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MINIREVIEWS

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MINIREVIEWS

Reno protective role of amlodipine in patients with hypertensive chronic kidney disease

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Abstract

Chronic kidney disease (CKD) and hypertension (HTN) are closely associated with an overlapping and intermingled cause and effect relationship. Decline in renal functions are usually associated with a rise in blood pressure (BP), and prolonged elevations in BP hasten the progression of kidney function decline. Regulation of HTN by normalizing the BP in an individual, thereby slowing the progression of kidney disease and reducing the risk of cardiovascular disease, can be effectively achieved by the anti-hypertensive use of calcium channel blockers (CCBs). Use of dihydropyridine CCBs such as amlodipine (ALM) in patients with CKD is an attractive option not only for controlling BP but also for safely improving patient outcomes. Vast clinical experiences with its use as mono-therapy and/or in combination with other anti-hypertensives in varied conditions have demonstrated its superior qualities in effectively managing HTN in patients with CKD with minimal adverse effects. In comparison to other counterparts, ALM displays robust reduction in risk of cardiovascular endpoints, particularly stroke, and in patients with renal impairment. ALM with its longer half-life displays effective BP control over 24-h, thereby reducing the progression of end-stage-renal disease. In conclusion, compared to other classes of CCBs, ALM is an attractive choice for effectively managing HTN in CKD patients and improving the overall quality of life.

Key Words: Amlodipine; Chronic kidney disease; Hypertension; End-stage-renal disease; Monotherapy; Combination therapy

Core Tip: Amlodipine (ALM) is a powerful, well-tolerated, and safe anti-hypertensive agent widely used alone or as a key component of combination therapy for hypertension in chronic kidney disease (CKD). Its effectiveness in reducing blood pressure has proven benefits in cardiovascular event reduction and progression of renal disease. Overall, ALM emerges as the drug of choice in comparison to the newer calcium channel blockers in terms of its effectiveness and potency in BP lowering in CKD patients.

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INTRODUCTION

Hypertension (HTN) – also known as high blood pressure (BP) – is a significant medical illness in which the arterial BP remains consistently high, with a systolic BP (SBP) of 140 mmHg or higher or a diastolic BP (DBP) of 90 mmHg or higher[1]. The World Health Organization has identified HTN as one of the most important risk factors for morbidity and mortality worldwide, with roughly 9 million people dying each year[2]. Even though other risk factors play a role, poor diets, such as excessive salt consumption, a diet high in saturated fat and trans-fats, low intake of fruits and vegetables, physical inactivity, tobacco/alcohol use, and being overweight/obese, appear to be the most common contributing factor to HTN. Non-modifiable risk factors include a family history of HTN, elderly age, and comorbidities such as diabetes or kidney disease[3]. According to recent analysis and observational research, people in Western countries have a higher prevalence of HTN and higher BP levels than those in other parts of the world, and this disparity is narrowing as non-Westerners adapt to Western culture and lifestyle[4].

HTN continues to be the greatest cause of premature mortality, affecting roughly 1.13 billion people globally and accounting for nearly 45% of deaths due to heart disease, 51% of deaths due to stroke, and 85%-95% of patients with chronic kidney disease (CKD)[5]. The overall prevalence of HTN in India was 29.8% from 1950 to 2014, according to data, and a meta-analysis of prior Indian prevalence studies showed a considerable increase in the incidence of HTN from the 1960s to the mid-1990s[6]. HTN prevalence studies in urban and rural populations from the mid-1990s to the present show a growing trend, with a bigger increase in urban (33.8%) than rural (27.6%) populations[6]. Early detection, consistent follow-up, and HTN control methods may be a cost-effective way to lower the worldwide disease burden associated with HTN.

HYPERTENSION AND CHRONIC KIDNEY DISEASE

CKD is characterized by persistent kidney damage, a decrease in the estimated glomerular filtration rate (eGFR), and the development of albuminuria. It is a long-term disorder that causes kidney function to deteriorate over time, eventually leading to kidney failure or end-stage renal disease (ESRD)[7]. CKD refers to all five stages of kidney damage, from very mild in stage 1 (eGFR ≥ 90 mL/min/1.73 m^2) to complete kidney failure in stage 5 (eGFR < 15 mL/min/1.73 m^2)[8] (shown in Table 1). In 2017, 12 million people died from CKD worldwide, with a global prevalence of 697.5 million. Women and girls had a greater age-standardized global prevalence of CKD (9.5%) than men and boys (7.3%), and China and India accounted for over one-third of all CKD cases (132.3 million and 115.1 million, respectively)[9]. Since the eGFR estimation equation and the Modification of Diet in Renal Disease formula have not been verified, the incidence of CKD in India is high[10]. The Indian Society of Nephrology established the Indian CKD Registry in 2005 as a comprehensive statewide data collection for examining all aspects of CKD. According to the initial research, diabetic nephropathy has emerged as the leading cause of CKD in India, according to a cross-sectional survey of 52273 adult patients[11].

HTN control is important in the care and well-being of CKD patients because it is both a cause and an effect of the disease, and it contributes to its progression[12]. Uncontrolled BP during the day causes a BP "load" in CKD patients, which is linked to eGFR decrease and proteinuria. Masked HTN, nocturnal

Table 1 Classification of chronic kidney disease Stages 1-5[8]

Stage	Description	GFR, mL/min/1.73 m^2
-	At increased risk	≥ 60
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney Failure	< 15 (or dialysis)

GFR: Glomerular filtration rate.

non-dipping, and 24-h day/night BP fluctuation are all seen in patients with CKD[12]. As evidenced by studies showing a higher risk of all-cause death, hemorrhagic strokes, and total cardiovascular (CV) events in people with CKD, BP fluctuation is a powerful predictor of end organ damage[13]. Furthermore, both HTN and CKD are independent risk factors for CVD, and when both are present, the risk of CVD morbidity and mortality is significantly enhanced. Furthermore, HTN has been recorded in 85%-95% of CKD (stages 3-5) patients[14]. The pathophysiology of HTN in CKD is multifaceted and complicated[15]. There is an upregulation of the renin–angiotensin–aldosterone system (RAAS) with a functional drop in eGFR, which increases salt and water retention even more, and this is compounded by an enhanced salt sensitivity of BP[16]. Proteinuria is a critical sign of renal impairment that is related with CKD progression and incident CVD in a gradual and independent manner. Reduced BP lowers proteinuria, which slows eGFR decline and lowers CV risk. When treating HTN in individuals with CKD, the influence of a medicine on proteinuria is a significant consideration in addition to its antihypertensive effects. Another emerging worry is the prevalence of treatment-resistant HTN in CKD, and including this patient population in large-scale randomized outcome trials may assist to guide future treatments[16].

BLOOD PRESSURE CONTROL IN CKD

Accurate and effective BP readings are required for optimal HTN therapy. Due to a lack of repeat measurements, diurnal variation in BP, and white-coat HTN, BP obtained in clinic or office BP recordings may provide an erroneous assessment of the clinical condition[17,18]. Different phenotypes of HTN have been identified and linked to varying degrees of CVD risk and all-cause death(shown in Table 2). In comparison to clinic measurements, 24-h ambulatory BP monitoring is more reliable, since it allows assessment of diurnal fluctuation in BP and serves as a stronger predictor of CVD events in people with CKD, according to the 2017 American College of Cardiology guidelines[19]. Home BP monitoring is a less resource-intensive alternative technique, and individuals who acquire data from home readings have better overall BP control than those who do not. HTN and CKD have a cause-and-effect connection that is intertwined. A rise in BP is linked to a reduction in kidney function, and a continuing rise in BP is linked to a faster development of renal function decline. As people get older, the prevalence of HTN rises, making BP control more challenging[20]. As a result, HTN control is an important part of CKD patient treatment, and medicines that provide 24-h BP control and thus minimize BP variability should be the preferred therapeutic option for CKD patients.

USE OF ANTI-HYPERTENSIVE AGENTS IN CKD

HTN management in CKD is critical for patients because HTN treatment can improve CV outcomes in patients with ESRD and CKD[20]. The treatment of HTN is crucial in the management of CKD. HTN is common in people with CKD and ESRD because it is both a cause and a consequence of the disease. In addition, HTN therapy is linked to better CV outcomes in both CKD and ESRD patients. As a result, both the patient and the practitioner must be vigilant when dealing with HTN in CKD[20]. Dietary salt restriction, maintaining an adequate dry weight, and lifestyle changes are among nonpharmacological therapies for HTN. These techniques, however, are ineffective in treating HTN and must be combined with pharmacological therapies for more efficient BP control in the CKD population[16].

Several anti-hypertensive drug types may be useful in the treatment of CKD with HTN[21]. Most patients with CKD and HTN should start with BP medications that also reduce proteinuria. Proteinuria reduction results in long-term improvements in both CV and renal outcomes, according to data[16].

Table 2 Association of hypertension phenotype with all-cause mortality[18]

BP phenotype	Description[1]	All-cause mortality hazard ratio (95%CI)
Normotension	Normal clinic BP, normal 24-h ABPM	Reference
White-coat hypertension	High clinic BP, normal 24-h ABPM	1.79 (1.38–2.32)
Sustained hypertension	High clinic BP, high 24-h ABPM	1.80 (1.41–2.31)
Masked hypertension	Normal clinic BP, high 24-h ABPM	2.83 (2.12–3.79)

[1]Normal clinic BP defined as < 140/90 mmHg, Normal 24-h BP defined as < 130/80 mmHg. Values represent patients on treatment and without chronic kidney disease. ABPM: Ambulatory blood pressure monitoring; BP: Blood pressure; CI: Confidence interval.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), which target the RAAS, are commonly used as first-line antihypertensive medications[22]. However, it is widely known that RAAS inhibitors cause hyperkalemia, and that when an ACE and an ARB inhibitor are coupled, renal function is worsened and hypotension occurs[22]. Hyperkalemia was found to be common in patients with CKD who were treated with RAAS inhibitors, and as a result, RAAS inhibitors should be used with caution in patients with underlying CKD and HTN[23]. A preferable first-line therapy in patients without proteinuria has not been firmly established, and drugs such as thiazides may be tried.

Patients with CKD and HTN frequently develop fluid retention/fluid overload, necessitating the use of diuretics in their treatment plan[24]. Thiazides are suggested for people with CKD stages 1 to 3 (GFR 30 mL/min) and have been shown to be beneficial in lowering BP and reducing the risk of CVD. In addition, loop diuretics are favored in patients with CKD stage 4 or 5 (GFR 30 mL/min) because they have been found to be more successful in lowering extracellular fluid volume in individuals with significantly reduced GFR[12,20]. Beta-blockers have a limited effect on CKD progression and proteinuria, thus they are only used as a second- or third-line treatment if the patient has a compelling reason to take one, such as coronary artery disease or chronic heart failure[25]. When first- and second-line therapy fails to reach BP targets, aldosterone receptor antagonists such as spironolactone and eplerenone may be used in CKD treatment[21]. When used with an ACE inhibitor or an ARB, these drugs reduce proteinuria. Aliskiren, a renin inhibitor, is the only drug approved for the treatment of HTN as a monotherapy or in combination with valsartan[26]. Because of the increased risk of renal impairment, hypotension, and hyperkalemia, the ALTITUDE trial has led to the contraindication of its usage with ACE/ARB inhibitors in patients with diabetes or renal impairment[27]. If a patient is unable to take an ACE inhibitor or an ARB, Aliskiren may be tried; however, it is not indicated for individuals with stage 4 or 5 renal failure.

Calcium channel blockers (CCBs) are drugs that relax blood arteries and enhance blood and oxygen supply to the heart while lowering the strain of the heart[28]. Based on electrophysiological and pharmacological features, CCBs are classified as L-, N-, P-, Q-, R-, and T-type[29]. L-type voltage-gated CCBs are potent vasodilators that are commonly utilized as first- or second-line treatments for HTN. In the treatment of HTN in patients with CKD, they are considered second- or third-line therapy[30]. Dihydropyridines (DP) and non-NDP are two types of CCBs that have been demonstrated to be effective in the treatment of HTN in patients with CKD[31]. In non-proteinuric CKD, DP CCBs [such as amlodipine (ALM), cilnidipine, felodipine, nifedipine, and others] can be utilized as first-line therapy alone or in combination, but their impact in proteinuric CKD is inferior to RAAS inhibition[32]. Adding DP CCB to proteinuric patients with RAAS inhibition improves BP control without worsening proteinuria, according to European Society of Hypertension/European Society of Cardiology guidelines, which recommend combination therapy with an ACE inhibitor and CCB as first-line therapy in proteinuric circumstances[33]. In conclusion, the decision to use one medication over another is based on patient-specific considerations such as probable adverse effects, cost, and other underlying comorbidities.

EMERGENT ROLE OF CCBS IN PATIENTS WITH HTN AND CKD

The most potent and common situation presently is the use of CCBs and RAAS inhibitors (ACE/ARB) as anti-hypertensive medicines for mild to moderate HTN. Although there is no consensus on which antihypertensive drugs should be given as first-line therapy in patients with CKD, a systematic review and meta-analysis of 21 randomized controlled trials (RCTs) involving 9492 patients found that CCBs and RAAS inhibitors had similar BP-lowering effects in HTN patients with CKD and ESRD[34]. In the test population, there were no significant changes in long-term BP maintenance, mortality, heart failure, stroke, cerebrovascular episodes, or renal function. Overall, this study demonstrated that CCBs are comparable to RAAS inhibitors and can protect the kidneys in CKD patients with HTN. This was in line

with a prior study (ALLHAT) that found CCBs to be particularly beneficial for long-term GFR maintenance when compared to diuretics and ACE inhibitors[35]. Furthermore, the INSIGHT study randomized 6321 HTN patients with one or more related risk factors to the DP CCB, nifedipine gastrointestinal therapeutic system, or the diuretic combination hydrochloro-thiazide amilozide for the treatment of HTN. The major composite end point of CV mortality, non-fatal myocardial infarction, stroke, and heart failure had no statistically significant difference in both groups throughout the trial [36]. The ACCOMPLISH (Avoiding CV Events *via* Combination Therapy in Patients Living with Systolic Hypertension) trial compared the effectiveness of ALM/ACE inhibitor against hydrochloro-thiazide/ACE inhibitor combination therapy in adults with HTN and CKD in lowering CVD mortality [37]. The superior efficacy of ALM plus ACE inhibitor on CVD mortality was revealed in this multicenter, double-blind, randomized experiment. Notably, the ALM group had a considerably decreased probability of CKD progression, which was independent of BP values obtained. In the HTN/CKD group, the addition of ALM to ACE inhibitor therapy appears to provide an additional Reno protective benefit compared to the addition of a thiazide diuretic. In summary, the anti-hypertensive use of CCBs in patients with CKD is an attractive option for reducing BP variability with minimal side effects.

In certain countries, DP CCBs are a common class of antihypertensive medicines. ALM and barnidipine, for example, are third generation DPs that are more lipophilic and have stable pharma-cokinetics with long-term effects. They are well tolerated in people with heart failure and advantageous for those with CKD since they are less cardio-selective[31].

AMLODIPINE-THE UNIQUE CCB

DP CCBs are a class of potent, well-tolerated, and safe medicines that are widely used to treat high BP as a monotherapy or as a crucial component of HTN treatment[38]. ALM was first released in the early 1990s and has a number of distinguishing characteristics that set it distinct from other agents in this category. ALM is a longer-acting DP CCB that has been proven in trials to block all channels as well as the N-type channel more effectively than cilnidipine[39]. The elimination half-life of 40-60 h confers various pharmacokinetic properties not found with other calcium-antagonist medications due to its low clearance. It has a high oral bioavailability (60%-80%) and a steady-state accumulation with once-daily dosage over a period of 1-1.5 wk. Furthermore, the pharmacodynamic profile is consistent with the drug's disposition, with BP steadily decreasing over 4-8 h following a single dose and returning to baseline over 24-72 h. Furthermore, stopping ALM therapy causes a delayed restoration of BP to baseline over 7-10 d, with no indication of a 'rebound' impact.

It has great selectivity for vascular smooth muscle, limited impact on heart rate, no negative inotropic effects/electrophysiological disturbances, and milder side events[40]. It is a well-studied classic medication with a wide range of capabilities, including BP regulation and anti-anginal and anti-athero-sclerotic effects[41]. Studies documenting ALM's gradual and protracted drop in BP due to a long elimination half-life and delayed receptor dissociation kinetics[42,43] demonstrate its function in delaying the onset of CKD. ALM also has a long duration of action of at least 24 h and good anti-hypertensive effects with high safety in clinical trials with HTN patients at doses of 2.5-5 mg once a day [44]. Furthermore, 35 HTN patients with renal dysfunction were given ALM at 2.5-5.0 mg/d for 8 wk to examine its clinical efficacy and safety in HTN patients with renal dysfunction. With moderate side effects, target BP reduction was reached in 28 of the 35 patients (80%), and ALM was deemed clinically helpful in 27 of the 35 patients (77.1%)[45]. In a clinical trial, individuals treated with telmisartan and ALM combined therapy had a 70% lower urine albumin-to-creatinine ratio (UACR) than those treated with ALM alone[46]. In a similar vein, compared to high dose monotherapy of either medication alone, a low dose telmisartan–ALM combination showed considerably higher BP reductions for both SBP and DBP[47]. ALM safely lowers SBP in hypertensive hemodialysis patients and has a favorable influence on CV outcomes[48]. The link between ALM and contrast-induced acute kidney injury is uncertain, although a retrospective, matched cohort investigation in a large Chinese hypertension population found that ALM medication prior to contrast exposure protected hypertensive patients from contrast-induced acute kidney injury and increased survival[49]. Results from several trials proving the superiority of ALM in decreasing hypertensive CKD are shown below and summarized in Table 3.

ACCOMPLISH trial

This is a double-blinded, randomized trial with 11506 patients randomized benazepril (20 mg) and ALM (5 mg; n = 5744) or benazepril (20 mg) plus hydrochlorothiazide (12.5 mg; n = 5762), orally once a day, as previously stated in Section 4. In comparison to the hydrochlorothiazide plus benazepril, ALM plus benazepril group demonstrated a 48% reduction in the progression of CKD and 49% reduction in doubling of serum creatinine. Initiating antihypertensive treatment in CKD with benazepril plus ALM preference to benazepril plus hydrochlorothiazide should be preferred as it slows progression of nephropathy to a greater extent[37].

Table 3 Summarized data from various trials demonstrating the role of amlodipine in reducing hypertension

Trial	Objective	Design/primary endpoints	Drug/procedures used	Main outcomes	Benefits on renal parameters
ALLHAT	To determine whether treatment with a CCB or an ACE inhibitor lowers the incidence of CHD or other CVD events *vs* treatment with a diuretic	A total of 33357 participants aged 55 yr or older with HTN and at least 1 other CHD risk factor from 623 North American centers were enrolled. Primary Endpoints: Combined fatal CHD or nonfatal MI analyzed by intent-to-treat	Participants were randomly assigned to receive chlorthalidone, 12.5 to 25 mg/d (n = 15 255); ALM, 2.5 to 10 mg/d (n = 9048); or lisinopril, 10 to 40 mg/d (n = 9054) for planned follow-up of approximately 4 to 8 yr	In patients with HTN, chlorthalidone, ALM, and lisinopril performed similarly in regard to fatal CAD and nonfatal MI	Post hoc analysis of the trial revealed that in hypertensive patients with reduced GFR, both ALM and lisinopril performed similarly in reducing the rate of development of ESRD
ACCOMPLISH	To evaluate the effect of ALM *vs* hydrochlorothiazide in patients with HTN who are at high risk CVD	Multi-centered, double-blind, randomized, controlled trial with 548 centers in the US and Europe. 11506 subjects were enrolled who received Benazepril/ALM (n = 5744) or Benazepril/HCTZ (n = 5762). Primary Endpoint: CV mortality, nonfatal MI, nonfatal CVA, UA, resuscitation after cardiac arrest, or coronary revascularization	Subjects received benazepril/ALM 20 mg/5 mg or benazepril/HCTZ 20 mg/12.5 mg daily. Benazepril component was increased to 40 mg after 1 mo.Increase of ALM to 10 mg or HCTZ to 25 mg to reach target BP < 140/90 or < 130/80	Among patients with HTN at high risk for CV complications, benazepril/ALM decreases the rate of CV events as compared to benazepril/HCTZ	Initial antihypertensive treatment with benazepril and ALM demonstrates a superior ability in reducing the progression of nephropathy
SAKURA	To clarify whether the L-/N-type CCB cilnidipine is more renoprotective than the L-type CCB ALM in patients with early-stage diabetic nephropathy	Prospective, multicenter, open-labeled, randomized trial in 77 clinics and hospitals in Japan, to probe the anti-albuminuric effects of cilnidipine and ALM in 367 RAAS inhibitor-treated patients with HTN (BP: 130-180/80-110 mmHg), type 2 diabetes, and microalbuminuria (UACR: 30-300 mg/g). Primary Endpoint: Change in the urinary albumin/Cr ratio after a 1-yr treatment	Study subjects were randomly allocated in two groups and treated with cilnidipine (started at 10 mg/d, then adjusted to 5-20 mg/d) or ALM (started at 5 mg/d, then adjusted to 2.5-10 mg/d). The target BP was < 130/80 mm Hg	Cilnidipine did not offer greater renoprotection than ALM in RAS inhibitor treated HTN patients with type 2 diabetes and microalbuminuria	In hypertensive patients with proteinuria, L/N- and L/T-type CCBs as add-on therapy to an ACEI or an ARB reduce albuminuria and proteinuria and improve kidney function compared with the use of an ACEI or ARB alone or in combination with other antihypertensive agents
ASCOT-BPLA	To evaluate whether treatment with a newer anti-hypertensive regimen of CCB with or without an ACE inhibitor is more effective than an older regimen of β-blocker with or without a diuretic, and whether it reduces CHD events in hypertensive patients with relatively low cholesterol levels	A total of 19257 patients with SBP ≥ 160 mm Hg and/or DBP ≥ 100 mm Hg (untreated) or SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg (treated); total cholesterol ≤ 6.5 mmol/L (250 mg/dL) and triglycerides ≤ 4.5 mmol/L (400 mg/dL); age 40-79 yr; ≥ 3 CVD risk factors; and no history of CHD were enrolled Primary Endpoints: Nonfatal MI and fatal CHD	Patients were randomized open-label to one of the two anti-hypertensive treatments: ALM 5 mg (n = 9639) or atenolol 50 mg (n = 9618). In order to achieve target BP goals of < 140/90 mm Hg, study drug doses were increased, and second-line drugs were added (perindopril 4 mg for the ALM group and bendroflumethiazide 1.25 mg for the atenolol group)	ALM-based regimen is superior to an atenolol-based regimen in regard to demonstrating a greater reduction in BP variability and prevention of major CV events in patients with HTN	ALM based arm demonstrated a significant reduction in new onset diabetes mellitus, development of peripheral arterial disease and renal impairment

ACEI: Ace inhibitor; ALM: Amlodipine; ARB: Angiotensin receptor blockers; BP: Blood pressure; CAD: Coronary artery disease; CCB: Calcium channel blocker; CHD: Chronic heart disease; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; GFR: Glomerular filtration rate; HCTZ: Hydrochlorothiazide; HTN: Hypertension; MI: Myocardial infarction; SBP: Systolic blood pressure; RAAS: Renin–angiotensin–aldosterone system; UACR: Urine albumin-to-creatinine ratio.

SAKURA trial

The Study of Assessment for Kidney Function by Urinary Microalbumin in Randomized (SAKURA) experiment was conducted to examine the anti-albuminuric effects of L-/N-type and L-type CCBs in HTN patients with diabetes and microalbuminuria. The anti-albuminuric effects of cilnidipine and ALM were investigated in RAAS inhibitor-treated patients with HTN (BP: 130-180/80-110 mmHg), type 2 diabetes, and microalbuminuria (UACR: 30-300 mg/g) in this prospective, multicenter, open-labeled, randomized investigation. Despite the fact that cilnidipine and ALM both reduced BP and showed

similar effects on UACR, ALM provided greater renoprotection in RAS inhibitor-treated hypertensive patients with type 2 diabetes and microalbuminuria. Clinidipine provided no more renoprotection than ALM in RAS inhibitor-treated hypertensive patients with type 2 diabetes and microalbuminuria.

ASCOT-BPLA trial

The Anglo-Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm (ASCOT-BPLA) trial found that an ALM-based regimen outperformed an atenolol-based regimen in terms of lowering BP variability and preventing major CV events in patients with HTN[51].

Treatment-resistant HTN is emerging as an increasingly recognized problem and is markedly over-represented in patients with CKD[52]. It is defined as uncontrolled BP despite maximally effective dosing of three drugs from different classes, one of which should be a diuretic. Recent evidence has highlighted the heightened risk for both adverse renal and CV outcomes associated with resistant HTN, even when BP control is attained[52]. In a study involving 157 resistant HTN patients (over 60-years-old) who were randomized to 8 wk of treatment and received double-blinded treatment with placebo, ALM (10 mg/d), olmesartan medoxomil (40 mg/d), and ALM (10 mg/d) + olmesartan medoxomil (40 mg/d), the research findings suggested that ALM and OM combination therapy had superior efficacy to ALM or OM monotherapy, Furthermore, patients who received combination therapy met their BP goals more often than those who received placebo, ALM, or OM monotherapies. The long-term CV effects of ALM were compared to other classes of anti-hypertensive medicines in high-risk HTN patient subgroups with diabetes and/or renal failure in another investigation[53]. Thirty-eight RCTs comparing ALM/CCBs to diuretics, -blockers, ACE/ARB inhibitors, and -blockers with a 6-mo follow-up were enrolled, with BP and CV events examined. ALM was found to be successful in lowering SBP and DBP, making it a promising treatment alternative for the long-term management of HTN in diabetic and renal failure patients. In terms of preventing major CV events and causing less diabetes, an ALM-based regimen was found to be superior than an atenolol-based regimen[54].

CONCLUSION

CCBs are a good choice of anti-hypertensive medications in HTN patients with CKD. ALM is a well-known medication having a wide range of effects, including BP regulation and anti-anginal and anti-atherosclerotic characteristics. ALM is a longer-acting DP CCB that controls BP for up to 24 h and minimizes BP variability. Several pharmacokinetic properties can be linked to it, including limited clearance and a longer rate of elimination (elimination half-life of 40-60 h). It also has a high oral bioavailability and a steady-state accumulation with once-daily treatment. In the absence of albuminuria and with a preserved GFR (> 60 mL/min), it can be used as a first-step therapy since it can block all calcium channels and the N-type channel more effectively than cilnidipine. It is a strong, well-tolerated, and safe antihypertensive drug that is commonly used for HTN in CKD, either alone or as part of a combination therapy. Its effectiveness in lowering BP has been linked to a reduction in CV events, as evidenced by large RCTs. ALM in combination with other medicines that elicit RAAS blockage (ACE/ARB) has been demonstrated to be an effective BP-lowering strategy in reducing CV risk and slowing the progression of renal impairment. AML substantially lowers BP in patients with HTN and renal impairment while causing minimal or little worsening of renal dysfunction. In terms of effectiveness and potency in decreasing BP in CKD patients, ALM emerges as the medicine of choice when compared to the newer CCBs.

FOOTNOTES

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MINIREVIEWS

Liposoluble vitamins A and E in kidney disease

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Abstract

Kidney disease (KD) is characterized by the presence of elevated oxidative stress, and this is postulated as contributing to the high cardiovascular morbidity and mortality in these individuals. Chronic KD (CKD) is related to high grade inflammatory condition and pro-oxidative state that aggravates the progression of the disease by damaging primary podocytes. Liposoluble vitamins (vitamin A and E) are potent dietary antioxidants that have also anti-inflammatory and antiapoptotic functions. Vitamin deficits in CKD patients are a common issue, and multiple causes are related to them: Anorexia, dietary restrictions, food cooking methods, dialysis losses, gastrointestinal malabsorption, *etc.* The potential benefit of retinoic acid (RA) and α-tocopherol have been described in animal models and in some human clinical trials. This review provides an overview of RA and α tocopherol in KD.

Key Words: Retinoic acid; α-Tocopherol; Oxidative stress; Kidney disease; Podocyte; Cardiovascular disease

Core Tip: Oxidative stress in patients with kidney disease (KD) is an important risk factor for cardiovascular disease. Vitamin A and E are important antioxidants with many roles in health and KD. High levels of vitamin A may have adverse health effects but higher levels of vitamin E have been associated with a lower overall mortality. Exogenous administration of these vitamins to patients with KD have shown controversial results.

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INTRODUCTION

Kidney disease (KD) is characterized by the presence of elevated oxidative stress and this is postulated to contributing to the high cardiovascular mortality in these individuals. Liposoluble vitamins (vitamins A and E) are potent dietary antioxidants that also have anti-inflammatory and antiapoptotic functions. Antioxidant therapies have been extensively used to decrease oxidative stress and cardiovascular disease (CVD) risk. In the kidneys, the beneficial effects of retinoic acid (RA) have been reported in multiple disease models, such as glomerulosclerosis, renal fibrosis, and acute kidney injury (AKI).

Vitamin E has a myriad of cellular effects, such as decreasing the synthesis of pro-inflammatory molecules and oxidative stress response, inhibiting the nuclear factor-kappaB (NF-kB) pathway, regulating cell cycle, and inhibiting the expression of pro-apoptotic factors that can have a positive impact on KD. The aim of this review is to present an overview about the impact of liposoluble vitamins on KD.

Vitamin A metabolism

Vitamin A, is the name of a group of fat-soluble retinoids, including retinol and retinyl-esters that are essential for human survival; vitamin A is available into the human diet by intake of either food containing preformed vitamin A (*e.g.*, red meats) or carotenoids (*e.g.*, carrots and green leafy vegetables).

Retinoids are vital for human health and play a crucial role in the regulation of nocturnal vision, reproduction, immune function, and cell differentiation[1,2]. Recent advances in the study of retinoids metabolism have highlighted their importance in adipose tissue biology, glucose metabolism, and bone mineralization[3,4].

Most actions of retinol are mediated by its metabolite all-trans (AT)RA, which is synthesized intracellularly in target tissues from retinol[5]. Retinol is stored primarily as retinyl ester in the hepatic stellate cells, and to a lesser extent, in adipose tissue and other extrahepatic sites.

Retinoids regulate a number of physiological processes and through regulating the expression of over 500 genes; retinoids bind to nuclear receptors called RA receptors and retinoid X receptors, which themselves are DNA-binding transcriptional regulators and members of the nuclear hormone receptor family[6].

The liver plays a central role in vitamin A physiology. The retinol-binding protein 4 (RBP4) is secreted from the liver to bind and transport vitamin A to extrahepatic target tissues for intracellular ATRA synthesis. The primary physiological role of RBP4 is to guarantee a constant and continuous supply of retinol to peripheral tissues despite fluctuations in dietary vitamin A intake[7,8].

Vitamin A homeostasis in kidney health and disease

The kidney plays a key role in vitamin A homeostasis; findings of kinetic studies have revealed that approximately 50% of the circulating retinol pool originates in the kidneys. Retinol is filtered through the glomerular barrier and is then taken up in the proximal tubule by the endocytic receptor megalin; kidney-specific megalin deletion in mice, increases the urinary excretion of retinol and RBP4; in these mice, the syntheses of hepatic retinol and retinyl esters is reduced. These findings suggests a more complex role of the kidney in retinoid homeostasis[9]. More than 99% of retinol is reabsorbed by the proximal renal tubule; RBP4 has been identified as a very sensitive biomarker for proximal tubular cells dysfunction[10].

Patients with impaired renal function have been reported to have high circulating levels of retinol and RBP4, possibly due to a combination of decreased retinol-RBP4 complex clearance, reduced conversion of retinol to ATRA, and tissue accumulation of RBP4[11]. Dialysis patients have elevated serum levels of retinol and RBP4[12].

Increased RBP4 concentrations has been associated with an increased risk for osteoporosis, heart disease, and dyslipidemia. Furthermore, many studies have demonstrated an important link of RBP4 with adiposity, insulin resistance, and type II diabetes[4,13,14]. Interestingly, ATRA has been shown to be inversely associated with CVD and mortality in dialysis patients[12].

Dietary intake of vitamin A in chronic KD

The most important food sources of vitamin A are liver, fish liver oil, dairy products (butter, milk, *etc.*), egg yolk, dark green leafy vegetables, and deeply colored yellow/orange vegetables and fruits[15]. The recommended dietary allowance for men and women is 900 and 700 μg retinol activity equivalents/d,

respectively[16].

The Kidney Disease Outcomes Quality Initiative guideline no recommends routinely vitamin A supplementation (grade opinion), and there are no studies about the nutritional requirements in chronic KD (CKD) population[17]. There is no information about dietary recommendations in the pediatric population with CKD.

There are only a few studies that have evaluated vitamin A intake in CKD and dialysis subjects. In a cross-sectional study of 91 hemodialysis patients, only 23% of individuals covered vitamin A dietary recommendation[18]. As most sources of vitamin A have high potassium and phosphorous contents, the intake of vitamin A may be limited in advanced stages of CKD. Cooking techniques used to lower potassium in foods affect carotene concentration; boiling decreases up to 20%-30% of carotene content after 30 min, thereby making it more difficult to achieve adequate vitamin intake[19].

Kidney development and vitamin A

Vitamin A and its metabolites have a pivotal role during prenatal development, and vitamin A status is critical for the fetus. Maternal vitamin A deficiency is associated with preterm delivery, fetal death, or major congenital malformations in the offspring[20]. Studies in rodents suggest that retinol availability is essential in order to have an adequate renal development. Fetal retinol crosses the placental barrier from the maternal circulation and is converted to ATRA in peripheral tissues. Vitamin A deficiency has been associated in pregnant rats with mild renal hypoplasia in term fetuses; and the addition of ATRA to fetal rat kidneys cultured *ex vivo* accelerates new nephron formation[21-23].

The expression of the proto-oncogene c-ret, which plays an essential role in renal organogenesis, is modulated by retinoid environment. This indicates that the control of nephron mass by vitamin A may partly be mediated by the tyrosine kinase receptor ret, and this receptor modulates the ureteric bud branching morphogenesis[21].

In a cohort of 9-13 years old children in Nepal whose mothers participated in a randomized controlled trial of vitamin A supplementation before, during, and after pregnancy, the rate of hypertension or microalbuminuria did not differ by supplement group[24]. In conclusion, adequate vitamin A supply is crucial in determining final nephron numbers, and whether these findings have a prime role in the further development of CKD or hypertension is still controversial[25].

Glomerular barrier and retinoids

The glomerular filtration barrier consists of three layers: Fenestrated endothelial cells, glomerular basement membrane, and podocytes. Podocytes are specialized epithelial cells, whose major function is regulation of the glomerular filtration. Podocyte injury is implicated in many glomerular diseases including focal segmental glomerular sclerosis, diabetic KD, and human immunodeficiency virus (HIV)-associated nephropathy; loss of podocytes contributes to progressive KD as these cells have a low proliferative capacity. Research on podocytes and retinoids has been the subject of recent excellent reviews [26,27]. The pleiotropic effects of retinoids in animal models of KD are shown in Table 1. In HIV-1-transgenic mice, ATRA inhibits proliferation and induces differentiation in podocytes through cAMP/PKA activation[28].

Retinoid treatment of rats with experimental mesangioproliferative glomerulonephritis causes a significant reduction in albuminuria, inflammation, and cell proliferation. Retinoids have been demonstrated to induce a marked reduction in renal transforming growth factor (TGF)-β1 and TGF receptor II expression[29]. NF-κB and nitric oxide synthase expression are reduced in mesangial cells after ATRA administration[30]. Renin-angiotensin system activity is also reduced[31]. Retinoids restore injured podocytes that regulate the transition of parietal epithelial cells to podocytes in rat models of glomerular inflammation (Figure 1)[32].

There are some reports of conspicuous clinical improvement in patients with lupus nephritis by using retinoid treatment[33]. In models of diabetic nephropathy, ATRA suppressed inflammatory changes and decreased proteinuria[34], and ATRA is significantly decreased in the cortex, which indicates that ATRA metabolism is markedly dysregulated in diabetic kidneys[35]. In Table 1 some postulated mechanisms of action of retinoid administration in animal models of KD and reported human clinical trials are described.

ATRA and AKI

ATRA has been used therapeutically to reduce injury and fibrosis in models of AKI. ATRA signaling is activated in tubular epithelial cells and macrophages and reduces macrophage-dependent injury and fibrosis after AKI[36]. In models of cisplatin and contrast-induced AKI, retinoids activate autophagy, inhibit apoptosis, and decrease the oxidative status[37].

Retinoids and erythropoietin in kidney failure

Erythropoietin (EPO) synthesis decreases in kidney failure, and some of the mechanisms proposed are the conversion of peritubular fibroblast into α-smooth muscle actin-expressing myofibroblasts, thereby losing their ability to secrete retinoids and EPO and defects in oxygen sensing[38]. Liver cells also synthesize EPO, and its contribution may increase when the kidneys are unable to maintain adequate

Table 1 Postulated mechanisms of action of retinoid administration in animal models of kidney disease and reported human clinical trials

Drug	Animal model/disease/*n*		Outcome
Animal			
atRA	anti-Thy1.1 model rats	Mesangioproliferative glomerulonephritis	RA limits glomerular proliferation, glomerular lesions, and albuminuria. Marked reduction in renal TGF-β1. Reduction RAS activity[29]
atRA	HIV-1–transgenic mice	HIV associated kidney disease	atRA inhibits proliferation and induces differentiation in podocytes through RAR-mediated cAMP/PKA activation[28]
atRA	Streptozotocin-induced diabetic rats	Diabetic kidney disease	atRA decreases MCP-1 urinary excretion. Decreases proteinuria[34]
Tamibarotene	Male C57BL/6 mice	Unilateral ureteral obstruction	Inhibits the accumulation of fibrocytes and alleviates renal fibrosis mediated by IL-17A[64]
atRA	$Atg5^{flox/flox}$:Cagg-Cre mice	Cisplatin nephrotoxicity	RA activates autophagy and alleviates cisplatin acute kidney injury[37]
atRA	Male rats	Unilateral ureteral obstruction	ATRA treatment can increase the angiopoitin-1 and decrease interstitial fibrosis[65]
Human			
Isotretinoin	FSGS; MCD (shase II study)	12 (only 6 completed the study)	No complete or partial remission at 6 mo (clinicaltrials.gov)
Tamibarotene	Lupus nephritis (phase II study)	20	Not published

atRA: All-trans-retinoic acid; MCP-1: Monocyte chemoattractant peptide; FGFS: Focal segmental glomerulosclerosis; MCD: Minimal change disease; TGF-β 1: Transforming growth factor-β1; HIV: Human immunodeficiency virus; RA: Retinoic acid; IL: Interleukin.

levels for erythropoiesis[39]. ATRA is essential for hepatic production of EPO in early developmental stages and potentiates the EPO production through hypoxia-inducible factor signals and effectively improves renal anemia in mice[38].

Conclusions and future perspectives

The available evidence in cell cultures and animal models regarding the potential use of retinoids in the prevention and treatment of KD suggests that these compounds can effectively restore injured podocytes and decrease inflammation and interstitial fibrosis; however, a better understanding of retinoid signaling in renal cells is necessary to decreased toxicity and side effects of these compounds.

Vitamin E metabolism

Vitamin E is a fat-soluble vitamin and the most abundant liposoluble antioxidant compound in the human body; α-tocopherol accounts for about 90% of the vitamin E activity in human tissues. Vitamin E is emulsified by the bile acids and absorbed in the form of micelles in the small intestine; α-tocopherol is mostly transported from the blood to the liver cells by chylomicrons, very low-density lipoproteins (LDL), and high-density lipoproteins (HDL)[40].

The specific α-tocopherol transfer protein (α-TTP) mediates the transport from the hepatic lysosomes into lipoproteins, whereas the excessive α-tocopherol and other forms of vitamin E are excreted in bile. The primary function of α-TTP is to maintain normal α-tocopherol concentrations in plasma and extrahepatic tissues. α-TTP is also expressed in the placenta, brain, spleen, lung, and kidney[41]. Besides the lipoprotein-lipase action, the delivery of α-tocopherol to tissues takes place by the uptake of lipoproteins throughout their corresponding receptors[42].

Vitamin E is present in various foods and oils such as nuts, seeds, vegetable oils, green leafy vegetables, and fortified cereals. The recommended dietary allowance for males and females aged ≥ 14 years is 15 mg daily (or 22 IU). In most countries, vitamin E deficiency is not prevalent and is usually associated with irregularities in the absorption of dietary fat. Previous studies have shown that subjects with CKD do not have the recommended micronutrient intake; however, the KDIGO nutritional guidelines do not recommend routine vitamin E supplementation[43].

Vitamin E metabolism and effects on health and KDs

Vitamin E localizes in the cell membrane and plays a key role in the regulation of redox interactions. Furthermore, it is considered one of the most important defenses against membrane lipid peroxidation and superoxide generation. It is the major antioxidant present in human lipoproteins, acts as a peroxyl-radical scavenger, and is a potent suppressor of LDL lipid oxidation; lipid oxidation has been implicated

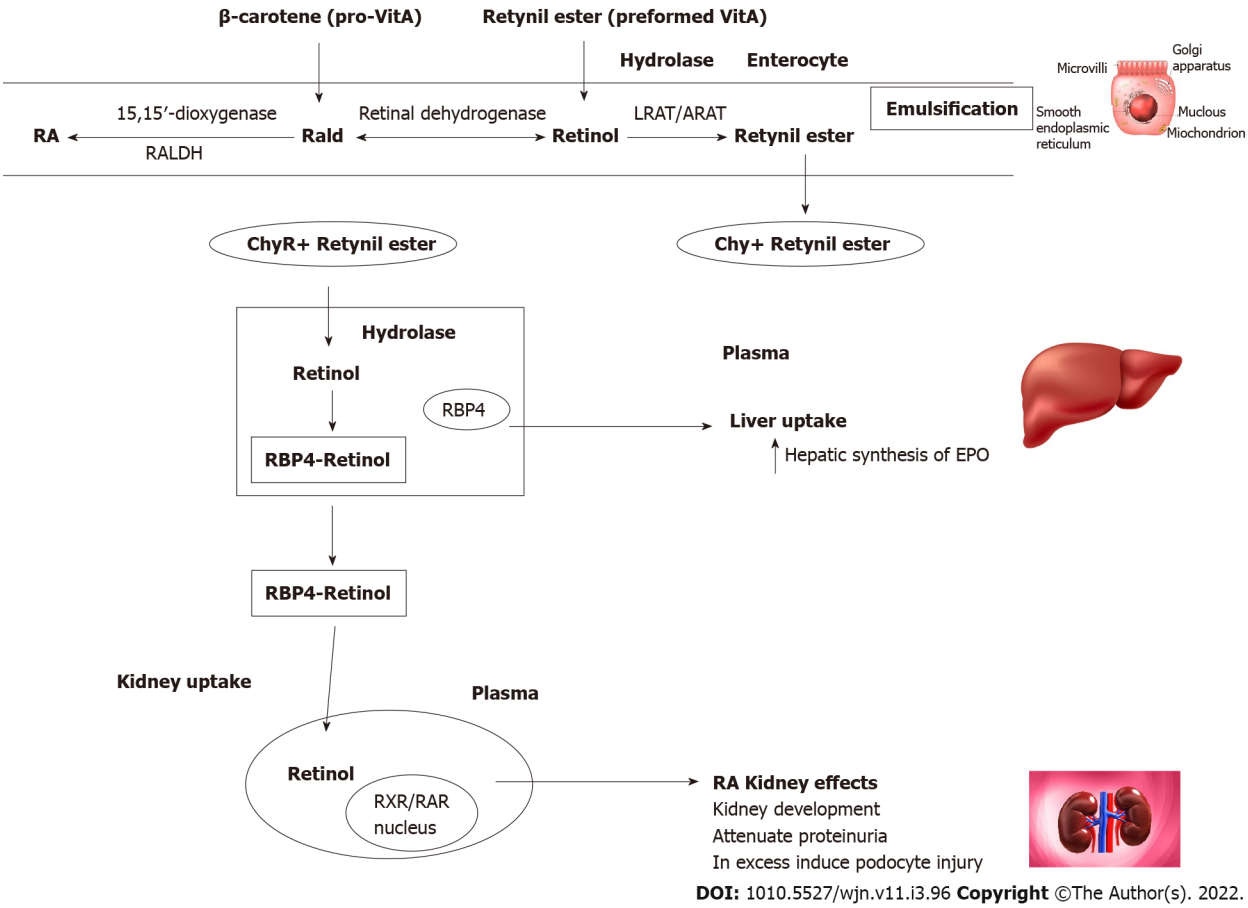

Figure 1 Retinoids restore injured podocytes that regulate the transition of parietal epithelial cells to podocytes in rat models of glomerular inflammation. LRAT: Lecithin retinol acyltransferase; RALDH: Retinal dehydrogenase; RBP4: Retinol binding protein 4; RA: Retinoic acid; EPO: Erythropoietin; VitA: Vitamin A; ARAT: Retinoic acid all-trans.

in chronic disease risk, including CVD and cancer[42,44]. Other important functions include the regulation of gene expression, improvement of immune response, inhibition of cell proliferation, and suppression of tumor angiogenesis[45]. In non-dialyzed and dialyzed CKD patients, plasma vitamin E levels are usually within the normal range; however, decreased α-tocopherol in red blood cell membranes of CKD subjects has been demonstrated[46].

Low levels of α-tocopherol in healthy subjects are associated with an increased risk for coronary artery disease[47], and higher intake has been shown to be protective; furthermore, recent studies suggest that higher α-tocopherol concentrations were related to a lower total mortality[48]. However, there is no information about tocopherol levels and mortality in CKD subjects, but some studies had been performed about vitamin E administration in this population.

Effects of vitamin E supplementation to ameliorate KD are controversial. The HOPE study found no beneficial effects of vitamin E administration on CVD mortality or renal complications[49]. Giannini *et al* [50] in a randomized trial in patients with Type 1 diabetes mellitus and persistent MA reported that vitamin E supplementation does not reduce albuminuria, but Khatami *et al*[51] found a significant decrease in urine protein excretion in T2 diabetic subjects.

The SPACE study performed in hemodialysis patients, found that high-dose α-tocopherol decreases the incidence of cardiovascular events but did not demonstrate a significant reduction in mortality[52]. Administration of α-tocopherol increases carboxy-ethyl-hydroxychromans with known potent anti-inflammatory and antioxidative properties[53], and a recent systematic review found that vitamin E administration reduces malondialdehyde in hyperactivity disorder (HD) patients; however, the effects on CVD or mortality were not particularly analyzed[54].

Vitamin E supplementation in HD subjects significantly improved the HDL function of cholesterol efflux capacity and in diabetic patients the endothelial function[55]. The use of vitamin E-coated dialyzer membranes may plausibly exert a site-specific scavenging effect on free radical species in synergy with reduced activation of neutrophils[56].

Vitamin E supplementation in CKD subjects is not recommended as has been shown to have no discernible effect on the overall mortality; one meta-analysis even demonstrated an increased mortality in healthy subjects who received a high dose of supplemented vitamin E[49,57]. Experimental and human clinical trials (Table 2) have demonstrated a role of vitamin E in preventing kidney injury. In the

Table 2 Reported human clinical trials of vitamin E administration in chronic kidney disease subjects

Ref.	*n*	Dose	Inclusion criteria	Outcome
Mann *et al*[49]	993	400 IU/d	1.4 ≤ SCr ≤ 2.3 mg/dL. Plus CV disease or DM	Follow-up 4.5 yr. No apparent effect on CV outcomes
Giannini *et al*[50]	10	1200 IU/d	Type 1 diabetes mellitus plus macroalbuminuria	Reduces markers of oxidative stress. No effect on MA
Khatami *et al*[51]	60	1200 IU/d	Diabetic nephropathy	Decrease in protein/creatinine ratio. Reduction in inflammatory markers
Boaz *et al*[52]	196	800 IU/d	Hemodialysis patients	Reduces CV disease
Himmelfarb *et al*[53]	30	300 IU/d	15 healthy subjects, 15 hemodialysis patients	Reduction on C reactive protein
Bergin *et al*[54]			Meta-analysis 16 papers	Reduction oxidative stress
Mune *et al*[55]	40	300 mg/d	Hemodialysis subjects	Improvement in endothelial function

CV: Cardiovascular.

subtotal (5/6) nephrectomy remnant kidney model in the rat, α-tocopherol has the capacity to modulate both tubulointerstitial injury and glomerulosclerosis, inhibit the expression of TGF-β, and reduce plasma and kidney malondialdehyde concentration[58].

Animal models have exhibited beneficial effects of vitamin E administration in the prevention of diabetic nephropathy by inhibition of the protein kinase C pathway and normalizing diacylglycerol cellular levels[59]. Tocotrienols are members of the vitamin E family with potent anti-oxidant activity; in *db/db* mice, T3β administration increased adiponectin levels and improved renal function[60].

Experimental immunoglobulin A nephropathy in rats is associated with increased renal oxidant injury, and dietary treatment with vitamin E has been reported to attenuate functional and structural changes[61]. The amelioration of renal injury by dietary α-tocopherol supplementation has also been observed in unilateral ureter obstruction[62] and puromycin aminonucleoside nephropathy[63]. There is still no robust evidence supporting the widespread use of vitamin E as a therapy for retarding chronic KD. Future studies with longer follow-up and larger sample size are necessary before any helpful recommendation.

CONCLUSION

RA and α-tocopherol have numerous cellular functions that can have an effect on kidney injury progression; however, further extensive research is needed before making clinical recommendations. Higher intake of natural carotenoids and tocopherols have been proven to have a beneficial impact on overall mortality, but supplementation with either of the two vitamins has not manifested any notable effect on the decrease in mortality of patients with CKD.

FOOTNOTES

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MINIREVIEWS

Multidisciplinary basic and clinical research of acute kidney injury with COVID-19: Pathophysiology, mechanisms, incidence, management and kidney transplantation

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Abstract

Acute kidney injury (AKI) linked to coronavirus disease 2019 (COVID-19) has been identified in the course of the disease. AKI can be mild or severe and that is dependent on the presence of comorbidities and the severity of COVID-19. Among patients who had been hospitalized with COVID-19, some were admitted to intensive care unit. The etiology of AKI associated with COVID-19 is multifactorial. Prevention of severe AKI is the prime task in patients with COVID-19 that necessitates a battery of measurements and precautions in management. Patients with AKI who have needed dialysis are in an increased risk to develop chronic kidney disease (CKD) or a progression of their existing CKD. Kidney transplantation patients with COVID-19 are in need of special management to adjust the doses of immunosuppression drugs and corticosteroids to guard against graft rejection but not to suppress the immune system to place the patient at risk of developing a COVID-19 infection. Immunosuppression drugs and corticosteroids for patients who have had a kidney transplant has to be adjusted based on laboratory results and is individualized aiming at the protection of the transplanted from rejection.

Key Words: Acute kidney injury; COVID-19; SARS-CoV-2; Kidney transplantation; Dialysis; Immunosuppressant; Intensive care unit; Mortality; Cytokine storm

Core Tip: Acute kidney injury (AKI) in patients with coronavirus disease 2019 (COVID-19) is initiated by multifactorial events including direct viral effect, cardiac causes, thromboembolic phenomenon and cytokine storm. AKI is attributed to collapsing glomerulopathy, acute tubular necrosis and mitochondrial dysfunction. Management of AKI is multidisciplinary dependent on severity of COVID-19, associated comorbidities, intensive care unit admission and artificial ventilation. Management is initial control of fluid balance and in severe cases an early initiation of renal replacement and extracorporeal organ support which would support the organs and prevent disease progression. Kidney transplantation patients are at risk of developing AKI due to the state of their immunocompromised status caused by regular use of immunosuppressants; this situation indicates the adjustment of immunosuppressors in the condition of treatment of cytokine storm with corticosteroids.

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INTRODUCTION

Coronavirus disease-2019 (COVID-19) is caused by one of the coronaviridae family that has single-stranded RNA and causes severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 11, 2022, following its rapid worldwide spread, the World Health Organization recognized the disease as a pandemic[1].

COVID-19 initially affects the lungs, but it also affects other organs including the heart, intestine, and the kidneys and causes acute kidney injury (AKI). Up to 25% of patients who had severe COVID-19 developed AKI[2,3]. Since 2019, the new variants of SARS-CoV-2 have been identified and these new variants have similar effects and can cause AKI.

Acute kidney injury due to COVID-19 is multifactorial and this includes cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of the immune system, hypercoagulopathy and endotheliosis, collapsing glomerulopathy and thrombotic microangiopathy[4-6].

Risk factors for AKI in patients with COVID-19 are older age, obesity, diabetes, hypertension, heart failure, chronic kidney disease, immunosuppression status and cancer chemotherapy. Additional factors are anemia, lymphopenia, leukocytosis, an increase in inflammatory markers (D-dimer and IL-6) and the need for mechanical ventilation and vasoactive drugs which all can aggravate the condition.

AKI is a complication of SARS-CoV-2 Infection and presents as mild or severe and is ranged from grade 1 to grade 3. AKI could be managed conservatively or the patient will be in need of hemodialysis which is dependent on severity. 10%-15% of all hospitalized patients had some degrees of AKI but patients in the intensive care unit (ICU) experienced an incidence that would exceed 50%[10].

The hemodialysis initiation timing depends on the severity of AKI and continuous venous-venous hemodiafiltration is preferable for patients requiring vasoactive drug infusion and/or having hypervolemia.

Kidney transplant recipients are at considerable risk for development of AKI due to chronic immunosuppression. Patients who had kidney transplantation and develop COVID-19 are on maintenance immunosuppressant drugs including corticosteroids and the doses of steroids should be adjusted for every case independently.

PATHOPHYSIOLOGY AND MECHANISM OF COVID-19-INDUCED AKI

Acute kidney injury due to COVID-19 is multifactorial including cardiovascular comorbidity, direct effects of the virus on the kidney, dysregulation of immune system, hypercoagulopathy and endotheliosis. Angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 which are present in the kidney are targeted by SARS-CoV-2 causing AKI. In the glomerulus, podocytes and endothelial cells have been found to be the sites for viral infection resulting in podocyte dysfunction that effects glomerular filtration leading to proteinuria and hematuria. Viral infection of endothelial cells leads to changes in glomerular capillary hemostasis that cause fibrin thrombi. SARS-CoV-2 was detected in the proximal tubular cells and was attributed to vacuolar degeneration and loss of the brush border of tubular epithelial cells. The tubular lumen contains necrotic epithelium and the interstitium shows massive macrophage infiltration. Other non-viral mechanisms that contribute to AKI includes focal segmental glomerulosclerosis, hemodynamic factors, cardiac dysfunction, high levels of mechanical

ventilation, hypovolemia secondary to decreased fluid intake, fever, sepsis and the use of nephrotoxic antibiotics.

Cardiac factors

COVID-19 pneumonia can cause right ventricular failure and lead to kidney congestion and finally AKI. Left ventricular dysfunction can lead to hypotension, decreased cardiac output and hypo perfusion of the kidneys and ultimately AKI[4].

Direct effects of COVID-19 virus on the kidney

The virus particles were reported to be present in renal endothelial cells, indicating viraemia as a cause of endothelial damage and a probable contributor to SARS-CoV-2 infecting the renal tubular epithelium and podocytes through ACE2 and causing acute tubular necrosis, collapsing glomerulopathy, mitochondrial dysfunction, protein leakage in Bowman's capsule and protein reabsorption vacuoles[5-7].

Cytokine stroke

Cytokines can alter the immune response and the development of lymphopenia. Hypercoagulability occurs that will cause microthrombi and microemboli ultimately leading to stroke.

Rhabdomyosis

Severe COVID-19 can lead to skeletal muscle damage leading to myoglobulin release which induces renal damage through formation of pigment casts that cause tubular obstruction and iron release that has a direct effect on tubular toxicity. Myoglobulin casts have been demonstrated in renal tubules[8,9].

Sepsis

Systemic inflammation due to sepsis leads to release of multiple molecular patterns that are damaging and pathogen-associated that enters the bloodstream and is filtered at the glomerulus.

Hypoxemia and dehydration

Hypoxemia and dehydration are caused by high fevers, fluid restriction and diuretics that are used for the management of acute respiratory distress syndrome. This is combined with mechanical ventilation which reduces renal perfusion.

Hypercoagulable state

It attributes to injury of renal microvasculature.

Macrophage-activation syndrome

Macrophage-activation syndrome involves cytokine storm and high plasma ferritin, which lead to AKI [10].

Direct effect of SARS-CoV-2 virus on tubular epithelium

The SARS-CoV-2 virus binds with ACE2 which is highly expressed in the kidney and there is also high expression in podocytes[11]. Direct viral infection is highly probable to contribute to injury mechanisms. Autopsies from 6 patients who died due to COVID-19 associates AKI and showed that kidney tissues, on light microscopy, exhibit severe acute tubular necrosis, infiltration of tubular interstitium with $CD68^+$ macrophage and deposition of C5b-9. An immunohistochemistry study demonstrated the presence of SARS-CoV-2 nucleocapsid protein in the kidneys[12]. High viral RNA titers were demonstrated in the kidneys[23]. Electron microscopic examination elicited clusters of SARS-CoV-2 particles with its distinctive spikes in the tubular epithelium and podocytes. The pathological changes of the kidney in AKI associated with COVID-19 include vascular, glomerular and tubulointerstitium damage.

Vascular events

Vasoconstriction of intrarenal vessels increased vascular permeability, formation of microthrombi and vascular endothelium damage. These events contribute to development of AKI[13].

Glomeruli

Autopsy studies of the kidneys of patients who died from COVID-19 showed focal and diffuse fibrin thrombi in glomerular capillaries, collapsing glomerulopathy, glomerular epithelial damage, loss of podocytes integrity with hyperplasia and hypertrophy of the glomerular epithelium, endothelial injury, erythrocyte stagnation in the glomerular capillary with glomerular loop occlusion by erythrocytes[14].

Proximal tubules

Autopsies from kidneys of COVID-19 patients shows on light microscopy diffuse kidney injury. The renal tubules showed loss of the brush border and necrosis associated with tubulointerstitial fibrosis

and vacuolar degeneration. Electron microscopy studies shows SARS-CoV-2 viruses were demonstrated in the tubular epithelium of the proximal tubule and podocytes[13,14].

Interstitium

It shows inflammatory cell infiltration and edema that is attributed to the increased permeability of the endothelium and leakage of the glomerular filtrate in the tubules to the interstitium[14].

Inflammation and thrombotic microangiopathy

COVID-19 initiates the release of a vast number of pro-inflammatory cytokines known as the cytokine storm syndrome (CSS) and can lead to multiple organ dysfunctions. It would also lead to endothelial dysfunction and a pro-thrombotic event that leads to small vessel vasculitis and extensive microthrombosis. A condition known as thrombotic microangiopathy is one of the main causes of mortalities in COVID-19. Its development might be mediated by inflammation, endothelial dysfunction and microthrombosis. Interleukin-6 (IL-6) has a critical leading role in CRS. An increase in plasma levels of IL-6 in patients with COVID-19 denotes a worse prognosis. CSS may cause renal medullary hypoxia and tubular cell damage that demonstrate the close relationship between the lungs and the kidneys[15-20].

INCIDENCE OF AKI LINKED TO SARS-CoV-2 INFECTION

Acute kidney injury is a complication of SARS-CoV-2 Infection and it can happen in either moderate or severe cases of COVID-19. AKI can manifest as a mild or more severe form. It could be managed conservatively or the patient may be in need of hemodialysis. Incidence of AKI of all hospitalized patients is 10-15% with varying degrees of severity while for patients in the ICU, the incidence can be higher and exceed 50%[10].

The development of AKI in patients with COVID-19 depends on the level of severity and whether they are outpatient, hospitalized or in the ICU. The incidence of AKI during a hospital stay is reported with a range of [11% (8%-17%)]. In the critically ill patient, the range is [23% (14%-50%)][20,21].

Several studies have reported the prevalence of AKI in COVID-19 patients. These studies are case series, observational study, retrospective single-center study, prospective cohort study and retrospective observational cohort study. The studies implemented the definition of acute kidney injury adopted by "Kidney Disease: Improving Global Outcome (KDIGO)"which is defined as an increase in the serum creatinine level up to 1.5 times the baseline level or an increase of at least 0.3 mg/dL within the past 48 h. Another useful definition of AKI was one established by the "Acute Kidney Injury Network" (AKIN) where the criteria of AKI is defined as an increase in the serum creatinine level up to 1.5 times the baseline level or an increase of at least 0.3 mg/dL within the past 48 h (Table 1)[21-29].

An established diagnosis of COVID-19 infection is by a positive PCR test for SARS-CoV-2, elevated laboratory values of D-dimer > 0.5 μg/ml, fibrinogen, ferritin, LDH, CK, CRP, serum creatinine, cystatin C, and hematuria with urine deposits, decreased eGFR, mL/min per 1.73 m^2, and computerized tomography (CT) of the chest that shows a round glass appearance. The incidence of AKI in published data ranges from 4.5% to 36.6%. The real incidence of AKI in COVID-19 remains uncertain due to a lack of reported studies.

In a retrospective Brazilian study on 102 patients who had COVID-19 and were admitted to the ICU, AKI was diagnosed in 54 (56.8%) of the cases that was grade 1 in 22.2%, being KDIGO 1; grade 2 in (7.4%), and grade 3 in (70.3%). Patients with grade 3 AKI were older adults (64.9 ± 15.1 years of age) and had comorbidities of diabetes and hypertension. Patients who had an immunosuppression condition secondary to chemotherapy treatment for cancer were (11.6%). Patients who had chronic kidney disease stages 2-4 were (16.8%). Patients who had comorbidities and developed AKI had received mechanical ventilation and vasoactive drugs that reflected the severity of the disease. Patients requiring hemodialysis were hypertensive, diabetic and immunosuppressed.

Patients under dialysis and/or on vasoactive drugs have a higher indication rate of mechanical ventilation (93, 8% *vs* non dialysis 38, 1%). Continuous renal replacement therapy was initiated in 26 patients (81.3%) out of 32 patients who were submitted to dialysis therapy. Eleven patients (34.4%) who received dialysis died, while 21 (65.6%) experienced recovery of renal function with maintained glomerular filtration rate. When comparing patients who died to those who are still alive and both had AKI due to COVID-19, it was found that those who died were older, diabetic, immunosuppressed, received mechanical ventilation and were on vasoactive drugs with a range of: (78.6 *vs* 61.9 years of age), (47.1 *vs* 23.1%), (29.4 *vs* 7.7%), (88.8 *vs* 72.2%), (94.1 *vs* 48.7%) respectively[29].

MANAGEMENT OF AKI RELATED TO COVID-19

Basic patient data for the planning of management in AKI linked to COVID-19 are gender, age, the

Table 1 Incidence of acute kidney injury linked to severe acute respiratory syndrome coronavirus 2 infection

Ref.	Country	Type of study	Coronavirus disease patients , *n*	Patients admitted to intensive care unit, *n* (%)	Patients developed acute kidney injury, *n* (%)
Arentz *et al* [22], 2020	United States	Case series	21	4 (19.1)	4 (19.1)
Hirsch *et al* [23], 2020	United States	Retrospective observational cohort study	5449	1395 (25.6)	1993 (36.6)
Thakkar *et al* [24], 2020	United States	Retrospectiveobservational study	300	300	224 (75)
Yidirim *et al* [25], 2021	Turkey	Retrospective study	331	17	17 (5.1)
Yan *et al*[26], 2020	China	Retrospective, observational cohort study	882	105 (11.9)	115 (13)
Zhang *et al* [27], 2020	China	Case series	221	55 (24.8)	10 (4.5)
Chen *et al*[28], 2020	China	Case series	274	50 (18.5)	29 (11)
Cheng *et al* [29], 2021	China	Prospective cohort study	701	73 (10.4)	36 (5.1)
Neves *et al* [30], 2021	Brazil	Retrospective study	102	95	54

presence of comorbidities such as diabetes mellitus, hypertension, CKD, presence of chronic obstructive pulmonary disease, associated malignancies and maintenance medications with immunosuppression drugs. Laboratory tests for COVID-19 are: D-dimer, C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, blood count, reverse transcription polymerase chain reaction (RT-PCR) for COVID-19 virus, blood urea, serum creatinine, liver function tests, ECG, echo cardiogram, and chest CT. AKI is defined according to the KDIGO criteria which is based on the creatinine values and urine output. The classification of AKI by KDIGO is 1, 2, or 3 according to clinical and laboratory data.

AKI KDIGO 1 is an increase of creatinine ≥ 0.3 mg/dL or 1.5-1.9 times baseline and/or urine output < 0.5 mL/kg/h for 6-12 h.

AKI KDIGO 2 is an increase of creatinine of 2.0-2.9 times baseline and/or urine output < 0.5 mL/kg/h for 12 h.

AKI KDIGO 3 is an increase of creatinine of 3.0 times baseline or an increase in serum creatinine to ≥ 4.0 mg/dL and/or urine output < 0.3 mL/kg/h for ≥ 24 h or anuria for ≥ 12 h, or initiation of renal replacement therapy (RRT).

Consideration includes medications for COVID-19: anti-IL6, ivermectin, and nitazoxanide. Ultimate evaluation of patients with AKI due to COVID-19 is: days of ICU stay, period of mechanical ventilation time and total hospitalization period.

The hemodialysis initiation timing depends on the severity of AKI. A hemodialysis catheter of 15.5 Fr is placed in the patients with continuous venous-venous hemodiafiltration and is preferable for patients requiring vasoactive drug infusion and/or having hypervolemia. The recommended dialysis dose is 25-30 mL/kg/h with regional citrate anticoagulation. For patients who do not need a vasoactive drug infusion, they would be on classic hemodialysis[29].

Measures to be considered in the management of Covid-19 and patient in the ICU to stabilize kidney function and to avoid AKI

Nephrotoxic drugs should be avoided; serum creatinine and urine output are regularly monitored.

Initiation of lung-protective ventilation to avoid hemodynamic changes and to diminish the sequences of cytokine burden on the kidneys[30].

Avoid volume overload that reduces the risk of pulmonary edema. Fluid balance should be adjusted according to volume responsiveness, restoration of normal volume status should avoid right ventricular overload, congestion and subsequent AKI.

Hypovolemia should be corrected to prevent AKI.

Renal replacements therapy and extracorporeal support

Renal replacements and extracorporeal support are indicated in case conservative management fails. Patients with volume overload should be considered for RRT. Patients with nonresponding hypoxemia are candidates for extracorporeal support. Early initiation of RRT and extracorporeal organ support (ECOS) will support the organs and prevent progression of COVID-19 and AKI[31].

Hypercoagulable state

Severely ill patients with COVID-19 often have a hypercoagulable state and anticoagulation protocols for the extracorporeal circuit should be implemented[32].

Cytokine storm

The application of hemoperfusion with sorbent cartridges might prevent cytokine-induced kidney damage[33].

Lung-protective ventilation

Ventilation is applied with appropriate tidal volume to avoid hypercapnia, respiratory acidosis, increased need for vasopressors and in severe cases of AKI. In these patients, extracorporeal carbon dioxide removal ($ECCO_2R$) might help to prevent progression of severity[34].

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation is indicated in cases where respiratory exchanges further deteriorate.

Bacterial infection

Patients with SARS-CoV-2 can develop a sepsis-like syndrome. The use of sequential extracorporeal therapies for immunomodulation and endotoxin and cytokine removal, extra corporeal organ support (ECOS) for various organs should be considered, as clinical progression can be rapid[33].

KIDNEY TRANSPLANTATION DURING COVID-19

Kidney transplant recipients (KTRs) are at considerable risk for development of AKI due to the maintenance use of immunosuppression and in addition to co-morbidities[35,36].

Since the Covid-19 pandemic, there is a significant reduction of kidney transplantation procedures[37,38].

Presentation of COVID-19 in this specific group of patients is fever and cough; atypical presentation is gastrointestinal symptoms. In a series of KTRs showed that the median age (51-62 years), duration between transplantation to diagnosis of COVID-19 was ranged from 2 years to 3 years. It is reported in two series that 2 patients had positive data of COVID-19 after 3 mo of kidney transplantation[39,40].

Indication for mechanical ventilation in KTRs who had COVID-19 was (22%-91%), while mortality rate was (7%-30%). These KTRs who had COVID-19 were on maintenance immunosuppression. Patients who had AKI was (30%-57%) and the need of with variable rates of RRT were (5%-43%). Mortality rate was as high as 32% (Table 2)[35,40-46,48].

Patients who had kidney transplantation and are COVID-19 positive while on steroids as a part of their maintenance immunosuppression because cessation would not be recommended, should have their dose adjusted depending on their personal case.

Patients who had transplantation and are on immunosuppressant corticosteroids and tacrolimus (TAC or FK506), the oral fast release of TAC is (Prograf) which is a calcineurin inhibitor employed to reduce the risk of acute rejection and allograft loss. For Tacrolimus and corticosteroids, the dose would be manipulated according to the level of FK506 in the blood which has been found to be decreased in patients who had a COVID-19 infection, consequently, the doses of tacrolimus and corticosteroid will be increased. Myfortic (mycophenolic acid) is an immunosuppressant that is given with cyclosporine and corticosteroid to prevent organ rejection after a kidney transplant. It weakens the immune system that helps to prevent kidney rejection. Myfortic should be stopped while tacrolimus and corticosteroids should be increased in cases where a patient who had kidney transplant and also have COVID-19 infection. Doses of myfortic and corticosteroids will be manipulated according to the regular laboratory data to guard against severity of COVID-19 and avoidance of kidney rejection.

CONCLUSION

Acute kidney injury in patients with COVID-19 is initiated by multifactorial etiopathology events including direct viral effect, cardiac causes secondary to right sided heart failure and cardiomyopathy, thromboembolic phenomenon, vascular factors, cytokine storm, toxic drugs to the kidney that are given during treatment of pneumonia from COVID-19. Pathophysiology of AKI is attributed to collapsing glomerulopathy, acute tubular necrosis, mitochondrial dysfunction and arterial occlusion.

Management of AKI is a multidisciplinary approach and should be personalized depending on several factors: severity of COVID-19 disease, ICU admission, induction of artificial ventilation and associated comorbidities. Patients who have all of these elements will have severe AKI and management is to preserve kidney function and prevent aggravation of the disease.

Table 2 Demographic data of kidney transplant recipients who had severe acute respiratory syndrome coronavirus 2 and developed acute kidney injury and the incidence of survival vs mortality

Study	*n*	Median age, yr	Median Transplant, yr	Acute kidney injury incidence, %	Renal replacement therapy, %	Mechanical ventilation, %	Mortality, %
Banerjee *et al*[40], 2020	7	54	2	57	43	14	14
Nair *et al*[42], 2020	10	57	7.7	50	10	40	30
Columbia *et al* [43], 2020	15	51	4	40	14	27	7
Alberici *et al*[35], 2020	20	59	13	30	5	0	25
Akalin *et al* [48], 2020	36	60	NR	NR	21	39	28
Lubetsky *et al* [44], 2020	54	57	4.7	51	10	28	13
Cravedi *et al*[41], 2020	144	62	5	52	NR	30	32
Caillard *et al*[45], 2020	279	62	5	44	11	30	23
Elias *et al*[46], 2020	6	54	NR	42	11	22	24

NR: Not reported.

Main treatment steps are to control fluid balance in severe cases and an early initiation of renal replacement and extracorporeal organ support which would support the organs and prevent progression of COVID-19 and AKI.

Kidney transplantation patients are at risk of developing AKI due to the immunocompromised status caused by regular doses of immunosuppressants. This situation indicates modification of immunosuppressors and the setting of treatment of cytokine storm with corticosteroids. In specific cases, there is an indication to stop myfortic immunosuppressant and to increase corticosteroid and modify the dose of tacrolimus.

Patients who are in regular hemodialysis need to adjust the anticoagulant dose when the patient receives anticoagulant to treat or prevent the hyper coagulopathy state resulting from COVID-19.

FOOTNOTES

Author contributions: Wishahi M and Nabawya M Kamal contributed equally to this work, designed the research study, performed the research, analyzed the data and wrote the manuscript; All authors have read and approve the final manuscript.

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