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Review

Renal Dysfunction in Primary Aldosteronism: How, When, and Who?

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Abstract: Primary aldosteronism (PA) is a major cause of hypertension, especially in younger patients. Early diagnosis and treatment are crucial to prevent damage to vital organs, including the heart and kidneys. Independent of blood pressure, aldosterone excess has direct deleterious effects on the kidneys, leading to tubulointerstitial fibrosis, glomerular hypertrophy, and glomerulosclerosis. Emerging biomarkers such as albuminuria and liver fatty acid-binding protein may have the potential to detect renal injury in PA, particularly in the setting of glomerular hyperfiltration. Comprehensive risk assessment of long-term renal dysfunction, based on both modifiable and non-modifiable risk factors, would aid clinicians in prediction and would even, in some cases, allow them to mitigate the risk of patients developing CKD in the setting of PA.

Keywords: primary aldosteronism; aldosterone; renal damage; chronic kidney disease

1. Introduction

Primary aldosteronism (PA), a relatively underdiagnosed endocrinopathy, is believed to be the cause of approximately 20–30% and 5–10% of resistant hypertension and secondary hypertension, respectively [1–3]. This clinical syndrome is characterized by autonomous aldosterone overproduction with suppressed plasma renin levels [1,4]. It may be of unilateral, most commonly aldosterone-producing adenoma (APA), or bilateral etiology, mostly idiopathic adrenal hyperplasia (IAH) [2]. Over the last two decades, a major shift in the management and treatment of PA has occurred, where standard routine medical practice and guidelines according to the European Society of Hypertension (ESH) also consider the severe long-term cardiovascular and renal health consequences [5]. Accordingly, the introduction of the accurate diagnosis and treatment of PA, and its target organ injuries in the early stages, remains crucial in preventing cardiovascular disease and chronic kidney disease (CKD) [6,7]. Furthermore, recent advances in renal protection by mineralocorticoid receptor antagonists (MRAs) have spurred interest in the direct effect of aldosterone in the kidney [8]. Thus, this review focuses on risk management, the diagnosis of renal disease in PA, and on the basic pathophysiologic pathways leading to renal impairment.

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2. Pathophysiology of Renal Dysfunction in PA

Aldosterone-Induced Injury

With an excess amount of aldosterone in untreated PA, reversible and irreversible renal damage could be exerted on the kidney through direct and indirect mechanisms. Higher levels of aldosterone before the treatment of PA have been associated with increased levels of N-acetyl-β-D-glucosaminidase, a higher urine albumin to creatinine ratio, and increased levels of liver fatty acid-binding protein (L-FABP) and β2-microglobulin, suggesting the impairment of both tubular and glomerular structures [9]. A histopathologic evaluation of kidney biopsies in 19 patients with PA showed enhanced glomerular and vascular pathology and interstitial fibrosis [10]. Stronger immunolabeling of the mineralocorticoid receptor and 11β-hydroxysteroid dehydrogenase type 2 was also found in renal tubules. The authors suggest that the enhanced expression of 11β-hydroxysteroid dehydrogenase type 2 could be a protective mechanism, decreasing steroid activation of the mineralocorticoid receptor (MR). The expression of this enzyme is regulated by estrogen, but little is otherwise known about its regulation in the kidney [11]. Excessive MR activation impairs renal tubular function through extensive tubulointerstitial fibrosis [10,12,13]. Apart from direct damage through increased blood pressure, the chronic overproduction of aldosterone also exerts glomerular injury through various other mechanisms. It is hypothesized that a high aldosterone/renin ratio will reduce tubuloglomerular feedback, leading to hyperfiltration and causing albumin leakage and glomerular hypertrophy. Aldosterone could also directly injure podocytes, causing foot process effacement, which manifests in overt proteinuria and exacerbated segmental or global glomerulosclerosis [10]. A summarized illustration of the above-mentioned mechanisms causing aldosterone-induced injury on glomerular and tubular structures can be found in Figure 1. Long-term elevation in aldosterone levels has been associated with systemic inflammation and endothelial dysfunction resulting in multiorgan impairment [14]. Increased vascular stiffness and arteriolosclerosis will also impair renal function in the long run. In PA, effects of MR activation are also observed on vascular smooth muscle cells (VSMCs), leading to increased levels of ICAM-1 [15]. Aldosterone-induced VSMC proliferation and hyalinization of the efferent arterioles are characteristically seen in PA [16,17]. In experimental animal models, aldosterone has been implicated in exerting damage on the renal microvasculature, independent of the renin–angiotensin–aldosterone system (RAAS) [18,19]. The aldosterone-induced injury and fibrosis of the kidneys observed in rats is, rather, attributed to the activation of profibrotic pathways and, more importantly, components of an inflammatory response (seen through the upregulation of cytokines and infiltration of macrophages) [20]. Moreover, the combination of high salt ingestion and an excess amount of aldosterone is hypothesized to be an determinantal factor causing vascular injury in target organs [21], with a possible involvement of aldosterone independent of MR activation. Hypokalemia as a consequence of hyperaldosteronism has also been implicated in endothelial dysfunction by increasing vasoactive mediators and causing tubulointerstitial damage through reduced medullary blood flow and impaired renal angiogenesis [22,23].

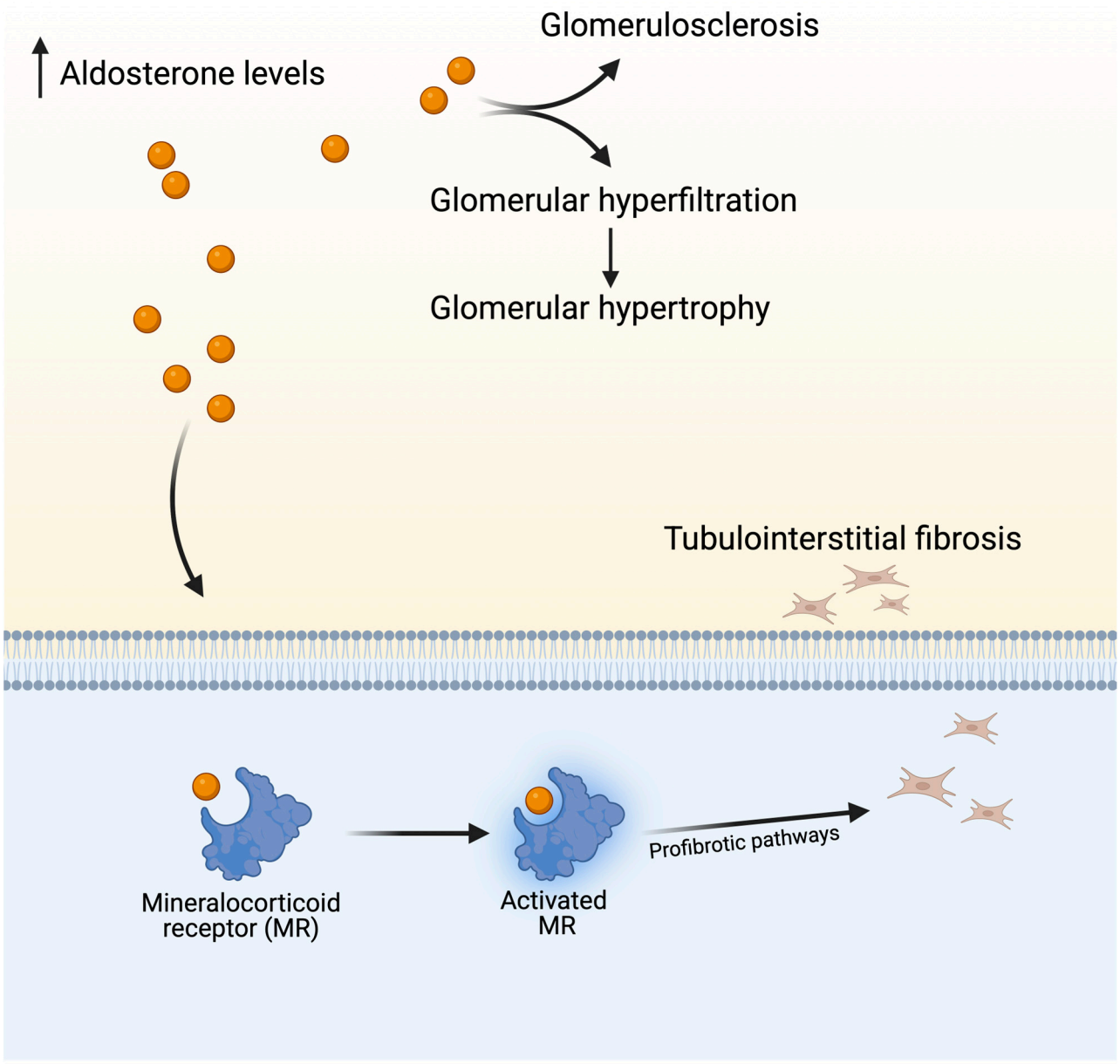

Figure 1. Illustration of main pathophysiologic mechanisms impairing glomerular and tubular structures in primary aldosteronism.

3. Genetic Mutations

Genomic mutations causing both adrenal dysfunction and impaired renal function could play a role in the pathogenesis of chronic kidney disease (CKD) among those with PA. Over the last decade, a handful of somatic mutations have been identified to partake in the pathogenesis of PA, one being of the potassium inwardly rectifying channel subfamily J member 5 (KCNJ5) gene. Mutations of the KCNJ5 gene are most commonly seen in patients with APAs and who typically have higher levels of aldosterone [24]. Still, the prognostic significance of KCNJ5 mutations and their role in vascular remodeling are not fully understood. It has been shown that independent of aldosterone levels prior to adrenalectomy, KCNJ5 mutations in patients treated for APA worsen vascular function, suggesting the existence of unknown pathways through which KCNJ5 mutations trigger endothelial dysfunction [25,26]. Patients with KCNJ5-mutated APA exhibit a significantly worse cardiovascular prognosis [27]. Yet, the impact of mutated KCNJ5 on renal function remains less elucidated. A short report from Yoshioka et al. analyzed predictors for renal

dysfunction among patients with APA treated with adrenalectomy and in those aged ≥50 years old, and they found KCNJ5 mutations to be associated with the progression of CKD [28]. Still, this association was only sex- and age-adjusted, and it is unknown whether this was due to the on average higher aldosterone levels or independent of them. On the other hand, another study failed to find an association between the presence of KCNJ5 mutations and renal function decline in PA [29]. It is possible that there remain rare or even undiscovered alterations in the genome that are involved in the pathogenesis of PA as well as have an impact on renal function. As an example, CACNA1H is a rare germline mutation connected with PA mostly seen in younger patients, and it harbors a clinically distinctive phenotype [30]. CACNA1H receptors are also expressed in other organs such as the heart and kidneys [31], but no data for its effect on short- or long-term renal function have been published.

4. Risk Factors for CKD

Guidelines by the ESH acknowledge the cardiovascular and renal complications seen in PA yet provide limited information on risk assessment and follow-up for high-risk groups [5]. With the extensive histopathological evidence of renal damage and with longitudinal studies revealing severely deteriorating renal function in patients with PA, ascertaining the diagnosis of PA is important. Also, identifying those at risk for CKD and the introduction of risk-adapted follow-up remains important to prevent cardiovascular morbidity and mortality. Despite the negative impact of excessive aldosterone production on tubuloglomerular components, there is a lack of convincing evidence for its effect on long-term eGFR decline. There appears to be a connection between plasma aldosterone concentration (PAC) [32] or the aldosterone/renin ratio [33,34] and eGFR changes. However, this is mostly shown in studies evaluating eGFR in the early postoperative setting, which in most instances reflects a transient eGFR dip rather than irreversible renal damage. A recent meta-analysis showed that only age, sex, high systolic blood pressure, and preoperative potassium could be used to predict long-term renal function deterioration in subjects with PA undergoing adrenalectomy [35]. Although PA can be successfully treated, it is not uncommon for hypertension to remain after treatment [36–38]. Therefore, proper blood pressure management, even after primary treatment for PA, remains crucial in decreasing the risk of CKD. Haze et al. found systolic blood pressure (SBP) to be associated with incident CKD 6 months after the treatment of PA, where the achieved SBP < 130 mmHg was linked to superior renal outcome [39]. Among patients with PA, wide blood pressure variability has been associated with an increased risk of renal damage [40]. Subjects with PA referred for ambulatory blood pressure measurement (ABPM) have higher 24 h, day, and night blood pressure, despite a similar number of antihypertensive drugs when compared to subjects without PA diagnosed with essential hypertension (EH) [41]. As target organ damage is more severe in PA when compared to EH [42], it remains to be clarified whether the monitoring of blood pressure at follow-up with more precise methods (such as, e.g., ABPM) would be more beneficial in PA.

As the above-mentioned meta-analysis on risk factors for CKD in PA focuses on the patient group undergoing surgical interventions, the implicated risk factors cannot be generalized for subjects with PA managed using non-surgical treatments. The type of targeted treatment for PA also interacts with the future risk of CKD. Retrospective studies indicate that those undergoing surgical adrenalectomy may have a more favorable renal prognosis as compared to those treated with MRAs [7,43]. This observation is hypothesized to be due to "residual" aldosterone among those treated with MRAs, still exerting negative effects on the kidneys. Short- and long-term eGFR changes depending on the type of treatment applied (i.e., MRAs or adrenalectomy) also have different features. It was

observed that an acute fall in eGFR after unilateral adrenalectomy was not necessarily associated with a long-term drop in renal function. On the contrary, among subjects with PA treated with MRAs, a small initial eGFR fall was associated with a steeper eGFR decline at long-term follow-up [32]. Moreover, a longitudinal study including 500 patients treated for PA with a follow-up of 10 years showed those treated with MRAs to be at a two-fold higher risk of ESRD as compared to those treated with adrenalectomy [43]. Therefore, risk stratification for the development of CKD in PA should take into consideration the type of treatment modality applied. As of now, the only such robust report comes from Watanabe et al., who found the eGFR decline 6 months post-treatment to be predicted by body mass index (BMI) among those treated for IAH with MRAs, and by PAC among those treated for APAs with unilateral adrenalectomy [44].

5. Biomarkers for Renal Damage in PA

In untreated PA, hemodynamic adaptations in response to elevated aldosterone levels induce glomerular hyperfiltration. As PA is treated via either adrenalectomy or MRAs, a rapid decline in eGFR is observed, which is believed to be due to hemodynamic changes following normalized aldosterone levels rather than actual functional renal damage [45–48]. Yet, the phenomenon of glomerular hyperfiltration in the setting of PA before therapy, just as with diabetic kidney disease, could provide an inaccurate estimation of renal function using creatinine-based or cystatin-C-based eGFR and might "mask" renal disease. Moreover, as an acute decline in eGFR following treatment is expected, the identification of acute kidney injury (AKI) or the progression of CKD is a challenge to physicians. The temporary dip in eGFR following adrenalectomy or MRA administration is reported to last even for a few months and usually starts to even out after 6 months following the start of treatment [48]. On the other hand, it may pose difficulty in the identification of whether a decline in eGFR after targeted treatment is due to normalized aldosterone levels leading to reduced tubuloglomerular feedback or due to presence of true renal damage. Thus, conventional eGFR measurements to predict renal function in the pre-treatment phase and a few months after may be of limited use. Albuminuria, on the other hand, may be a more reliable biomarker of renal damage and was found to be elevated in PA when compared to matched patients with EH [49,50]. As mentioned, albuminuria in untreated PA could be due to hyperfiltration or aldosterone-induced injury, normalizing with a decrease in aldosterone and improved glomerular function after interventions for PA. Nonetheless, Yoon et al. still found preoperative albuminuria to independently predict the progression of CKD 6 months after adrenalectomy in patients with APAs [33]. With similar findings, another investigation found urinary albumin levels to be correlated with the estimated glomerular filtration rate percentage decline 12 months after adrenalectomy [51]. Thus, the presence of preoperative albuminuria may reveal renal damage in subjects with preserved eGFR, or damage masking glomerular hyperfiltration, while after adrenalectomy, new-onset or worsened postoperative albuminuria could imply perioperative renal damage or progressive CKD. Another study explored biomarkers for kidney tubular impairment at diagnosis of PA and at follow-up after treatment [52]. It was found that biomarkers for proximal renal tubular injury, namely, L-FABP/creatinine and kidney injury molecule-1/creatinine, decreased after adrenalectomy and/or MRA treatment. However, interestingly, L-FABP/creatinine independently predicted the likelihood of developing kidney failure 12 months after treatment of PA, while age, pre-treatment eGFR, proteinuria, blood pressure, diabetes, or serum aldosterone at diagnosis did not.

6. Future Directions and Unexplored Aspects

Although PA is reported to be an etiologic factor in up to 10% of all secondary hypertension cases, it still remains underdiagnosed, with low screening rates even in the presence of indicative factors for secondary causes of hypertension such as hypokalemia and resistant disease [53–55]. Irrespective of hypertension duration and blood pressure levels, target organ damage is much more severe in PA, which is seen early by the higher prevalence of left ventricular hypertrophy, microalbuminuria, and increased carotid intima thickness [42]. As renal damage in PA is speculated to occur mainly due to increased levels of aldosterone, it can, via targeted treatment (i.e., adrenalectomy or MRAs), be effectively treated, preventing further systemic multiorgan damage to such an extent. Thus, timely diagnosis, screening for target organ damage, and investigations of secondary causes for hypertension remain important in patients with hypertension.

As curative adrenalectomy in PA has an impact on the RAAS, it is uncertain how this affects the safety and efficacy of antihypertensive treatment with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Considering the already impaired RAAS in unilateral adrenalectomy, it is uncertain whether additional RAAS blockade would be beneficial. The pharmacological aim of treating hypertension is to target multiple systems affecting the complex regulation of blood pressure, and as the RAAS is already affected by surgical interventions, it can be speculated that this unique group of patients might achieve an adequate blood pressure target with a lower starting dose of ACE/ARBs than the typical patient with EH.

Apart from ACE and ARBs, there is no information on whether the utilization of other nephroprotective agents, such as sodium–glucose transport protein 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, may decrease the risk of ESRD or CKD progression in patients with PA. Spironolactone and eplerenone are the most widely used MRAs for the treatment of PA with bilateral disease. With newer agents, such as finerenone, a nonsteroidal MRA, the usefulness and safety are to be elucidated in subjects with PA. Despite having a similar potency to spironolactone, finerenone is a more specific blocker of the MR [56]. Treatment with finerenone in PA might lead to less side effects than the current standard regimes.

A transient reduction in eGFR is common after treatment initiation. In this context, it is highly important to accurately assess kidney function and distinguish it from true renal damage, as well to identify those predisposed to eGFR decline at follow-up. Despite studies suggesting a difference in renal prognosis depending on the type of treatment for PA, data on risk factors for renal damage specifically in those treated with MRAs are less solid, calling for additional studies exploring factors associated with CKD in patients with PA with this treatment modality. Further exploration of genetic mutations in PA (e.g., KCJN5) and their impact on long-term renal outcome would also be of great benefit in terms of patient counselling and follow-up management.

7. Conclusions

PA exerting evident systemic organ damage requires a multidisciplinary approach, with one of these being nephrological care in both the pre- and post-therapy setting. With severe target organ damage linked to aldosterone-induced injury, the early diagnosis and treatment of PA represent a unique clinical scenario and a curable cause of kidney disease with preventable suffering. Further advances in the understanding of the intrinsic pathophysiological mechanisms and the discovery of precise biomarkers for AKI or progressive CKD in this population would allow clinicians to accurately examine renal function and manage such high-risk individuals.

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