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Thiazides and mineralocorticoid receptor antagonists in chronic kidney disease

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Abstract

The latest treatment guidelines for patients with arterial hypertension continues to indicate as the first line therapy a minimal association between renin-angiotensin system (RAS) blockers and a thiazide-type or a thiazide-like diuretic. In addition, according to 2018 ESC/ESH (European Society of Cardiology/European Society of Hypertension) guidelines for the management of arterial hypertension, a mineralocorticoid receptor antagonist may be added in resistant hypertension cases (uncontrolled hypertension under at least 3 classes of antihypertensive drugs including a RAS blocker, thiazide diuretic and a calcium channel blocker) for general population. For chronic kidney disease (CKD) patients, achieving the optimal blood pressure (BP) level can be difficult because high complication rates can be encountered in any antihypertensive class mentioned, especially for RAS blockers and mineralocorticoid receptor inhibitors. This brief review aims to highlight the importance of diuretics use in CKD patients and the boundaries of their usage.

Keywords: thiazides, mineralocorticoid receptor antagonist, hypertension, CKD, adverse effects

INTRODUCTION

The prevalence of chronic kidney disease (CKD) stage G1-G5 ranges worldwide between 3.7-15% in general population, with an incidence often below 5% in moderate to severe CKD stage (G3 and G4). In CKD G1-G2 stage, one third of patients are hypertensive, while in G3 stage the prevalence will increase to 80% of patients and almost all individuals with CKD G4-G5 stage are hypertensive. Therefore, it is important to understand the benefits, risks and pathways of action of antihypertensive agents used in CKD patients [1]. Despite high prevalence of hypertension in CKD patients, there are a few trials with low cohorts, which include subjects with renal involvement to establish blood pressure (BP) control. The 2021 revised KDIGO (*Kidney Disease Improving Global Outcomes*) clinical practice guideline for the management of BP in CKD subjects suggests that CKD and high BP patients to be treated up to an optimal target of systolic BP < 120 mmHg. Main study data that supports this recommendation is provided by Systolic Blood Pressure Intervention Trial (SPRINT), the largest study which included a CKD subgroup (approximately 2648 subjects) defined according

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to the estimated glomerular filtration rate (eGFR) and proteinuria (proteinuria <1 g/day and eGFR 20-60 mL/min/1.73 m^2). SPRINT trial reported fewer cardiovascular events in CKD population with BP managed with an intensive regimen [2]. As in ACCORD trial [3], SPRINT study used as antihypertensive regimen a combination between renin-angiotensin system (RAS) blockers and a thiazide diuretic (with priority for thiazide-type chlorthalidone). If the BP was not controlled, the authors added calcium-channel blocker, loop diuretics for advanced CKD, and beta-adrenergic blockers in patients with coronary artery disease. For resistant hypertension SPRINT used mineralocorticoid inhibitors, vasodilators or alpha-adrenergic blockers [2]. It seems, thiazide and mineralocorticoid inhibitors diuretics are important antihypertensive classes. However, using them in low eGFR function can lose their efficiency or may induce electrolytic disturbances, hypotension, eGFR decline, severe acidosis, arrhythmias or event sudden death hyperkalemia related.

Thiazide related issues in CKD

Thiazides are classified in thiazide type, a benzothiadiazine derivate, named Hydrochlorothiazide (HCTZ), Chlorothiazide (CTZ), Bendroflumethiazide and thiazide-like, a sulfonamide derivate, Chlorthalidone (CLT) and Metolazone [4].

Less effective in low eGFR

High BP in CKD patients can be explained by water and sodium retention with increased sympathetic and renin-angiotensin-aldosterone system activity [1]. Therefore, using a diuretic and an aldosterone inhibitor in CKD seems reasonable. Thiazides in advanced kidney disease (eGFR <30 mL/min/1.73 m^2) is believed to be a diuretic class quasi-ineffective in promoting diuresis and most old guidelines (KDOQI – *Kidney Disease Outcomes Quality Initiative*, and JNC-8 – *Eighth Joint National Committee*) suggest to replace it with short or even better, long-lasting loop diuretics (Torasemide). Thiazides diuretics acts through sodium chloride co-transporters (SCC) from the distal convoluted tube (DCT) of the nephron, which is responsible only for 5-7% of the filtered sodium load. Thereby when eGFR is low, only small amounts of sodium loads pass through DCT, most of it being reabsorbed already by the proximal tubule, and Henle's loop. Furthermore, SCC inhibition will increase distal sodium delivery and subsequently enhance sodium reabsorption through ENaC (epithelial sodium channels) from principal cell in the collecting tubes and pendrin exchanger (Cl/HCO3 exchanger) from B intercalated cells (Figure 1) [4, 5]. Thus, inhibiting SCC, the effect will be minimal in advanced CKD. In 1972 was reported the first observational study on 14 CKD patients with creatinine clearance (CrCl) between 1.2-12 mL/min who received high dose of Metolazone (equivalent to 200-1500 mg HCTZ) and showed a greater natriuresis but with no benefits in BP [6]. Another trial from 1973, on 20 patients with CKD and CrCl 4-48 mL/min received 5-25 mg of Metolazone, evidenced, in a 3-month period of study a 1.5 kg weight reduction, and 12.5 mmHg BP reduction in 12 patients, but with an increment of serum creatinine from 4.7 to 5.6 mg/dL. Additionally, there were reported higher rates of hypokalemia and hyperglycemia. Approximately 10 years later another study evidenced a significant weight reduction and BP, after the treatment was supplemented with HCTZ 25-50 mg BID in 5 patients with advanced CKD and unresponsive to high doses of loop diuretic (furosemide 480 mg/day) [7]. In 2005 was reported the first double-blind, randomized, crossover trial with furosemide (60 mg/day) on top of HCTZ (25 mg/day) versus furosemide or HCTZ alone. After 1 month of treatment, the study showed no statistical significance in adding HCTZ on top of furosemide, but apparently HCTZ in contrast to furosemide group had a greater natriuresis [8]. Nevertheless, recent data from the second double-blind, randomized and crossover trial, showed that HCTZ is as effective as furosemide in CKD stage G4-G5 and after co-administrating both diuretics effects were synergistic [9]. In another 2020 pilot study on 26 subjects with CKD stage G3-G4, combination of amilorid and hydrochlorothiazide versus sodium restriction acquired substantial control in BP, natriuresis, diuresis, serum renin and serum aldosterone [10].

Main adverse effects of thiazides use in CKD patients:

- **Hypokalemia** – the most encountered adverse effect in thiazides usage. Collecting tubules will try to compensate sodium wasting through basolateral Na^+/K^+-ATPase and apical ENaC with subsequent urinary potassium secretion.
- **Metabolic alkalosis** – high distal sodium delivery will induce H^+ and K^+ ions secretion from alpha intercalated cells and principal cells. Potassium depletion will induce a greater PCT (proximal convoluted tubule) sodium reabsorption in exchange with H^+ ions secretion. In addition, ammonia production will increase and subsequently, the net urinary acid excretion. This can be corrected by acetazolamide (which inhibits Na^+-H^+ TCP antiporter) or by spironolactone (representing a mineralocorticoid inhibitor diuretic) [11].
- **Hypercalcemia** – SCC inhibition will lead to a decrease of intracellular sodium concentrations and subsequent apical hyperpolarization of DCT epithelium cell. This will increase Ca reabsorption through apical TRPV5 (transient receptor potential V5) an basolateral SCX (sodium and calcium exchanger) channels, guided by an electrical potential gradient [12]. Increased Ca reabsorption can induce hyper-

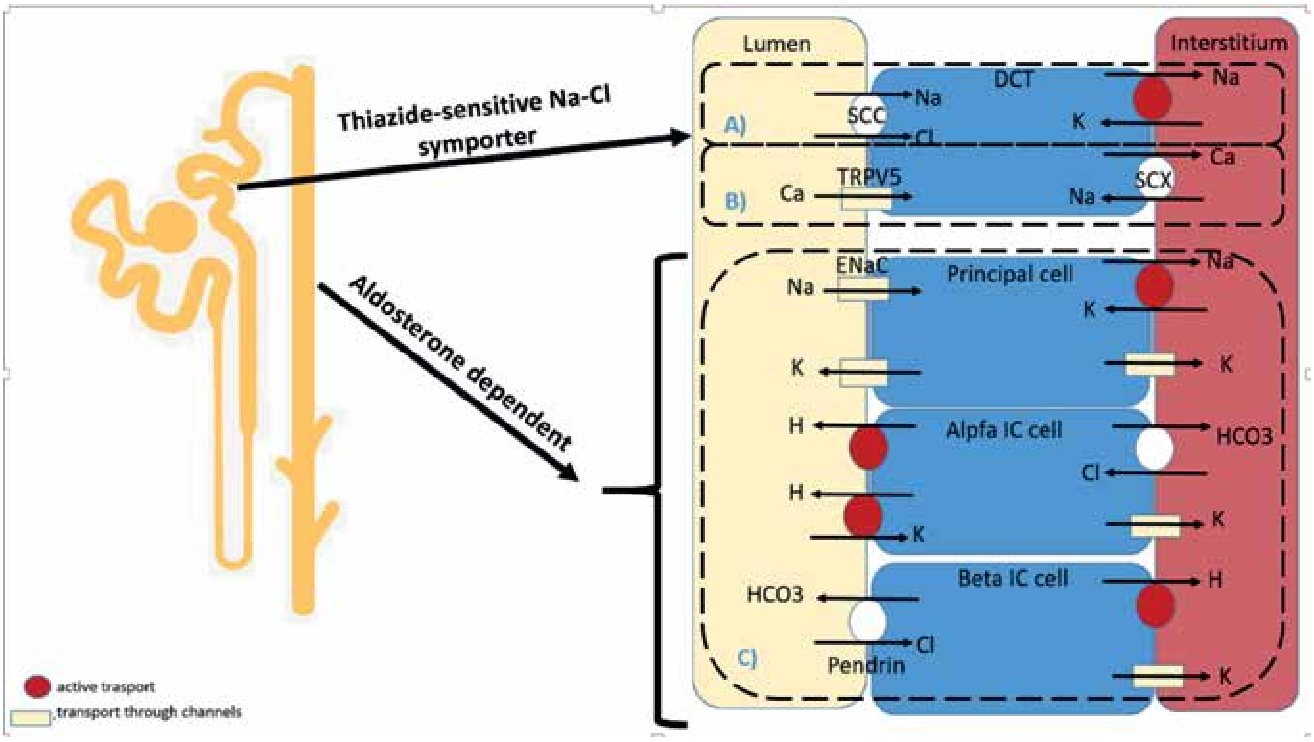

FIGURE 1. *Thiazide and aldosterone dependent pathways. A) Thiazide diuretics act on DCT, through SCC inhibition. B) Hipercalcemia and hypocalciuria thiazide related is induced by SCC inhibition and subsequent apical hiperpolarization that will lead Ca influx through TRPV5 and SCX. C) Pathways that stimulate aldosterone will increase sodium reabsorbtion by EnaC, increase potasium and H-ions secretion.*

Abreviations: SCC-Sodium chloride CO-Trasporter; SCX-Sodium and Calcium Exchanger; TRPV5-Transient Receptor Potential V5; DCT-Distal Convoluted Tubule; ENAC-Epithelium Sodium Channels; PENDRIN-Bicarbonate and Chloride Exchanger; IC-Intercalated Cell; H-Hidrogen Ions.

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calcemia with hypocalciuria. Therefore, thiazides can be useful for osteoporotic patients or in kidney stone prophylaxis (Figure 1).

- **Hyperuricemia** – induced by urate reabsorption incrément in the proximal tubules through OAT4 (organic anion transporter 4) channel. This exchanger will interchange thiazide diuretic with urate, increasing the interstitial urate concentration [13].
- **Hyperglycemia** – the mechanism involved seems to be related to low potassium serum levels induced by thiazides. Some studies evidenced a relationship between hypokalemic state and impaired insulin secretion leading to impaired glucose tolerance. However an exact mechanism for insulin resistance thiazide-induced has not been clarified [14].

Among thiazides diuretics, Chlorthalidone (CLT) is preferred for blood pressure control due to its longer acting effects and it may be more effective in low eGFR. SPRINT and ACCORD trials, the only large studies that included a subcategory of patients with CKD, used 12.5-25 mg/day of CLT [2,3]. A recent study used CLT up-titrated until 50 mg/day versus placebo, in 160 patients with advanced CKD (eGFR = 15-30 mL/min) and evidenced a mean difference of -10.5 mmHg in CLT group. Additionally, they mentioned the most efficient dose in blood pressure control was the lowest dose used (CLT = 12.5 mg/day). Main adverse effect encountered were hypokalemia, hypercalcemia, orthostatic hypotension, hyperuricemia and hyperglycemia [15].

Mineralocorticoid inhibitors in CKD

The main action of aldosterone, a steroid hormone with mineralocorticoid activity in kidney function is represented by distal nephron reabsorption mediated by principal and intercalated cells. Apart from this well-known action this hormone is involved in pro-inflammatory and pro-fibrotic kidney, heart and blood vessels processes, particularly in high salt diets. Aldosterone blockers are classified in selective steroidal mineralocorticoid antagonist like **eplerenone**, non-selective steroidal mineralocorticoid antagonist, **spironolactone** and **canrenone** or non-steroidal mineralocorticoid antagonist **finerenone** [16]. Steroid hormone receptors incorporate a subfamily of nuclear receptors consisting of a progesterone receptor, glucocorticoid receptor, androgen receptor and estrogen receptor, which are behaving like nuclear transcription factors and intracellular receptors. Some researchers sustain also aldosterone implications in podocyte injury and mesangial cell proliferation. Several studies have demonstrated that aldosterone antagonists like spironolactone or eplerenone may have a role not only in BP control but also in proteinuria reduction and CKD delay progression in diabetic or non-diabetic nephropathies on top of a RAS blocker therapy [17].

Main adverse effects of mineralocorticoid antagonist use in CKD patients:

- **Hyperkaliemia** – is the main concern in aldosterone antagonists' treatment in CKD patients, especially on top of RAS blockers, also known for hyperkaliemia adverse effects. Under these circumstances it may be appropriate to use them in patients with diuretic induced-hypokalemia, heart failure or other hypokalemia situations but with a careful monitoring of serum potassium [1]. Patiromer, an intestinal potassium binder can be a way to manage hyperkaliemia aldosterone inhibitors-induced. AMBER trial, a phase 2 study from 2019 revealed encouraging data using Patiromer on top of spironolactone in CKD patients [18].
- **Gynecomastia** – documented in spironolactone usage. It can be overcome by changing with a selective aldosterone inhibitor (i.e., eplerenone) [19].

Recently, finerenone, a selectively non-steroidal mineralocorticoid receptor antagonist was discovered, apparently with low rates of hyperkalemia, which significantly lowered the risk in cardiovascular events and CKD progression on diabetic population. FIDELIO-DKD a phase III, randomized, multicenter, double-blind, placebo-controlled trial, randomized 5734 patients with type 2 diabetes and CKD stage G3-G4 (eGFR between 25 and 59 mL/min/1.73 m^2). The subjects were randomized 1:1, finerenone (n = 2833) to placebo (n = 2841) and received a dose of 10 mg of finerenone if eGFR was under 60 mL/min/1.73 m^2 with the possibility to up-titrate to 20 mg finerenone/day QD after 1 month, if eGFR was stable or if potassium serum concentration was under 4.8 mmol/L. Placebo or finerenone was interrupted if potassium concentration exceeded 5.5 mmol/L and restarted to 5 mmol/L or to a less concentration. The results presented last year, showed fewer patients (17.8% finerenone group versus 21.1% placebo group) which achieved primary outcome (kidney failure, a sustained >40% eGFR decrease from baseline or death for renal causes). Secondary outcomes over 2.6 years for finerenone versus placebo showed also fewer cardiovascular events (cardiovascular death, hospitalization for heart failure, myocardial infarction, and stroke) – 13% versus 14.8%, but failed to demonstrate reduced risk of hyperkalemia (18.3% vs. 9%). In terms of hospitalization due to hyperkalemia 40 patients needed assistance in contrast to only 8 from the placebo group. Baseline subjects medication was RAS blocker (99.9%), potassium lowering agent (2.4%), GLP-1 receptor agonist (6.9%), SGLT2-inhibitor (4.6%), diuretic (56.6%), statin (74.3%) [20].

Current guidelines for essential arterial hypertension recommend mineralocorticoid receptor antagonists as a fourth line therapy. According to PATHWAY-2 study from 2015, spironolactone is the most effective drug when added over RAS blockers with CCB (calcium channel blockers) and thiazide diuretics for resistant hypertension [21]. National and international guidelines do not make any difference between the two approved drugs, spironolactone and eplerenone [22]. It should be emphasized that the studies described earlier were conducted in non-CKD patients. As already mentioned before, only SPRINT and ACCORD studies included a subgroup of patients with CKD. Spironolactone doses used in SPRINT trial for hypertension control were 25-50 mg/day. The American College of Cardiology Foundation/American Heart Association (ACC/AHA) recommends to use a MRAs (mineralocorticoid receptor antagonists) in patients with heart failure with ejection fraction <35%, with eGFR over 30 mL/min and with a serum potassium level under 5 mmol/L [23]. Despite these recommendations MRAs are still prescribed even in patients with more advanced CKD for their beneficial effects on cardiovascular risk [24]. Main concern in MRAs use is hyperkalemia which needs close monitoring. Spironolactone, in particular, can determine gynecomastia which can be managed by switching with eplerenone.

Thiazides and mineralocorticoid inhibitors pharmacokinetics

Thiazides diuretics have different duration of action, metabolism and potency (Table 1). CLT use is associated in a recent study with 30% higher risk of eGFR decline and cardiovascular events, in contrast with HCTZ but without differences in electrolytic disturbances or all-cause mortality [25]. In addition, CLT might induce a greater antihypertensive effect and subsequently improved left ventricular hypertrophy in contrast with HCTZ [9]. According Ernest ME et al study, CLT induces a 1.5-2 times greater reduction in BP in contrast with HCTZ [26].

As thiazides, eplerenone and spironolactone also have different pathways of action, half-life and metabolism. Spironolactone has a greater affinity for mineralocorticoid receptors. A few trials comparing these two MRAs suggested that spironolactone may be more potent and has a prolonged effect in lowering blood pressure due to its longer half-life active metabolites [27,28].

CONCLUSIONS

eGFR decline in CKD patients is a frequent cause of withdrawal of RAS blockers, thiazide or mineralocorti-

***TABLE 1.** Thiazides and mineralocorticoid inhibitors pharmacokinetics*

Drug	Dosage forms	Usual and Max dose*	CrCl/eGFR	Onset	Protein bound	Half-life
CTZ [29]	250 mg 500 mg	0.5-1 g/day QD or BID	CrCl: <10 mL/min - restricted <30 mL/min - ineffective	2-4 h	-	120-145 min
HCTZ [30]	12.5 mg 25 mg 50 mg	25 mg/day QD or BID 200 mg/day*	CrCl: <10 mL/min - restricted <30 mL/min - ineffective without loop diuretic	4-6 h	40-68%	5.6-14.8 h
CTL [31]	5 mg 15 mg 25 mg 50 mg 100 mg	12.5-25 mg/day 200 mg/day*	CrCl: <10 mL/min - restricted	1.5-6 h	75%	eGFR >60mL/min 40-60 h anuria 81 h
Metolazone [32]	2,5 mg 5 mg 10 mg	2.5-10 mg/day QD	Not necessary to adapt	1 h	95%	20 h
Spironolactone [33]	25 mg 50 mg 100 mg	25-200 mg QD or divided BID 100-400 mg QD*	Monitor hyperkalemia closely	2-4 h	90%	16.5 h
Eplerenone [34]	25 mg 50 mg	25-50 mg/day QD or BID	CrCl <50 mL/min - restricted or SCr >2 mg/dL - restricted	1-2 h	50%	3.5-6 h
Finerenone [35]	10 mg 20 mg	20 mg/day QD	eGFR-related: >60 mL/min 20 mg QD 20-60 mL/min 10 mg QD <25 mL/min- not recommended	0.5-1 h	92% primarily to albumin	2-3 h

Maximum doses were marked with "*".
Abreviations: HCTZ-hydrochlorothiazide; CTZ-chlorothiazide; CLT-chlorthalidone; CrCl-creatinine clearance; eGFR-estimated glomerular filtration rate; SCr-serum creatinine.
Data extracted from: https://reference.medscape.com; accessed 11/01/2022.

coid inhibitors in order to gain a residual kidney function and delay the need for renal replacement therapy. However, hypertension control is an important factor in cardiovascular events prevention and clinicians should take in consideration all means to achieve targeted BP values after risk-benefit assessment. It appears that thiazide diuretics are useful in correcting hypertension or volume overload in advanced CKD, either as combined with loop diuretics, or alone, and seemed to have fewer adverse effects compared to loop diuretics. Furthermore, frequent complications like hypokalemia or metabolic alkalosis can be managed by associating a TCP diuretic (acetazolamide) or a mineralocorticoid inhibitor, which increase potassium serum and exerts anti-inflammatory and anti-fibrotic properties with benefits in kidney progression decline and cardiovascular status. Thiazides and mineralocorticoid inhibitors should be further explored, in single or crossover studies, and, additionally, larger cohorts with advanced CKD subjects are needed to validate these results.

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