, along with the inferior vena cava, which are subsequently analyzed for levels of aldosterone and cortisol. A contradiction between the readings from the left and right veins typically indicates a unilateral pathology, pinpointing the specific side where an adenoma may be located. Conversely, a harmonious reading usually points towards a bilateral pathology. Patients who are deemed unsuitable candidates for AVS sampling are typically individuals under the age of 35, particularly those with potassium deficiencies, elevated aldosterone levels, and indications of adrenal carcinoma on imaging scans. Furthermore, an elevated pH level in the tissue has been linked to hyperaldosteronism, providing additional insights into the underlying physiological conditions associated with this disorder [13,14].

Radiographic Imaging in PA:

Computed tomography (CT) scans have been widely recognized as the most effective radiographic modality for diagnosing primary aldosteronism (PA). It is crucial to note that adrenocortical carcinomas typically manifest as masses that exceed 4 cm in size, and it is imperative to utilize CT scans to eliminate the possibility of this condition. When an adrenal nodule is found in isolation and its size measures less than 2cm, it indicates an aldosterone-producing adenoma (APA), underscoring the significance of CT scans in the diagnostic process. Despite the utility of CT scans, certain research studies have shown limitations in their ability to differentiate between adenoma and bilateral adrenal hyperplasia, with the radiological findings often lacking correlation with the functional status of the adrenal glands. [15].

Management of Hyperaldosteronism

Primary aldosteronism (PA) management is intricately linked to the identification and understanding of the underlying etiological factors contributing to the disease. The overarching goal of treating PA comprehensively lies in mitigating the adverse consequences stemming from heightened aldosterone levels within the body, such as myocardial infarction, heart failure, and stroke, among others. Furthermore, an essential component of effective PA treatment involves addressing imbalances in potassium levels and achieving optimal control over blood pressure fluctuations to ensure the restoration of physiological equilibrium. [16].

The most common treatment mode involves using surgical procedures that are carried out using a laparoscope, a minimally invasive tool. The utilization of laparoscopy in medical interventions has been associated with enhanced levels of comfort for patients, primarily due to the reduction in the time required for recovery post-surgery and a decrease in the length of hospital stay. It is recommended that patients undergo either complete or partial removal of the adrenal glands, known as Adrenalectomy, to lower the levels of aldosterone within the body effectively. Notably, research indicates that complete removal of the adrenal glands yields superior outcomes compared to partial removal, as it decreases chances of recurrence and more pronounced alleviation of symptoms. A contemporary and innovative approach to surgical intervention is radiofrequency ablation, a technique typically performed in cases of unilateral Aldosterone-Producing Adenomas (APAs). This method involves precisely placing a needle guided by imaging techniques and applying ablation to the targeted area. While radiofrequency ablation offers numerous advantages, such as accelerated healing times, non-invasive management, and heightened patient comfort levels, it is imperative to acknowledge its inherent limitations. These drawbacks include the complete obliteration of pathological tissue, which impedes the clinician's ability to conduct histopathological examinations, potentially limiting the diagnostic capabilities. Furthermore, patients have reported experiencing hypertensive episodes, abdominal pain, formation of abscesses in the adrenal glands, as well as pancreatic inflammation, among other adverse effects [17,18].

Abscission and extraction of the adrenal glands have been found to tend to decrease hypertension and reverse hypokalemia. The success rates for unilateral adrenalectomy vary widely, ranging from 30% to 70%, with cases of failure often linked to a pre-existing family history. It is crucial to exercise caution both before and after the procedure to ensure effective management. Before surgery, it is essential to carefully regulate blood pressure and potassium levels by incorporating a mineralocorticoid receptor antagonist (MRA) into the treatment plan. Following the operation, some patients may experience elevated potassium, salt depletion, dehydration, and hypotension due to reduced aldosterone secretion from the remaining gland. The administration of MRAs and potassium should be discontinued to prevent such complications. The overall amelioration of hypertension and other associated symptoms typically occurs within one to six months post-surgery. It is imperative for healthcare providers to closely monitor patients during this period to address any potential issues that may arise postoperatively. Additionally, patient education regarding adherence to postoperative care instructions and follow-up appointments is crucial for long-term success and optimal health outcomes. Furthermore, ongoing research in this field is essential to advance our understanding of the effects and outcomes of adrenal gland removal on hypertension and hypokalemia reversal [19,20].

Patients who choose a non-invasive treatment strategy, those with Bilateral Hyperplasia, or scenarios where surgery is not a viable option are managed through the application of Mineralocorticoid Receptor Antagonists (MRAs). The main pharmaceutical options utilized are Spironolactone or eplerenone. As per the guidelines of the Endocrine Society in 2016, the recommended initial spironolactone dosage ranges from 50 to 400mg per day, taken once daily, with the possibility of gradual increments over two weeks based on the changes in clinical manifestations. The adverse effects linked with spironolactone differ between males and females. Males have reported instances of gynecomastia and erectile dysfunction, while females commonly exhibit menstrual irregularities. Eplerenone is typically administered at an initial dose of 25 mg twice daily, which can be adjusted to 100 mg per day depending on the patient's requirements. Additionally, medications such as amiloride and calcium channel blockers have displayed efficacy in reducing hypertension and are often prescribed in conjunction with spironolactone. Furthermore, implementing lifestyle modifications such as discontinuation of alcohol consumption, avoidance of smoking, engaging in regular physical exercise, reducing sodium intake, and maintaining a healthy body weight are also beneficial in the overall management of the condition. [21,22].

Treatment of secondary hyperaldosteronism typically focuses on enhancing renal function, managing blood pressure, and addressing cardiovascular conditions. One approach to managing secondary hyperaldosteronism involves utilizing a combination of medical interventions and revascularization techniques. Primary angioplasty is commonly employed in situations involving fibromuscular dysplasia within the renal artery. At the same time, cases of atherosclerotic renovascular disease may necessitate the use of a stent in conjunction with angioplasty. The preferred pharmacological agents for medical treatment often include ACE inhibitors and ARBs due to their ability to lower blood pressure levels and protect renal functions. The primary complications associated with Hyperaldosteronism are severe cardiovascular events such as myocardial infarction, left ventricular hypertrophy, atrial fibrillation, and stroke. These complications can significantly impact the overall health and well-being of individuals with this condition, emphasizing the importance of timely and effective management strategies to mitigate risks and improve outcomes. In clinical practice, a comprehensive approach that addresses the underlying causes and the associated complications of secondary Hyperaldosteronism is essential for optimizing patient care and promoting long-term health and quality of life [23].

Conclusion:

Hyperaldosteronism, also known as the excess of aldosterone, is a medical condition that sets it apart from other hormonal excess states due to its specific effects on cardiovascular tissues, which consequently heightens the risk of fatality. The recent advancements in technology have revolutionized the diagnosis of this condition, allowing for a more precise and accurate identification of Hyperaldosteronism. This improved diagnostic capability plays a crucial role in enhancing the efficacy of treatment planning for individuals afflicted with Hyperaldosteronism. Cognizance of the underlying causes of this condition holds paramount importance as it significantly influences the choice of management strategies to be implemented. Procedures such as radiofrequency ablation and Laparoscopic surgeries have emerged as effective techniques in managing Hyperaldosteronism, contributing to enhanced patient compliance and ultimately leading to a more favorable prognosis for individuals grappling with the disease. By leveraging these innovative treatment modalities, healthcare professionals can better address the complexities of Hyperaldosteronism and improve the overall quality of care provided to affected individuals.

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