ACCSCIENCE PUBLISHING

Gene & Protein in Disease

REVIEW ARTICLE

A review of current diagnostic and treatment methods for key aldosterone-related diseases

Sujuan Wang[1,2], Qiaohui Zhao[2], and Tianyun Wang[1]*

[1]Henan International Joint Laboratory of Recombinant Pharmaceutical Protein Expression System, Xinxiang Medical University, Xinxiang 453003, Henan, China

[2]Zhengzhou Immuno Biotech Co., Ltd., Henan, China

Abstract

Aldosterone is a steroid hormone secreted from the adrenal cortex and metabolized primarily in the kidneys. It promotes sodium retention and potassium excretion. Most plasma aldosterone exists in free form, with a rapid turnover rate. The increased in aldosterone in the body may lead to various metabolic diseases, such as primary aldosteronism, diabetes, and chronic kidney disease. The clinical detection methods for aldosterone include radioimmunoassay, chemiluminescence immunoassay, and liquid chromatography tandem mass spectrometry (LC-MS/MS). In addition to addressing the issue of false negatives and false positives from cross-reaction in immunoassays, the advantages of high-throughput detection are reflected through the use of LC-MS/MS. Furthermore, there is also new progress in the development of a related mineralocorticoid receptor (MR) antagonist, from spironolactone to eplerenone, and to a third-generation MR antagonist, and finerenone, which has been approved by the United States Food and Drug Administration in 2021. The side effects of spironolactone and eplerenone can be overcome by finerenone, and the third-generation antagonist has shown significant effect in the treatment of chronic kidney disease associated with Type 2 diabetes. In this paper, aldosterone-related diseases, the clinical detection methods, and the corresponding treatment methods are discussed.

Keywords: Aldosterone; Primary aldosteronism; Liquid chromatography tandem mass spectrometry; Mineralocorticoid receptor antagonist

***Corresponding author:**
Tianyun Wang
(wtianyuncn@126.com)

Citation: Wang S, Zhao Q, Wang T, 2022, A review of current diagnostic and treatment methods for key aldosterone-related diseases. *Gene Protein Dis*, 1(2):136.
https://doi.org/10.36922/gpd.v1i2.136

Received: June 15, 2022
Accepted: September 12, 2022
Published Online: October 3, 2022

1. Introduction

Aldosterone (ALD), which was first discovered in the 1950s, is a mineralocorticoid secreted by the adrenal cortex in the face of physiological stimuli, such as angiotensin II. It can increase potassium ion (K^+) levels and decrease sodium ion (Na^+) levels in the plasma[1]. In human kidneys, aldosterone is metabolized to dihydro and tetrahydro derivatives, and subsequently glucuronidated to form aldosterone 18β-glucuronide, which plays an important role in daily aldosterone clearance[2]. Aldosterone not only regulates sodium-potassium balance in the body, but also blood pressure in the extracellular space as well as in secondary hypertension, atherosclerosis, diabetes, cardiovascular diseases, and other diseases. Aldosterone has an independent pro-inflammatory effect, leading to varying degrees of damage to target organs, such as

the heart, brain, and kidney, through inflammatory responses[3]. It is activated in a mineralocorticoid receptor (MR)-dependent and -independent manner through both, genomic and non-genomic pathways, but its effects are mediated primarily through the MR. On binding to MR, the aldosterone-MR complex is translocated to the nucleus to regulate gene expression (genomic pathways)[4]. Non-genomic effects, which may be mediated by MR or other receptors (e.g., G protein-coupled estrogen receptor I or angiotensin receptor Type I), are exerted within minutes, independent of transcription or translation. Whether through aldosterone itself or other receptors, aldosterone can affect vascular smooth muscle cells and endothelial function without involving MR[5].

Therefore, the early detection and regulation of aldosterone levels are crucial for the prevention of chronic metabolic diseases, such as hypertension, diabetes, and atherosclerosis[6]. Considering the importance of early detection of aldosterone levels, this review focuses on aldosterone-related diseases, the clinical detection methods, and the corresponding treatment methods.

2. Relationship between aldosterone and diseases

2.1. Relationship between aldosterone and hypertension

Hypertension is a chronic disease that is prevalent worldwide. There are about 245 million hypertensive patients in China, and the prevalence is still rising. Hypertension can be divided into primary hypertension and secondary hypertension. The causes of primary hypertension are unknown, and there is no cure for it. Secondary hypertension is a condition that occurs during the onset of certain diseases and resolves when the primary disease is cured[7]. Among them, primary aldosteronism (PA), which is related to abnormal aldosterone secretion, is one of the common causes of secondary hypertension. Its clinical manifestations include hypertension, hypokalemia, and decreased renin secretion.

The synthesis of physiological aldosterone is mainly regulated by potassium ions and the renin-angiotensin-aldosterone system (RAAS); it also has an acute response to adrenocorticotropic hormone[8]. RAAS is usually activated in the context of intravascular volume depletion or decreased renal artery perfusion. It increases intravascular volume by promoting sodium and water reabsorption in distal renal tubules and collecting ducts. The hyperactivation of the renal MR by aldosterone leads to intravascular volume expansion, which increases the risk of hypertension with or without hypokalemia[9]. Sodium and aldosterone together, in excess, promote inflammation, fibrosis, and vascular remodeling in various target organs. Therefore, compared with essential hypertension (EH), an excess of aldosterone caused by PA is more likely to induce cardiovascular complications, including coronary artery disease, myocardial infarction, stroke, transient ischemic attack, atrial fibrillation, heart failure, and other diseases[10].

2.2. Relationship between aldosterone and diabetes

Diabetes is a hyperglycemic metabolic disease caused by insulin deficiency or insulin insensitivity. The number of diabetic patients is gradually increasing with the improvement of the population's standard of living[11]. As of 2021, statistics from the International Diabetes Federation have shown that there are about 537 million diabetic patients worldwide, of which the number of adult diabetic patients in China is about 140 million; moreover, the trend has been increasing year after year with the average age of patients decreasing. Although the specific pathogenesis of diabetes is still unclear, islet B cell damage has become a recognized pathogenesis and basis for the disease. According to several reports, excess aldosterone may easily lead to decreased responsiveness of peripheral target organs such as liver and skeletal muscle to insulin. In addition, increased aldosterone levels not only affect the function and survival of islet B cells, but also lead to oxidative stress in islet B cells, which may, in turn, result in functional impairment and apoptosis of islet B cells[12,13]. There are many reasons for islet B cell damage: High glucose and lipids, inflammatory factors, and common mineralocorticoids and glucocorticoids, among which aldosterone is an indispensable mineralocorticoid, involved in physiological regulation and the regulatory system of RAAS[14]. On RAAS activation, the level of aldosterone increases, which leads to metabolic diseases, such as diabetes, hypertension, and obesity. According to epidemiological data, there is a gradual increase in plasma aldosterone level in diabetic patients[12].

In a study of safflower ginger leaf aqueous extracts in diabetes mellitus, streptozotocin-induced mice were divided into a control group (treated with distilled water), HC group (*Hedychium coronarium* and ginger lily extract), and SO group (ginger lily, a supplement that aids blood sugar regulation and contains two substances: Red yeast rice [RYR, 15%] and HC [7.2%], called SugarOut). After dissolving the two test substances in distilled water, the mice were gasserized in accordance with the dosage standards in FDA guideline. Fasting glucose and oral glucose tolerance tests as well as aldosterone and insulin tests were performed. The results showed that in the detection of fasting blood glucose and glucose tolerance, the rate of weight gain of mice after gastric HC and SO was slower than that of the

control group, and the fasting blood glucose and glucose tolerance of the mice in the HC group were significantly reduced. Furthermore, the insulin levels of the mice in both the HC and SO groups were significantly higher than those in the control group. Significant reductions in aldosterone were also found in both the HC group and the SO group compared to the control group. The increase in aldosterone may lead to impaired glucose tolerance, decreased islet ß-cell function, decreased insulin sensitivity to tissues, and thus increase the risk of diabetes. The study also confirmed that aldosterone levels are closely related to the action of insulin and RAAS plays a key role in diabetes[15].

2.3. Relationship between aldosterone and atherosclerosis

PA increases the risk of cardiovascular disease (CVD) and independent of blood pressure. Animal models have suggested that aldosterone accelerates atherosclerosis through pro-inflammatory changes in innate immune cells[16]. According to the study, patients with PA are more likely to develop atherosclerotic cardiovascular events compared to essential hypertension. This suggests that chronic exposure to high aldosterone levels, which is increasingly prevalent, has adverse effects on the cardiovascular system. A growing number of clinical studies have also emphasized that excessive activation of RAAS not only leads to hypertension, but also causes atherosclerosis, congestive heart failure, and other diseases[17]. The activation of MR in endothelial cells promotes infiltration of inflammatory cells, followed by inflammation and fibrosis. The infiltrating macrophages engulf oxidized low-density lipoprotein and become foam cells, thereby promoting atherosclerosis[9].

2.4. Relationship between aldosterone and chronic kidney disease

Chronic kidney disease (CKD) is also a significant public health concern. Based on evidence, the excessive activation of RAAS is one of the key pathogeneses in its complex pathophysiology. RAAS is distributed throughout the blood vessel walls, heart, kidneys, and other organs of the body, but the kidneys, which secrete renin, are the initial organs of the RAAS[9]. Therefore, when RAAS is overactivated, renin secretion increases, which, in turn, stimulates angiotensin I receptors, leading to vascular endothelial cell growth, oxidative stress, and vascular inflammation. This exacerbates arterial stiffness and accelerates vascular aging. The increased angiotensin II and aldosterone levels may promote cardiomyocyte inflammation, fibrosis, and hypertrophy, leading to cardiovascular remodeling and dysfunction[17].

2.5. Relationship between aldosterone and obesity

It is still unclear whether elevated aldosterone levels in the body lead to obesity or whether obesity leads to elevated aldosterone levels. Studies have yet to determine which factor is the cause and which is the effect. In a study, obese patients who had excess aldosterone before losing weight continued to have lower plasma aldosterone levels after losing weight[18]. There are also studies that have investigated the correlation between fat tissue and aldosterone in obese men and women with normal blood pressure. The findings revealed that only the aldosterone levels in women were significantly positively correlated with adipose tissue and body mass index (BMI) independently of renin. The study raised a possibility for investigating the sex-specific effect of adipose tissue on aldosterone[19].

In obese patients, the level of leptin is significantly increased. Leptin can increase the aldosterone level through RAAS and adrenal spherical cells[20]. Studies have shown that leptin stimulates sympathetic activity by releasing renin through β-adrenaline receptors and the sympathetic nervous system activates RAAS by elevating angiotensinogen in nerve tissue[21]. Renin can also act with adrenal globular band cells to enhance the expression of CYP11B2 (cytochrome P450, subfamily XIB, and polypeptide 2 gene) by relying on the signaling pathway of calcineurin, thereby promoting elevated aldosterone levels[22]. In addition, since aldosterone impairs the insulin signaling pathway only at concentrations that may activate glucocorticoid receptors, elevated aldosterone levels may also reduce insulin sensitivity in fat cells. However, the direct relationship between the two is still being studied[23,24].

3. Diagnostic methods for aldosterone-related diseases

Aldosterone is a steroid hormone. Since the levels of steroid hormones in the body are extremely low, the general detection level is in nmol/L or pmol/L, which increases the difficulty of clinical diagnostic testing. At present, PA is considered one of the most common causes of hypertension. Hiramatsu *et al.* first introduced the aldosterone-renin ratio (ARR) as an indicator of PA screening[25]. Although ARR is now an important screening method for the diagnosis of PA, the high false-positive rates exhibited by ARR methods are a concern. Therefore, each measurement of aldosterone and renin as well as the calculated ARR value is all extremely important[26]. According to another piece of evidence, low renin activity or concentrations are seen in the majority of hypertensive individuals, especially when renin levels are undetectably low, and aldosterone concentrations are also significantly lower than normal[27].

Therefore, to improve the accuracy of PA screening, new diagnostic methods need to be explored.

3.1. Radioimmunoassay

At present, radioimmunoassay (RIA) is used to detect plasma aldosterone concentration (PAC) and plasma renin activity (PRA). PRA is reflected by measuring the rate of conversion of angiotensinogen to angiotensin I (Ang I) per unit time. However, its downside is that it cannot directly reflect the active concentration of renin[28]. RIA detection of PAC is based on the principle of homogeneous competition, in which the content of aldosterone in samples is detected by radioiodine labeling[29]. RIA is one of the commonly used methods for clinical testing internationally. Although RIA has an ideal and mature technical process, it has several limitations: (1) Its detection of PRA is affected by the activity of renin itself and the interaction with its own substrate, which reduces the repeatability of the experimental results; additionally, its performance is poor, and the detection differences between each product are inconsistent; (2) plasma aldosterone and plasma renin activities are detected separately, and its operation process is cumbersome and time-consuming; and (3) it has certain radioactivity, with higher requirements for the experimental environment and experimental operators[27].

3.2. Chemiluminescence immunoassay (CLIA)

Although RIA is commonly used in China, the sensitivity of renin detection cannot be overlooked. Hence, the novel active/direct renin concentration (ARC/DRC) measurement method has become a new trend. CLIA is an emerging method that enables automated simultaneous measurement of renin and aldosterone concentrations[30]. CLIA is a method often used in biochemical immunoassays, usually by means of using chemiluminescence reagents that label antigens or antibodies and react with antibodies or antigens coated on the sample/magnetic particles. The antigen or antibody, which is bound or separated, will be labeled with the luminescent agent in its free state to evaluate the content of the target quantitatively or qualitatively in the sample to be tested[27-29]. CLIA can directly measure plasma renin concentration. Studies have successively proven that the effect of using this method for screening PA is not only equivalent to that of the RIA method, but that it can also overcome the shortcomings of RIA. Therefore, in 2008, this method was included in the European Endocrine Society Clinical Practice Guidelines. However, since most of the fully automatic equipment used in China is imported, it requires imported reagents. Considering the cost and the equipment itself, this method has yet to be widely employed in clinical practice in China[24].

3.3. Liquid chromatography tandem mass spectrometry

RIA and CLIA are two commonly used methods based on immune technology in China. However, they are prone to cross-reactions with other steroid hormones or metabolites, resulting in false positives or false negatives[31,32]. Liquid chromatography tandem mass spectrometry (LC-MS/MS) is a detection method that combines chromatographic separation and mass spectrometry analysis. LC-MS/MS is predominantly used for small molecule detection and newborn screening, prenatal care, *etc*. Having several advantages, including high sensitivity, high specificity, and high throughput, LC-MS/MS is taking the lead in the detection field[33]. However, this technology uses liquid-liquid extraction, which takes a long time for chromatographic analysis and requires a substantial amount of samples to address the issue of sensitivity. In addition to its high requirements for the laboratory environment and operators, its equipment cost is also high. Therefore, it has not been widely used in local clinical practice. In the screening of PA, although the RIA method has several disadvantages, it is still one of the commonly used methods due to its mature technology and high consistency with CLIA results. LC-MS/MS, as a novel approach in the detection field, has not gained sufficient market recognition in China. Therefore, hospitals and laboratories have not conducted enough research to collect clinical data, thus making it impossible to establish a definitive correlation with RIA and CLIA in the detection of ARR and other methods[31]. While promoting LC-MS/MS, it would be beneficial to compare the detection performance of immunoassay and mass spectrometry through experimental data, determine the correlation and difference, as well as identify the best entry point between them, so as to improve the diagnostic accuracy[34].

4. Drugs related to the treatment of aldosterone-related diseases

Aldosterone is a mineralocorticoid secreted by the adrenal cortex, and it is the last active substance of the RAAS. Aldosterone is named as such due to the oxidation of methyl by cholesterol to an aldehyde group at position C18 following a series of enzymatic reactions[2,3]. Aldosterone promotes potassium excretion and sodium reabsorption in the distal convoluted tubules and cortical collecting ducts, and it is a key hormone that regulates sodium-potassium balance and maintains homeostasis in the body. A large number of data have proven that aldosterone is related to various target organ damage diseases, which can be effectively treated by inhibiting the excessive activation of aldosterone on the MR. Studies have shown that MR

antagonists (MRAs) can competitively bind to MR with ALD, thus inhibiting the effect of ALD, and subsequently improving blood pressure[35]. At present, steroidal MRAs (spironolactone and eplerenone) are widely available, and the third-generation non-steroidal MRA, which will benefit patients with hypertension and aldosteronism, is now also in the clinical stage.

4.1. First-generation MRA: spironolactone

When sodium ion content in the body decreases or potassium ion content increases, the secretion of aldosterone will be stimulated. However, the sensitivity to potassium ion content is higher compared to sodium ions. The increase of serum potassium by 0.1 mmol/L can stimulate the secretion of aldosterone[36]. Spironolactone is the first-generation of synthetic steroid-based MRA, and its chemical structure is similar to that of aldosterone. It binds to MRA non-selectively, so that the K^+ and Na^+ exchange across the membrane of the distal convoluted tubule and collecting duct is blocked, and Na^+ excretion is increased, thus lowering blood pressure[35,37]. Other than binding to MRs, spironolactone can also bind to glucocorticoid receptors. Hence, there are certain side effects with its use, such as male impotence, sexual dysfunction, and masculinization caused by the decrease of progesterone, testosterone, and other sex hormones. However, these side effects will resolve on withdrawal[38,39].

4.2. Second-generation MRA: eplerenone

A new generation of selective aldosterone antagonist, eplerenone, was developed by Pfizer-Pharmacia under the trade name Inspra and was first marketed in the United States in 2002[38]. Eplerenone is a selective MRA with a long half-life and good tolerance. It only binds to MRs and has low affinity for receptors such as androgen and progesterone; thus, it can reduce the side effects caused by the first-generation MRA and be used in the treatment of heart failure and hypertension following myocardial infarction[35,36]. According to a study, the combined use of eplerenone and standard treatment drugs reduced the total mortality rate of the treatment group with heart failure following acute myocardial infarction by 15% ($P = 0.008$)[35].

4.3. Third-generation of MRA: finerenone

Finerenone is an oral non-steroidal MRA, discovered by Bayer in Germany. It is based on the previous two generations. Finerenone can block the adverse effects caused by excessive activation of MRs caused by aldosterone. It has shown a significant curative effect on chronic heart failure and chronic kidney disease[40,41]. Its mechanism of action involves the maintenance of sodium and potassium excretion in the epithelial cells of the distal nephron, thereby maintaining the stability of the electrolyte homeostasis. In this case, it plays a key role in maintaining a constant extracellular volume and regulating blood pressure. Studies have shown that it also has a significant effect on cardiovascular disease, but its mechanism of action needs to be further studied[42]. As a new generation of non-steroidal antagonists, its steroidal structure endows it with high selectivity and affinity for MR, allowing it to overcome the adverse effects of hyperkalemia associated with spironolactone and eplerenone (Table 1) as well as achieve maximum cardiovascular activity. The findings from animal experiments have revealed that finerenone can effectively protect the heart and kidney.

In terms of clinical research, the results of clinical Phase I trials have shown that MR antagonists are well absorbed *in vivo*. Pharmacokinetic studies have found that finerenone has an effect when its plasma concentration reaches 5–20 ng/mL. It has high oral availability, reaching about 40%, with a half-life of 15 h. Its average plasma concentration reaches a peak after 1-3 h following oral administration. In the clinical Phase II trial, 764 patients with diabetic nephropathy were observed for 60 days, and it was found that there was no difference in adverse effects between the 10 mg/day finerenone group and the placebo group compared with the control group. In the 2015 Annual Report of the European Society of Cardiology, it was reported that finerenone plays a role in improving heart failure caused by Type 2 diabetes or chronic kidney disease to a certain extent. Phase III clinical trials have shown that finerenone is safe and effective and can effectively reduce the incidence of hyperkalemia; it helps maintain a good hemodynamic effect and contributes to the prognosis of patients[39-42].

5. Summary and prospect

Aldosterone is an important steroid hormone among mineralocorticoids. It is difficult to detect aldosterone accurately because its content in blood ranges in units as low as pg/mL. CLIA addresses the limitations of radioimmunoassay and enables the simultaneous detection of renin and aldosterone concentrations; nevertheless, it is unable to solve the cross-reaction problem. In addition, reducing costs and improving the research and application of equipment and imported reagents are also major issues to be solved. The stability of the test data of the emerging liquid chromatography technology in clinical diagnosis and its correlation with RIA and CLIA should also be ascertained to determine the best entry point for the detection and diagnosis of this method.

In recent years, the number of patients with metabolic diseases caused by abnormal aldosterone

Table 1. Comparison of three generations of MRAs

Drug type	First generation	Second generation	Third generation
Representative drug name	Spironolactone	Eplerenone	Finerenone
Molecular structure	Steroidal	Steroidal	Non-steroidal
Selectivity for MR	Non-selective	Non-selective	Selective
Half-life (h)	1.4	4–6	1.7–2.8
IC50 (nM)	24	990	17.8
Usual dosage (mg/d)	25–50 (RHTN)	50–100 (RHTN)	10–20 (hypertension)
Status	Listed	Listed	Listed
Adverse reactions	Gynecomastia, irregular menstruation in women, renal insufficiency, and hyperkalemia	Renal insufficiency and hyperkalemia	Increased levels of creatine kinase and blood glucose levels, headache, dizziness

IC_{50}, drug concentration required to inhibit 50% of receptor activation; RHTN: Refractory hypertension

levels is still increasing and it is difficult to effectively treat the complications associated with these diseases. Spironolactone, as a non-selective competitive antagonist with the longest clinical application, can regulate the balance of salt and water in the body as well as improve the adverse cardiovascular effects caused by abnormal ALD levels. However, it is challenging to overcome the hormonal disorders caused by the long-term use of spironolactone, such as male-female emulsification and irregular menstruation in women. Therefore, if the aforementioned adverse reactions occur during treatment, another antagonist known as eplerenone will be used in place of spironolactone. Eplerenone is a selective antagonist that can effectively overcome the adverse reactions caused by the long-term use of spironolactone. However, it is imperative to address the adverse reactions including hyperkalemia caused by spironolactone and eplerenone. Finerenone has shown absolute advantage in lowering blood pressure and serum potassium, with some improvement in diabetes, chronic kidney disease, and other diseases. Therefore, finerenone, a third-generation antagonist that has been approved for marketing by the FDA, not only plays a role in the treatment of chronic kidney disease with Type 2 diabetes, but also has great potential in the treatment of cardiovascular disease.

Acknowledgments

None.

Funding

This work was supported by the Basic Research Project of Henan Provincial Key Scientific Research Program (No. 20zx013).

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceptualization: Sujuan Wang

Writing – original draft: Sujuan Wang

Writing – review & editing: Sujuan Wang, Qiaohui Zhao, Tianyun Wang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

References

1. Wannachalee T, Turcu AF, 2021, Primary Aldosteronism: A Continuum from Normotension to Hypertension. *Curr Cardiol Rep*, 23(8): 105.

   https://doi.org/10.1007/s11886-021-01538-8

2. Knights KM, Winner LK, Elliot DJ, *et al.*, 2009, Aldosterone glucuronidation by human liver and kidney microsomes and recombinant UDP-glucuronosyltransferases: inhibition by NSAIDs. *Br J Clin Pharmacol*, 68(3): 402–412.

   https://doi.org/10.1111/j.1365-2125.2009.03469.x

3. Gideon A, Sauter C, Ehlert U, *et al.*, 2021, Aldosterone hyperreactivity to acute psychosocial stress induction in men with essential hypertension. *Horm Behav*, 134: 105018.

   https://doi.org/10.1016/j.yhbeh.2021.105018

4. Ambroisine ML, Milliez P, Nehme J, *et al.*, 2004, Aldosterone and anti-aldosterone effects in cardiovascular diseases and diabetic nephropathy. *Diabetes Metab*, 30(4): 311–318.

https://doi.org/10.1016/s1262-3636(07)70122-2

5. Dooley R, Harvey BJ, Thomas W, 2012, Non-genomic actions of aldosterone: from receptors and signals to membrane targets. *Mol Cell Endocrinol*, 350(2): 223–234.

https://doi.org/10.1016/j.mce.2011.07.019

6. Chen ZW, Tsai CH, Pan CT, *et al*., 2019, Endothelial dysfunction in primary aldosteronism. *Int J Mol Sci*, 20(20): 5214.

https://doi.org/10.3390/ijms20205214

7. Yanan L, 2021, Value of parathyroid hormone level in differential diagnosis of patients with primary aldosteronism and nonfunctional adrenal tumors. *J Chin Pla Postgrad Med Sch*, 42(9): 913-917.

8. Tomilin VN, Pyrshev K, Khayyat NH, *et al*., 2021, With-no-lysine kinase 1 (WNK_1) augments $TRPV_4$ function in the aldosterone-sensitive distal nephron. Cells, 10(6): 1482.

https://doi.org/10.3390/cells10061482

9. Yanai K, Ishibashi K, Morishita Y, 2021, Systematic review and meta-analysis of renin-angiotensin-aldosterone system blocker effects on the development of cardiovascular disease in patients with chronic kidney disease. *Front Pharmacol*, 12: 662544.

https://doi.org/10.3389/fphar.2021.662544

10. Ting C, 2022, Correlation among systolic blood pressure load, renin-angiotensin-aldosterone system and cortisol in patients with salt-sensitive hypertensive. *Chin J Evid Bases Cardiovasc Med*, 14(1): 84-86.

11. Nianrong Z, 2021, Treatment of hypertension in diabetic patients. *Chin J Clin*, 49(12): 1399-1401.

12. Colussi G, Catena C, Lapenna R, *et al*., 2007, Insulin resistance and hyperinsulinemia are related to plasma aldosterone levels in hypertensive patients. *Diabetes Care*, 30(9): 2349–2354.

https://doi.org/10.2337/dc07-0525

13. Bakris GL, Agarwal R, Anker SD, *et al*., 2019, Design and baseline characteristics of the finerenone in reducing kidney failure and disease progression in diabetic kidney disease trial. *Am J Nephrol*, 50(5): 333–344.

https://doi.org/10.1159/000503713

14. Briet M, Schiffrin EL, 2010, Aldosterone: effects on the kidney and cardiovascular system. *Nat Rev Nephrol*, 6(5): 261–273.

https://doi.org/10.1038/nrneph.2010.30

15. Tse LS, Liao PL, Tsai CH, *et al*., 2019, Glycemia lowering effect of an aqueous extract of *Hedychium coronarium* leaves in diabetic rodent models. *Nutrients*, 11(3): 629.

https://doi.org/10.3390/nu11030629

16. Van der Heijden C, Smeets EM, Aarntzen EH, *et al*., 2020, Arterial wall inflammation and increased hematopoietic activity in patients with primary aldosteronism. *J Clin Endocrinol Metab*, 105(5): e1967–e1980.

https://doi.org/10.1210/clinem/dgz306

17. Zhu Z, 2021, Causes and countermeasures of cardiovascular events in chronic kidney disease. *Chin J Integr Trad Western Nephrol*, 22(10): 847-853.

18. Berney M, Vakilzadeh N, Maillard M, *et al*., 2021, Bariatric surgery induces a differential effect on plasma aldosterone in comparison to dietary advice alone. *Front Endocrinol* (*Lausanne*), 12: 745045.

https://doi.org/10.3389/fendo.2021.745045

19. Do Carmo JM, da Silva AA, Hall V, 2021, Impact of mineralocorticoid receptor and angiotensin II Type 1 receptor antagonism on blood pressure regulation in obese Zucker rats: Role of sex differences. *Am J Hypertens*, 34(9): 999–1005.

https://doi.org/10.1093/ajh/hpaa170

20. Wang P, Luo C, Zhu D, *et al*., 2021, Pericardial adipose tissue-derived leptin promotes myocardial apoptosis in high-fat diet-induced obese rats through janus kinase 2/reactive oxygen species/Na^+/K^+-ATPase signaling pathway. *J Am Heart Assoc*, 10(18): e021369.

https://doi.org/10.1161/JAHA.121.021369

21. Kalil GZ, Haynes WG, 2012, Sympathetic nervous system in obesity-related hypertension: Mechanisms and clinical implications. *Hypertens Res*, 35(1): 4-16.

https://doi.org/10.1038/hr.2011.173

22. Wang Y, Li CX, Lin YN, *et al*., 2021, The role of aldosterone in OSA and OSA-related hypertension. *Front Endocrinol* (*Lausanne*), 12: 801689.

https://doi.org/10.3389/fendo.2021.801689

23. Lin X, Ullah MH, Wu X, *et al*., 2021, Cerebro-cardiovascular risk, target organ damage, and treatment outcomes in primary aldosteronism. *Front Cardiovasc Med*, 8: 798364.

https://doi.org/10.3389/fcvm.2021.798364

24. Van der Heijden C, Horst RT, van den Munckhof IC, *et al*., 2020, Vasculometabolic and inflammatory effects of aldosterone in obesity. *J Clin Endocrinol Metab*, 105(8): 2719–2731.

https://doi.org/10.1210/clinem/dgaa356

25. Morimoto R, Omata K, Ito S, *et al*., 2018, Progress in the management of primary aldosteronism. *Am J Hypertens*, 31(5): 522–531.

https://doi.org/10.1093/ajh/hpy018

26. Shidlovskyi VO, Shidlovskyi OV, Tovkai OA, *et al*., 2019, Topical diagnosis and determination of the primary hyperaldosteronism variant. *J Med Life*, 12(4): 322–328.

https://doi.org/10.25122/jml-2019-0072

27. Fenghua L, 2015, Evaluation of two plasma renin and aldosterone detection methods for screening efficiency of primary aldosteronism. *Chin J Hyperten*, 23(2): 150-153.
28. Yangning H, 2019, Comparison of the diagnostic effects of chemiluminescence and radioimmunoassay on primary aldosteronism. *J Third Mil Med Univ*, 41: 2080-2086.
29. Fengfan Z, 2019, On the consistency of different methods for detecting aldosterone concentration in blood. *Chin J Endocrinol Metab*, 35(11): 934-938.
30. Jing F, 2021, Screening value of urinary aldosterone concentration in primary aldosteronism and comparison of mass spectrometry and chemiluminescence detection. *J Sun Yat Sen Univ*, 41(4): 563–571.
31. Chenfei J, 2021, Advances in the application of liquid chromatography-tandem mass spectrometry in the detection of steroid hormones in CAH screening. *Int J Lab Med*, 42(7): 881–885.
32. Zi-yun C, 2021, Diagnostic value of liquid chromatography tandem mass spectrometry in primary aldosteronism. *Chin Clin Med*, 28(5): 858–863.
33. Pilz S, Keppel MH, Trummer C, *et al*., 2019, Diagnostic accuracy of the aldosterone-to-active renin ratio for detecting primary aldosteronism. *J Endocr Soc*, 3(9): 1748–1758.

    https://doi.org/10.1210/js.2019-00145
34. Chen F, Chen Z, Peng Y, *et al*., 2021, A liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based assay for simultaneous quantification of aldosterone, renin activity, and angiotensin II in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*, 1179: 122740.

    https://doi.org/10.1016/j.jchromb.2021.122740
35. Lingli W, 2020, Application status of mineralocorticoid receptor antagonists in refractory hypertension. *Adv Cardiovasc Dis*, 41(10): 1026–1030.
36. Junfeng X, 2019, Research progress of mineralocorticoid receptor antagonists. *Chin J Gerontol*, 34(3): 724–727.
37. Ping Z, 2019, Research Progress of Aldosterone Receptor Antagonists. Vol. 21. United States: Southwest Military Doctor, p.521–524.
38. Ying-ying W, 2020, Virtual screening of antagonists for mineralocorticoid receptor. *Chin J N Drugs*, 29(6): 655–61.
39. Yuan X, Wang X, Li X, *et al*., 2019, Aldosterone promotes renal interstitial fibrosis via the AIF1/AKT/mTOR signaling pathway. *Mol Med Rep*, 20(5): 4033–4044.

    https://doi.org/10.3892/mmr.2019.10680
40. Haitao Z, 2021, Clinical application of new mineralocorticoid receptor antagonists. *Chin J Nephrol Dial Transplant*, 30(5): 449–50.
41. Yujie MM, 2016, Nonsteroidal mineralocorticoid receptor antagonist finerenone. *Modern Med Clin*, 31(1): 111–115.
42. Stewart Coats AJ, Shewan L, 2015, Eplerenone's role in the management of complex cardiovascular disorders. *Int J Cardiol*, 200: 1–2.

    https://doi.org/10.1016/j.ijcard.2015.05.128