**Original Article**

**Aldosterone Renin Ratio and Chronic Kidney Disease**

Wessam Osman¹, Hayam Al Dohani¹, Al Shaima Al Hinai¹, Suad Hannawi², Faissal A. M. Shaheen³, Issa Al Salmi⁴

¹Department of Internal Medicine, The Royal Hospital, Muscat, Oman, ²Department of Medicine, Ministry of Health and Prevention, Dubai, United Arab Emirates, ³Dr. Soliman Fakeeh Hospital, Jeddah, Saudi Arabia, ⁴Department of Renal Medicine, The Royal Hospital, Muscat, Oman

**ABSTRACT.** As a component of the metabolic syndrome, hypertension (HTN) is increasing throughout the world with variable percentages, but mostly among developing world. Aldosterone plays a role in the relationship between aldosterone and nephropathy. We aimed to evaluate the relationship between aldosterone renin ratio (ARR) and chronic kidney disease (CKD). Variables drawn from the computerized hospital information database were all patients who had an ARR above 35 (if aldosterone reading was above 300 pmol/L). A total of 1584 patients, of whom 777 were male and 807 were female, with a mean \([\text{standard deviation (SD)}]\) of 43.3 (16.5) years were studied. The mean ARR was 210.1 (SD: 246.4) in males and 214.3 and 210.1 in females, \(P = 0.51\). The mean estimated glomerular filtration rate (eGFR) was 50.2 (SD 12.6); in males, it was 49.99 (0.90) and in females, it was 50.48 (0.92), \(P = 0.70\). The regression model revealed a negative relationship between ARR and GFR with a coefficient of \(-2.08\), 95% confidence interval: \(-4.6, 0.21\), \(P = 0.07\). CKD population with HTN tends to have a very high level of ARR, and those with advanced CKD have higher ARR. However, high ARR could have low eGFR and kidney dysfunction on follow-up. In view of high prevalence of noncommunicable disease and high early CKD population, there is an important need to consider comprehensive management strategies that involve the blockage of high renin-angiotensin-aldosterone and the use of mineralocorticosteroid receptor blockers.

**Introduction**

Hypertension (HTN) continues to be one of the main risk factors for cardiovascular disease (CVD) worldwide. It is a leading risk factor for morbidity and mortality in the world. The reported prevalence of HTN varies around the world, with the lowest prevalence being in rural India (3.4% in men and 6.8% in women) and the highest prevalence in Poland (68.9% in men and 72.5% in women).¹ Approximately 75 million adults have been diagnosed with HTN in the United States, and among indus-
trialized countries, it affects 25%–35% of individuals globally. HTN is estimated to cause 4.5% of the current global disease burden and is prevalent in many developing countries as in the developed world.\(^1\)

In Oman, the age-adjusted prevalence of the metabolic syndrome was 21.0%, and over 87% of Omanis had at least one CVD risk factor (38% had hyperglycemia, 19% HTN and 34.5% had high total cholesterol).\(^2,3\) In the Gulf Collaboration Countries (GCC) consisting of six countries, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates, the prevalence of HTN ranged from 20.9% to 53%.\(^4,5\) The prevalence of HTN was also high among women in GCC countries.

Data from the Second Gulf Registry of Acute Coronary Events (GulfRACE-2) showed that 47.2% of the registered individuals were hypertensive, and women were more likely to have HTN than men. It is forecast that the number of people affected by HTN will endure a very high upsurge and, by 2025, approximately 1.5 billion individuals will be affected.\(^6\)

Chronic kidney disease (CKD) is a key problem that touches a huge percentage of people across the planet. In Oman, almost 1% of patients have severe renal failure, 9% have moderate renal failure and 29% have mild renal failure. Researchers of large-scale epidemiological studies have demonstrated that CKD patients have an increased risk of cardiovascular disorders including death, congestive cardiac failure (CCF), myocardial infarction, and cerebrovascular accidents. Several biologic pathways have been associated with this established relationship between various kidney disorders and cardiovascular outcomes, particularly the activation of the renin-angiotensin-aldosterone system (RAAS). Impaired kidney function results in RAAS activation, which in turn leads to multiple, deleterious cardiovascular effects such as increased fluid and salt resorption, vasoconstriction, and fibrosis. The understanding of these mechanisms has led to the initiation of various therapies, including aldosterone antagonists or mineralocorticoid receptor blockers (MRBs), angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), which all efficiently lessen cardiorenal complications.

Noncommunicable disease is a major problem in our region with high prevalence of diabetes, HTN, and obesity along with CKD and other end-organ dysfunction with very limited studies on aldosterone renin ratio (ARR) in our region. The ARR has been suggested as a screening tool for all groups of patients, especially those with blood pressure (BP) >160/100 mm Hg. The CKD population at our center with high BP, obesity, and various kidney function based on their estimated glomerular filtration rate (eGFR) were evaluated in this study.

**Methods**

Our hospital is the main tertiary hospital in the Sultanate of Oman, which also has nephrology as a subspecialty. Our main variables drawn from the hospital database included all patients who had an ARR over 35 (if aldosterone reading was above 300 pmol/L) and was conducted between 2006 and 2018. The medical records of participants were checked. Most of these patients are referred from other institutions, and their medication history was cross-checked. None of the patients were diagnosed to have primary hyperaldosteronism. The investigations were performed to screen them as part of our protocol for resistant HTN. The eGFR was calculated in our system according to the four-variable Modification of Diet in Renal Disease formula. The eGFR was estimated at the time of sending a sample for ARR. The eGFR is automatically calculated by an algorithm in the hospital computer system whenever renal function was requested as a blood test. It was requested every time by default, requiring no further input. Serial eGFR was not examined as a separate parameter. CKD was defined as an eGFR <60 mL/min/1.73 m\(^2\) consistent with the definition of CKD ≥ Stage 3 proposed by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. We also extracted data for the same patients for the following variables: readings of low-density lipoprotein (LDL)
>2.7 mmol/L, and glycosylated hemoglobin (HbA1C) >6.5%.

All patients were hypertensive (as per the WHO classification, defined as systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg or self-reported intake of antihypertensive medication), with body mass index above 25.

A limitation of our study was our inability to extract information relevant to our target population in terms of kidney biopsy etiologies. This is due to the indications for this procedure exceeding our sample inclusion criteria, and hence, a very small number from our sample had biopsies performed for other reasons. The same problem was applicable to radiological imaging since our hospital protocols dictate that ARR be done mainly for hypertensive patients being investigated for causes of secondary HTN, which may or may not require imaging as per clinical presentation. The number of patients undergoing the correct radiological imaging required for scientific correlation was sparse and unrepresentable.

All the 1584 patients in our study had correct ARR readings. Many of them had missing data about eGFR (n = 1199), LDL (n = 776), and HbA1c (n = 932). Patients on ARR altering medications (diuretics, aldosterone antagonists, beta-blockers, or other anti-adrenergic agents, calcium channel blockers, ACE inhibitors, or ARBs) were not excluded.

No consent was obtained since this study was done retrospectively from our own hospital’s database. It was reviewed by our Hospital Research Ethical committee and approved.

The clinical characteristics of our study population were reported as proportions for categorical data and as median for continuous data. The analysis software used for processing these data was STATA software statistical packages, StataCorp, Texas, USA. Descriptive and frequency were obtained for defined variables of interest. Chi-square test was used to test for statistical significance between categorical variables. P < 0.05 was considered statistically significant. The associations between ARR with eGFR were assessed by multivariable analyses of variance and linear regression models.

**Results**

This study included patients in our database from 2006 to 2018. We had a total of 1584 patients of whom 777 were male and 807 were female, with a mean age [standard deviation (SD)] of 43.3 (16.5) and age-range of 13 to 96 years.

The mean ARR was 210.1 (SD: 246.4, range 36–3866). In males, it was 214.3 (267.2), and in females, it was 206.1 (224.4) with P = 0.51. The mean eGFR was 50.2 (SD 12.6) ranging from 7 to 60; in males, it was 49.99 (0.90), and in females, it was 50.48 (0.92) with a P = 0.71.

Logistic regression models revealed a negative correlation between ARR and GFR with a coefficient of −2.08, 95% confidence interval (CI): −4.6, 0.21, P = 0.07.

There was a positive correlation between ARR and age with a coefficient of 1.12, 95% CI: 0.39–1.85, P = 0.003. The remaining correlations are highlighted in Table 1. It shows that in males, the mean (SD) was 214.3 (9.6), 49.99 (0.9), 16.9 (0.4), and 3.56 (0.04) for ARR, GFR, HbA1c, and LDL, respectively. In females, these values were 210.1 (6.2), 50.5 (0.9), 16.3 (0.4), and 3.47 (0.04) for ARR, GFR, HbA1c, and LDL, respectively. The ARR level was 208.07 (243.8) for those with GFR ≥30 mL/min/m² and 293.5 (186.9) for those with GFR <30 mL/min/m², P < 0.05.

**Discussion**

Among CKD patients enrolled in the present study, there was a very high ARR with an overall mean of 210. The mean ARR in those with eGFR <30 mL/min/m² was higher than those with eGFR ≥30 mL/min. The ARR showed a positive relationship with age in years, whereas the relationship with GFR was negative, where patients with low GFR had higher ARR. All participants were hypertensive with no statistical difference among their LDL and HbA1c levels was found. To the best of our knowledge, this study is the first to evaluate systematically aldosterone’s associations with CKD in a well-characterized population of CKD patients in our region.
Aldosterone plays a role in the genesis of nephropathy, where salt loading caused kidney damage with HTN, massive proteinuria, and advanced kidney lesion. These findings may stem from underlying RAAS dysregulation that is already present in the setting of CKD. Studies of kidney disease have demonstrated upregulation of aldosterone synthase with elevated aldosterone concentrations and adrenal hypertrophy that precede the development of HTN, proteinuria, and glomerulosclerosis. It is possible that mere universal dysregulation in RAAS limits the use of serum aldosterone to prognosticate mortality risk in individuals with CKD. However, it is found that all these findings are dramatically ameliorated by the use of mineralocorticoid receptor inhibitors.

Table 1. Mean (standard deviation) for aldosterone renin ratio, glomerular filtration rate, glycated hemoglobin and low-density lipoprotein for female and male participants and stratified by age group.

| Parameter                  | ARR  | GFR  | HbA1C | LDL   |
|----------------------------|------|------|-------|-------|
| **Mean (SD)**              |      |      |       |       |
| Males                      | 214.3 (9.6) | 49.99 (0.90) | 16.90 (0.41) | 3.56 (0.04) |
| Females                    | 210.1 (6.19) | 50.48 (0.92) | 16.29 (0.40) | 3.47 (0.04) |
| **Mean (SD) Age <40**      |      |      |       |       |
| Male                       | 199.46* (12.7) | -    | 18.40 (0.59) | 3.56 (0.05) |
| Female                     | 175.11 (8.95) | -    | 18.39 (0.66) | 3.38 (0.04) |
| **Mean (SD) Age 40–65**   |      |      |       |       |
| Male                       | 220.77* (14.3) | -    | 15.38 (0.62) | 3.58 (0.06) |
| Female                     | 241.75 (14.49) | -    | 15.01 (0.56) | 3.56 (0.08) |
| **Mean (SD) Age >65**     |      |      |       |       |
| Male                       | 274.22* (44.08) | -    | 15.63 (1.11) | 3.46 (0.12) |
| Female                     | 190.96 (19.51) | -    | 13.98 (0.92) | 3.40 (0.09) |
| **Mean (SD) GFR ≥30**     |      |      |       |       |
| Male                       | 208.07 243.8)* | -    |       |       |
| Female                     | 293.5 (186.9)* | -    |       |       |
| **Mean (SD) GFR <30**     |      |      |       |       |
| Male                       | 206.2 (240.5)* | -    |       |       |
| Female                     | 279.3 (325.7)* | -    |       |       |

*P <0.05, SD: Standard deviation, ARR: Aldosterone renin ratio, GFR: Glomerular filtration rate, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein.

Aldosterone plays a role in the genesis of nephropathy, where salt loading caused kidney damage with HTN, massive proteinuria, and advanced kidney lesion. These findings may stem from underlying RAAS dysregulation that is already present in the setting of CKD. Studies of kidney disease have demonstrated upregulation of aldosterone synthase with elevated aldosterone concentrations and adrenal hypertrophy that precede the development of HTN, proteinuria, and glomerulosclerosis. It is possible that mere universal dysregulation in RAAS limits the use of serum aldosterone to prognosticate mortality risk in individuals with CKD. However, it is found that all these findings are dramatically ameliorated by the use of mineralocorticoid receptor inhibitors.

CKD and its progression are associated with increasing risk for various cardiac problems. Heart failure and poor ejection fraction are major issues with CKD population. Aldosterone levels are an independent risk factor for incident heart failure. RAAS activation and elevations in aldosterone concentrations induce inflammatory and oxidative stresses that result in cardiac fibrosis. These effects are known to occur despite high or low renin levels. In addition, although the RAAS is regulated by cardiac function and intravascular volume, recent findings suggest that the aldosterone-heart failure link is independent of cardiac strain, kidney function, and total body water.

Various management strategies with ACE inhibitors and ARBs slow the progression of kidney disease; however, treatment with these drugs has not been proven in clinical trials to reduce cardiovascular morbidity and mortality in patients with CKD. Aldosterone is positively associated with BP suggesting that increased adrenal activity may partially clarify the amplified CVD hazard in end-stage CKD patients, especially at early stages. Nonetheless, the management with such medications could partially suppress RAAS stimulation and hence, may result in an escape phenomenon that is termed “aldosterone escape” or the continuing initiation of aldosterone making. Hence, investigators are viewing for a technique to comprehend whether more wide-ranging suppression of the RAAS with aldosterone blockers or MRBs can improve cardio renal outcomes. These mechanisms and hence, management strategy, have also motivated...
evaluation of serum aldosterone as a hazard sign and likely beneficial target particularly in CKD-population with HTN.

The activation of the RAAS has been found, which may possibly explain some of the racial discrepancies detected in the incidence of high BP, left ventricular hypertrophy, heart failure, and end-stage kidney disease.20–22 The higher rate of HTN-related complications seen in non-Caucasian patients such as CKD, CCF, and death may be ascribed to the possibly higher activity of downstream mediators of the RAAS including angiotensin II and aldosterone.23,24 A consensus statement acclaims that Blacks may be particularly susceptible to the effects of RAAS action and may have a better response to RAAS blockade than the Caucasian population.21,22,25

Researchers have reported that aldosterone acts not only on the classical target of distal tubules but also on many other structures and cells in the kidney.26 The traditional actions of aldosterone are mediated by the mineralocorticoid receptor in the kidney; recently, however, a number of effects of aldosterone with probable clinical importance have been documented that do not depend on the conventional mechanisms of mineralocorticoid-receptor-nuclear transcription.27–31 A Japanese observational study found that higher ARR was associated with the development of CKD in the general population, suggesting that they are independent predictors of CKD.32 Also, they found that adverse renal outcome was predicted by a higher baseline ARR.32 Similarly, aldosterone provides incremental information regarding risk for incident CKD and microalbuminuria beyond traditional risk factors among participants of the 6th prospective Framingham offspring study.33 These findings go along our findings that people with CKD have very high ARR, but more advanced CKD has even higher ARR.

In the present study, ARR was negatively correlated with eGFR, a coefficient of –2.08, 95% CI: −4.6, 0.21, P = 0.07, but more strongly at those aged <40 years and the middle-aged compared to elderly >65 years old. A causal role of aldosterone in primary renal disease is also plausible in view of past findings that serum aldosterone correlated negatively with creatinine clearance (P <0.01) and positively with renal scarcing (P <0.05).34

The statement that aldosterone is an aggravating factor in CKD is surely practical since patients with hyperaldosteronism, increased albuminuria and kidney dysfunction, have a beneficial effect after treatment with eplerone or spironolactone.7,13,35,36

Recent studies found that pro-oxidative and genotoxic effects of aldosterone occur in both \textit{in vitro} and \textit{in vivo} environments, implicating that aldosterone causes BP-independent kidney damage due to oxidative and nitrate stress.37,38 In Oman, we have reported that 0.9% had severe renal failure, with an eGFR <30 mL/min/1.73 m²; 9% had moderate renal failure with eGFR between 30 and 59 mL/min/1.73 m²; and 29% had mild renal failure with eGFR of 60 to 90 mL/min/1.73 m². This high prevalence of CKD may be ameliorated by various management strategies including control of BP.39–41 Researchers found that aldosterone contributes to the progression of renal injury, whereby aldosterone increased the expression of intercellular adhesion molecule-1 and connective tissue growth factor.42–44 This, in turn, increases the inflammatory pathways, further arguing that this pathway is a potential therapeutic target where glomerular injury was prevented by a mineralocorticoid receptor antagonist.42–44

Cardiometabolic abnormalities such as glucose and lipids were noted in our study to be high, but there was no statistical difference between early versus late CKD population. Animal studies found a role of the local as well as the systemic RAASs in the production of cardiometabolic abnormalities of visceral adiposity.29,45–47 The RAAS is inappropriately activated in obesity.7,24,29,45 In prediabetic individuals, inhibition of the RAAS protects against CKD.48 Furthermore, recent studies suggest that RAAS-inhibition protects by reducing the incidence of diabetes.48 The activation of the RAAS has consequences outside of the kidney as well: at a cellular level, angiotensin II and aldosterone cause
insulin resistance by increasing oxidative stress, attenuating insulin signaling and thus decreasing glucose transport. Evidence suggests that enhanced activation of the RAAS is a key factor in the development of endothelial dysfunction and HTN. Insulin resistance is induced by activation of the RAAS and resulting increases in reactive oxygen species. Aldosterone also diminishes glucose-stimulated insulin secretion, both in vivo and in vitro, through a mineralocorticoid receptor-independent mechanism. Pharmacologic blockade of the RAAS not only improves BP, but also has a beneficial impact on inflammation, oxidative stress, insulin sensitivity, and glucose homeostasis.

Researchers recommend that aldosterone should be considered a fresh kidney management target in CKD patients with the additional potential “off-target” effects on cardiac and vasculature.

Although aldosterone has a partial ability in prognosticating risk amongst CKD population worldwide, evolving evidence in various geographical areas and populations is of vital importance. Its importance is growing because of noncommunicable diseases spreading throughout the world, particularly with metabolic syndrome and its various components, which is highly prevalent worldwide and, in many populations, particularly in developing world such as in Oman. Hence, activation of the mineralocorticoid receptor may still occur through circulating cortisol and subsequently contribute to cardiovascular injury in individuals with CKD.

Clinicians use aldosterone inhibitors as part of the comprehensive management strategy to combat various CKD-related comorbidities. Dialysis Outcomes Heart Failure Aldactone Study is an open-label randomized trial among ESKD patients on hemodialysis, which has demonstrated a significant reduction in death or hospitalization from cardiovascular events in patients treated with Aldactone. However, new prospective multicenter studies are needed to evaluate the use of MRBs in patients across the whole spectrum and range of CKD worldwide.

There are several limitations in our study that deserve mention. First, it is a retrospective analysis of prospectively collected data. It is a single-center study, but it is also the only center under the Ministry of Health with the capacity to comprehensively conduct the tests needed. We also did not use cortisol in this study. Furthermore, aldosterone, renin, and their ratio were only measured at one visit and a single point in time in this study. Variations in aldosterone concentrations occur throughout the day based on salt intake, body positioning, and other physiologic parameters, which were not taken into account.

However, we did measure serum renin and aldosterone levels at a single laboratory using a well-validated assay and obtained their ratio to differentiate cases of primary versus secondary aldosteronism. In addition, we measured the LDL and HbA1c to further evaluate the metabolic impact of aldosterone effect on our CKD population. Finally, all our study patients were assumed to be not on any medications including ACE inhibitor/ARB therapy at the time of evaluation at the baseline visit.

In conclusion, this study is the first to evaluate systematically aldosterone’s associations with CKD in a well-characterized population of CKD patients in our region. CKD patients with HTN tend to have very high level of ARR. This is associated with elevated LDL and glycated HbA1c levels. In view of the high prevalence of non-communicable disease and large early CKD population, there is an important need to consider comprehensive management strategies that involve the blockage of high RAA and the use of MRBs. However, patients with high ARR may develop decrease in eGFR and kidney dysfunction on follow-up.

Conflict of interest: None declared.

References

1. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: A systematic review. J Hypertens 2004; 22:11-9.

2. Al-Lawati JA, Jousilahti P. Body mass index,
waist circumference and waist-to-hip ratio cutoff points for categorisation of obesity among Omani Arabs. Public Health Nutr 2008;11:102-8.
3. Al-Lawai JA, Mohammed AJ, Al-Hinai HQ, Jousilahi P. Prevalence of the metabolic syndrome among Omani adults. Diabetes Care 2003;26:1781-5.
4. Al-Said J. The prevalence of hypertension in Persian Gulf countries and its correlation with demographic and socio-economic factors. J Hypertens 2005;23:1275-7.
5. Shaheen FA, Al Wakeel J, Al-Ghamdi SM, et al. Cardiovascular and cerebrovascular comorbidities in haemodialysis patients from the Gulf Cooperation Council countries enrolled in the dialysis outcome and practice pattern study phase 5 (2012-2015). Saudi J Kidney Dis Transpl 2016;27:S24-30.
6. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: Analysis of worldwide data. Lancet 2005;365:217-23.
7. Flack JM, Peters R, Shafi T, Alrefai H, Nasser SA, Crook E. Prevention of hypertension and its complications: Theoretical basis and guidelines for treatment. J Am Soc Nephrol 2003;14:S92-8.
8. Jovanovich AJ, Chonchol MB, Sobhi A, et al. Mineral Metabolites, Angiotensin II Inhibition and Outcomes in Advanced Chronic Kidney Disease. Am J Nephrol 2015;42:361-8.
9. Spatz C, Saadulla L, Lapsiwala A, Parhizgar A, Ghahramani N. Effect of renin-angiotensin-aldosterone system blockade therapy on incidence of contrast-induced nephropathy in patients with chronic kidney disease. Iran J Kidney Dis 2012;6:432-6.
10. Hammer F, Edwards NC, Hughes BA, et al. The effect of spironolactone upon corticosteroid hormone metabolism in patients with early stage chronic kidney disease. Clin Endocrinol (Oxf) 2010;73:566-72.
11. Kim IY, Park IS, Kim MJ, et al. Change in kidney function after unilateral adrenalectomy in patients with primary aldosteronism: Identification of risk factors for decreased kidney function. Int Urol Nephrol 2018;50:1887-95.
12. Abraham AG, Betoko A, Fadrowski JJ, et al. Renin-angiotensin II-aldosterone system blockers and time to renal replacement therapy in children with CKD. Pediatr Nephrol 2017;32:643-9.
13. Gant CM, Laverman GD, Vogt L, et al. Renoprotective RAAS inhibition does not affect the association between worse renal function and higher plasma aldosterone levels. BMC Nephrol 2017;18:370.
14. Iwasaki M, Joki N, Tanaka Y, et al. Declining prevalence of coronary artery disease in incident dialysis patients over the past two decades. J Atheroscler Thromb 2014;21:593-604.
15. Kadappu KK, Abhayaratna K, Boyd A, et al. Independent echocardiographic markers of cardiovascular involvement in chronic kidney disease: The value of left atrial function and volume. J Am Soc Echocardiogr 2016;29:359-67.
16. Bhandari S, Ives N, Brettell EA, et al. Multi-centre randomized controlled trial of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker withdrawal in advanced renal disease: The STOP-ACEi trial. Nephrol Dial Transplant 2016;31:255-61.
17. Ikeda M, Nakao M, Hirano K, et al. Possible prevention of dialysis-requiring congestive heart failure by angiotensin-II receptor blockers in non-dialysis Japanese patients with Stage 5 chronic kidney disease. J Renin Angiotensin Aldosterone Syst 2015;16:1175-84.
18. Shibata H, Itoh H. Mineralcorticoid receptor-associated hypertension and its organ damage: Clinical relevance for resistant hypertension. Am J Hypertens 2012;25:514-23.
19. Khan UA, Garg AX, Parikh CR, Coca SG. Prevention of chronic kidney disease and subsequent effect on mortality: A systematic review and meta-analysis. PLoS One 2013;8:e71784.
20. Deo R, Yang W, Khan AM, et al. Serum aldosterone and death, end-stage renal disease, and cardiovascular events in blacks and whites: Findings from the chronic renal insufficiency cohort (CRIC) Study. Hypertension 2014;64:103-10.
21. Bobenko A, Bartels I, Munch M, et al. Amount or intensity? Potential targets of exercise interventions in patients with heart failure with preserved ejection fraction. ESC Heart Fail 2018;5:53-62.
22. Lindhorst J, Alexander N, Blignaut J, Rayner B. Differences in hypertension between blacks and whites: An overview. Cardiovasc J Afr 2007;18:241-7.
23. Manrique C, Lastra G, Gardner M, Sowers JR. The renin angiotensin aldosterone system in
hypertension: Roles of insulin resistance and oxidative stress. Med Clin North Am 2009;93:569-82.
24. Manrique C, Lastra G, Whaley-Connell A, Sowers JR. Hypertension and the cardiometabolic syndrome. J Clin Hypertens (Greenwich) 2005;7:471-6.
25. Roscioni SS, Heerspink HJ, de Zeeuw D. The effect of RAAS blockade on the progression of diabetic nephropathy. Nat Rev Nephrol 2014;10:77-87.
26. Nguyen G, Blanchard A, Curis E, et al. Plasma soluble (pro)renin receptor is independent of plasma renin, prorenin, and aldosterone concentrations but is affected by ethnicity. Hypertension 2014;63:297-302.
27. Lea WB, Kwak ES, Luther JM, et al. Aldosterone antagonism or synthase inhibition reduces end-organ damage induced by treatment with angiotensin and high salt. Kidney Int 2009;75:936-44.
28. Luther JM. Is there a new dawn for selective mineralocorticoid receptor antagonism? Curr Opin Nephrol Hypertens 2014;23:456-61.
29. Luther JM. Aldosterone in vascular and metabolic dysfunction. Curr Opin Nephrol Hypertens 2016;25:16-21.
30. Luther JM, Luo P, Wang Z, et al. Aldosterone deficiency and mineralocorticoid receptor antagonism prevent angiotensin II-induced cardiac, renal, and vascular injury. Kidney Int 2012;82:643-51.
31. Qi Y, Wang X, Rose KL, et al. Activation of the endogenous renin-angiotensin-aldosterone system or aldosterone administration increases urinary exosomal sodium channel excretion. J Am Soc Nephrol 2016;27:646-56.
32. Terata S, Kikuya M, Satoh M, et al. Plasma renin activity and the aldosterone-to-renin ratio are associated with the development of chronic kidney disease: The Ohasama Study. J Hypertens 2012;30:1632-8.
33. Fox CS, Gona P, Larson MG, et al. A multi-marker approach to predict incident CKD and microalbuminuria. J Am Soc Nephrol 2010;21:2143-9.
34. Quinkler M, Zehnder D, Eardley KS, et al. Increased expression of mineralocorticoid effector mechanisms in kidney biopsies of patients with heavy proteinuria. Circulation 2005;112:1435-43.
35. Currie G, Taylor AH, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: A systematic review and meta-analysis. BMC Nephrol 2016;17:127.
36. Ellam TJ, El Nahas M. Proteinuria thresholds are irrational: A call for proteinuria indexing. Nephron Clin Pract 2011;118:e217-24.
37. Queisser N, Amann K, Hey V, Habib SL, Schupp N. Blood pressure has only minor influence on aldosterone-induced oxidative stress and DNA damage in vivo. Free Radic Biol Med 2013;54:17-25.
38. Schupp N, Queisser N, Wolf M, et al. Aldosterone causes DNA strand breaks and chromosomal damage in renal cells, which are prevented by mineralocorticoid receptor antagonists. Horm Metab Res 2010;42:458-65.
39. Al Alawi I, Al Salmi I, Al Mawali A, Al Maimani Y, Sayer JA. End-stage kidney failure in Oman: An analysis of registry data with an emphasis on congenital and inherited renal diseases. Int J Nephrol 2017;2017:6403985.
40. Al Alawi IH, Al Salmi I, Al Mawali A, Sayer JA. Kidney Disease in Oman: A View of the Current and Future Landscapes. Iran J Kidney Dis 2017;11:263-70.
41. Al Ismail F, Al Salmi I, Al Maimani Y, et al. Epidemiological transition of end-stage kidney disease in Oman. Kidney Int Rep 2017;2:27-35.
42. Terada Y, Kuwana H, Kobayashi T, et al. Aldosterone-stimulated SGK1 activity mediates profibrotic signaling in the mesangium. J Am Soc Nephrol 2008;19:298-309.
43. Terada Y, Ueda S, Hamada K, et al. Aldosterone stimulates nuclear factor-kappa B activity and transcription of intercellular adhesion molecule-1 and connective tissue growth factor in rat mesangial cells via serum- and glucocorticoid-inducible protein kinase-1. Clin Exp Nephrol 2012;16:81-89.
44. Tsugita M, Iwasaki Y, Nishiyama M, et al. Glucocorticoid receptor plays an indispensable role in mineralocorticoid receptor-dependent transcription in GR-deficient BE(2)C and T84 cells in vitro. Mol Cell Endocrinol 2009;302:18-25.
45. Boscaro M, Giachetti G, Ronconi V. Visceral adipose tissue: Emerging role of gluco- and mineralocorticoid hormones in the setting of cardiometabolic alterations. Ann NY Acad Sci 2012;1264:87-102.
46. Ronconi V, Turchi F, Appolloni G, di Tizio V, Boscaro M, Giachetti G. Aldosterone, mineralocorticoid receptor and the metabolic
syndrome: Role of the mineralocorticoid receptor antagonists. Curr Vasc Pharmacol 2012;10:238-46.
47. Rossi G, Boscaro M, Ronconi V, Funder JW. Aldosterone as a cardiovascular risk factor. Trends Endocrinol Metab 2005;16:104-7.
48. McFarlane SI, Provilus A, Shin JJ. Diabetes prevention between RAAS inhibition and PPAR-gamma stimulation: The diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial. J Cardiometab Syndr 2007;2:149-50.
49. Lubanda JC, Chochola M, Mlček M, et al. The effect of renal denervation in an experimental model of chronic renal insufficiency, The REMnant kidney Denervation In Pigs study (REDIP study). J Transl Med 2017;15:215.
50. Shavit L, Lifschitz MD, Epstein M. Aldosterone blockade and the mineralocorticoid receptor in the management of chronic kidney disease: Current concepts and emerging treatment paradigms. Kidney Int 2012;81:955-68.
51. Shavit L, Neykin D, Lifschitz M, Slotki I. Effect of eplerenone on blood pressure and the renin-angiotensin-aldosterone system in oligo-anuric chronic hemodialysis patients a pilot study. Clin Nephrol 2011;76:388-95.
52. Shavit L, Silberman S, Tauber R, Merin O, Bitran D, Fink D. Preoperative aldosterone receptor blockade and outcomes of cardiac surgery in patients with chronic kidney disease. Clin Nephrol 2018;89:187-95.
53. Quach K, Lvtyyn L, Baigent C, et al. The safety and efficacy of mineralocorticoid receptor antagonists in patients who require dialysis: A systematic review and meta-analysis. Am J Kidney Dis 2016;68:591-8.

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