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Diuretics in Chronic Kidney Disease

Abstract

The issues of diuretic therapy in patients with chronic kidney disease, pharmacokinetics of diuretics, the problem of diuretic resistance, the tactics of using thiazides and loop diuretics in patients with various stages of chronic kidney disease, according to the recommendations of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative are discussed in the article. Particular attention is paid to the prescription of this group of drugs to patients with end stage renal disease, as well as those undergoing renal replacement therapy (hemodialysis). Diuretics play an important role in the management of patients with chronic kidney disease with the development of hypertension and an increased extracellular fluid volume. In case of impaired renal function, the leading position in the treatment approach belongs to loop diuretics. Their combination with thiazide diuretics can increase the diuretic effect. The results of clinical trials assessing the effectiveness of the use of diuretics during decline of residual renal function are provided. It is reported about the effect of potassium-sparing diuretics on the incidence of cardiovascular complications, the development of hyperkalemia in patients undergoing dialysis treatment. The importance of continuation of intensive study about the possibility of antagonists of mineralocorticoid receptors usage, in particular the spironolactone, eplerenone, and finerenone in order to reduce cardiovascular complications and mortality, is indicated.

Key words: *chronic kidney disease, loop diuretics, potassium-sparing diuretics, thiazide diuretics, dialysis*

Conflict of interests

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ACE inhibitors — angiotensin-converting enzyme inhibitors, AMCRs — antimineralocorticoids, ARBs — angiotensin II receptor blockers, BP — blood pressure, CKD — chronic kidney disease, Cl^- — chlorine, EFV — extracellular fluid volume, GBM — glomerular basement membrane, GFR — glomerular filtration rate, HF — heart failure, K^+ — potassium, LDs — loop diuretics, LV — left ventricle, Na^+ — sodium, NS — nephrotic syndrome, RCT — randomized clinical trial, RRF — residual renal function, TDs — thiazide diuretics

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In memory of our teacher

Introduction

Diuretics are currently one of the common classes of drugs used in medical practice, including internal diseases, neurology, endocrinology, urology and other medical specialties [1-7]. Such a wide range of their use is explained by their different mechanisms of action and clinical effects.

Diuretics are widely used in the management of patients with various kidney diseases due to their main effects in controlling extracellular fluid volume (EFV) and hypertension, as well as their different effects on electrolyte levels due to the various pharmacodynamic characteristics of several groups of diuretics widely used in clinical nephrology [8-13]. At the same time, there are still many problems in treatment with diuretics which include the following: the lack of large-scale clinical studies on the impact of diuretics on the length of hospital stay and survival of patients with chronic kidney disease (CKD), including those receiving dialysis treatment. The aim of this review was to discuss the use of different groups of diuretics in patients with CKD, including patients undergoing dialysis treatment.

Chronic Kidney Disease: Definition

The term CKD means structural or functional kidney damage that affects the health state of the patient and persists for 3 months or longer [7]. CKD criteria are (one of the following, persisting for more than 3 months):

1. Markers of kidney damage (one or more): albuminuria (albumin excretion level ≥30 mg/24 h; albumin to creatinine ratio ≥30 mg/g (or ≥3 mg/mmol)); changes in urine sediment; electrolyte disorders due to tubular dysfunction; histological changes in kidneys; structural changes in kidneys revealed with imaging studies; history of kidney transplantation.
2. Decreased glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 [7].

CKD is a global medical and social problem. According to large population studies, approximately 10-13% [14] of the adult population have CKD, which can be explained by catastrophically increase of hypertension, type 2 diabetes mellitus, chronic obstructive pulmonary diseases, heart failure (HF), and obesity incidence, unreasonable and uncontrolled use of medications, tobacco smoking, alcohol abuse [2, 5-7, 15]. We should also note the high risk of cardiovascular complications related to CKD which progressively increases with renal function failure [10, 16]. Cardiovascular risk due to impaired renal function starts increasing in the earlier stages of renal pathology than it was previously assumed [16], which determines increased attention to the state of the cardiovascular system and has influence on the management of patients with CKD [17].

Possible development of cardiorenal syndrome in patients with cardiovascular diseases emphasizes the importance of the question about the optimal choice of diuretics, since symptomatic treatment for HF is limited by a progressive decrease in renal function [1, 6, 10].

Using Diuretics for Chronic Kidney Disease

Diuretics are successfully used in patients with CKD and [10, 12, 18, 19]. They have a hypotensive effect due to EFV decrease. The addition of diuretics to other classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), β-blockers, calcium channel blockers) intensifies their hypotensive effect [6, 7, 18-21].

Potassium-sparing diuretics, primarily antimineralocorticoids (AMCRs) of aldosterone, are used for nephro- and cardioprotection (usually in combination with ACE inhibitors and ARBs), as well as for resistant hypertension, for hypokalemia which developed due to the use of loop (LD) and thiazide diuretics (TD) [8, 12, 18-20, 22]. Nephro- and cardioprotective effects of AMCRs are caused by the offsetting of the adverse effects of the activated renin-angiotensin-aldosterone system. Prescribing AMCRs is not recommended for hyperkalemia (potassium (K^+) > 5.5 mmol/L), for creatinine clearance less than 30 mL/min/1.73 m^2; it is prescribed with dose adjustment for patients with creatinine

clearance less than 60 mL/min/1.73 m² [23, 24]. Exceeding the recommended K^+ level is dangerous due to the increased risk of heart rhythm and conduction disorders, sudden cardiac death [25, 26] and mortality in patients receiving hemo- and peritoneal dialysis [27-29]. The combination of AMCRs with ACE inhibitors, non-steroidal anti-inflammatory drugs, cardiac glycosides, heparin, and β2-blockers sharply increases the possibility of developing hyperkalemia, increased creatinine and acute kidney damage [23, 30].

Data on the antihypertensive and antiproteinuric effects of AMCRs of aldosterone, spironolactone and eplerenone justify their use for CKD combined with hypertension and proteinuria (>1 g/day) under the strict control of K^+ and creatinine clearance [9, 31].

Pharmacokinetics of Diuretics, Resistance to Diuretic Treatment in Patients with Chronic Kidney Disease

The effect of diuretic drugs takes place after they enter the lumen of tubules. Specific gravity of glomerular filtration, which is responsible for the delivery of LDs and TDs in the lumen of tubules, is small, since the molecules of diuretics are closely connected to plasma proteins, and, therefore, their passage through glomerular filter is limited [32]. Acetazolamide, LDs and TDs are weak organic anions that are secreted into the lumen of the proximal tubule through the secretory pathway of organic acids [13, 33]. Amiloride and triamterene are secreted through the pathway of organic bases. As soon as diuretics reach the lumen of the proximal tubule, they go further down in the glomerular filtrate to the specific places of their action [13, 32]. Only a small quantity of albumin in physiological state is filtered and subsequently almost completely reabsorbed in proximal convoluted tubules [34]. LDs predominantly bind to plasma proteins (>90%) and, therefore, only a small fraction of drug is filtered in glomeruli. However, they are actively secreted into the lumen in proximal convoluted tubules through a transporter system.

LDs act at the level of the thick ascending loop of Henle. LDs combining with $Na^+/K^+/2Cl^-$ (NKCC2) by a co-transport protein localized in tubule membrane inhibit its effect while impairing the reabsorption of sodium (Na^+), K^+ and chlorine (Cl^-). The secretory ability of proximal renal tubules determines the quantity and, thus, the activity of diuretics, which then go to the distal nephron [1, 9, 35]. Both LDs and TDs reach the lumen of the proximal tubule by secretion by tubular cells with the help of transporters. However, the key mechanism of TDs action is inhibition of the Na^+/Cl^- co-transporter in the first segments of distal tubules. This protein regulates the reabsorption of Na^+ and Cl^- in distal tubular cells; therefore, its inhibition provides increased renal excretion of these electrolytes [36, 37].

Pharmacokinetic determinants that are responsible for LD and TD diuretic response include dose, route of administration, bioavailability, level of intestinal absorption, tubular secretory capacity, systemic blood pressure (BP) and renal blood flow [1, 9, 18, 37]. Some pharmacokinetic parameters of basic diuretics are shown in the table.

In the case of a drop in systemic blood pressure, decreased GFR, which is observed in relation to various kidney diseases and renovascular pathology, leads to a decrease in the filtered load of extracellular fluid and Na^+, limits the maximum achievable response to any diuretic, and is especially relevant for patients with renal failure [9]. However, although decreased GFR limits the effect of diuretics in patients with CKD, an adaptive increase in fluid delivery from the proximal tubule together with excessive expression of the transporter (both in the loop of Henle and in the distal tubule) retains a diuretic response even in patients with severe CKD [38]. In patients with GFR of about 15 mL/min/1.73 m², only 10-20% of the LD amount is secreted, which then goes into tubular fluid — in comparison with individuals with normal GFR and similar doses of diuretics [39]. Thus, in patients with severe CKD, the diuretic dose should be increased for its adequate delivery to the tubular fluid in order to induce diuretic response [9]. Even if TDs dosing corresponds well to the renal function, their use is limited in such patients since these drugs have low efficiency and a flat dose-response curve. Widely used TDs, even prescribed in large doses, can not help to achieve such a level of Na^+ reabsorption inhibition [9].

Table 1. *Pharmacokinetic parameters of basic diuretics*

Diuretic	Oral bioavailability, %	Elimination, $T_{1/2}$, h	
		Normal	CKD
Furosemide	50 (10-100)	1.5-2	2.8
Bumetanide	80-100	1	1.6
Torasemide	68-100	3-4	4-5
Hydrochlorothiazide	55-77	6-15	Prolonged
Indapamide	93	14	n/d
Chlorthalidone	64-72	40-60	Prolonged
Metolazone	70-90	14-20	Prolonged
Amiloride	About 50	6-26	100
Spironolactone	>90	1.5*	*
Eplerenone	50-69%	3-5	4-6

Notes: CKD — chronic kidney disease; n/d — no data; * — active metabolites of spironolactone have elimination $T_{1/2}$ more than 15 hours and accumulate in patients with CKD. Adapted from D. H. Ellison, 2019 [11]

Studies of patients with severe CKD revealed that maximum natriuretic response (approximately 20% of filtered Na^+ load) is achieved with intravenous administration of furosemide, bumetanide, and torasemide at doses of 160-200 mg, 6-8 mg, and 80-100 mg, respectively [40, 41]. Moreover, using dosages exceeding the indicated ones does not increase natriuretic response, which is rarely applicable in the course of clinical practice. LDs are suitable for patients with CKD at stages IV-V with hypertension. They can be taken per os 2-3 times a day [6, 21, 30, 42].

The normal dose-response ratio for LDs, which is observed in patients with CKD without edematous syndrome, can be distorted in a wide range of clinical conditions, ranging from decreased volume of intercellular fluid to HF or nephrotic syndrome (NS), as well as when taking various drugs, including non-steroidal anti-inflammatory drugs that can adversely change this relationship due to inhibition of prostaglandin synthesis, which significantly weakens the effect of LDs [43].

At the initial stages of treatment with PDs and TDs, increased natriuresis and diuresis are observed, which in most cases leads to a negative balance of Na^+, especially if its consumption is limited. Later, as diuretic treatment continues, a decrease in EFV and compensatory activation of neurohumoral mechanisms are present, which lead to increased Na^+ reabsorption in the proximal and distal tubule segments. These adaptive mechanisms that contribute to the development of diuretic resistance are called the "braking phenomenon" [5, 6, 21, 35].

Patients with NS often develop diuretic resistance even with normal GFR values [9]. Changes in both pharmacokinetic and pharmacodynamic properties of LDs cause a decrease in their efficacy. Patients with NS may also develop a less pronounced response to diuretic treatment due to orthostatic changes in hemodynamics. In addition, LD delivery in patients with hypoalbuminemia worsens due to the strong dependence of renal secretion of diuretics on plasma albumin concentration [39, 44, 45]. Decreased renal secretion of LDs in patients with NS is associated with the migration of these drugs from intravascular channel to interstitial space. For example, low serum albumin content can lead to a 10-fold increase in the distribution of furosemide. Finally, in addition to reducing LD secretion in patients with NS, the metabolism of diuretics increases along with an increase in the rate of conjugation with glucuronic acid in kidneys, which is applicable to furosemide [46].

According to KDIGO recommendations-2012, oral administration of LD once or twice a day is recommended for the patients with NS, taking into account that the effect of diuretics with this route of administration lasts longer in comparison with the parenteral one [47]. However, patients with severe NS may require intravenous (bolus or infusion) administration of diuretic drugs due to the development of edema of the intestinal wall and

impaired absorption. The combination of LDs with TDs can also be used for correction of diuretic resistance. A combination of diuretics with albumin infusion is also possible. However, the benefit of this approach has not yet been proven. Furthermore, it is believed that exogenously administered albumin can increase the severity of hypertension [47, 48]. Based on the results, the authors of Cochrane review 2019 argue that additional studies are necessary to define the role of albumin in the treatment of patients with NS [49].

LDs are the drugs of choice in patients with terminal stage of renal failure. They can produce a diuretic effect even in cases with GFR below 30 mL/min, which is particularly important in the presence of increased EFV, hypertension and HF often existing in such patients [50].

The change of one class of diuretics to another, as well as the replacement of drugs within one class, taking into account their bioavailability, can lead to increased diuretic response. So, if TDs take a certain place in diuretic treatment of patients with CKD stage I-III, then for more significant impairment of renal function (CKD stage IV-V) their diuretic effect is significantly reduced, and therefore, LDs should be preferred [30].

To achieve a diuretic effect in case of impaired renal function, high doses of TD are required: hydrochlorothiazide 50-100 mg/day for mild and moderate renal failure and 100-200 mg/day for severe one [9, 36, 51]. However, even at such dosages, the efficacy of TD in patients with severe renal impairment is negligible, and therefore, in the cases of severe renal failure (GFR <30 mL/min), a combination of TD with LD is recommended for achieving diuretic effect [30, 36]. This combination not only causes additional diuresis with underlying resistance to LDs but is also associated with a number of electrolyte disorders, including hypokalemia, hypomagnesemia, hypochloremia, leading to the development of metabolic alkalosis. In addition, adverse effects such as hyperuricemia, impaired glucose tolerance and hyperlipidemia may be observed [20, 30, 52].

This figure shows the tactics of using TDs and LDs in patients at different stages of CKD, which is recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) and summarized by D. Sica (2011) [9].

GFR (ml/min/1.73 m²)

Thiazide-like diuretics, metolazone and chlortalidone, are long-acting natriuretic agents due to their accumulation in red blood cells. Their pharmacokinetic characteristics cause a longer diuretic effect, as well as a more significant decrease in blood pressure in patients with CKD than TDs, both as a first-line drug and in combination with diuretics of other groups. In this connection, these drugs, and not TDs, should be preferred for the patients with I-III stages of CKD. However, for a more detailed study of the effects of thiazide-like diuretics, as well as for the assessment of their safety and effectiveness, randomized clinical trials (RCTs) are necessary [9, 20].

Potassium-sparing diuretics include drugs that block apical sodium channels (amiloride and triamterene) and do not interact with aldosterone receptors, and AMCRs (spironolactone and eplerenone).

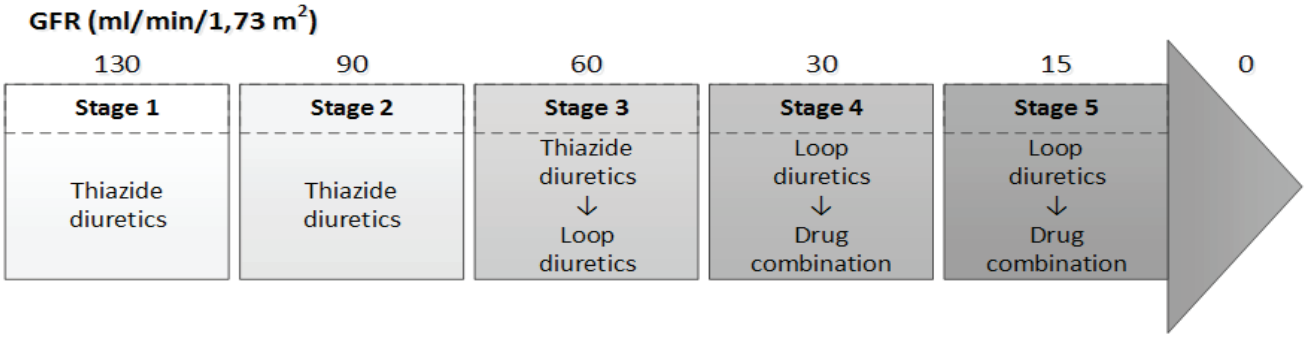

Figure 1. *Diuretic use at various stages of chronic kidney disease in accordance with the recommendations of NKF KDOQI*

Note: more intensive staining of the picture means an increased frequency of side effects observed in patients with GFR <60 ml/min/1.73 m². Adapted from D. Sica (2011) [9]

The mechanism of diuretic action of these classes of diuretics is similar and includes the inhibition of Na^+ absorption in the distal convoluted tubule and in the first part of the collecting tube, as well as a significant decrease in the secretion of K^+ and hydrogen cations [10, 53]. Although it was shown that mineralocorticoid receptor blockade has a positive effect on the condition of patients with CKD, the widespread use of common AMCRs with serious side effects is limited in clinical practice [54].

In a study by N. Tsuboi et al., it was demonstrated that the addition of eplerenone at the dose of 25-50 mg/day for 12 months to the treatment of patients with chronic renal failure and persistent proteinuria of non-diabetic origin, which persisted during use of ACE inhibitors, was associated with a decrease in protein excretion with urine by 38%. A decrease in the proteinuria level was more significant in patients with a moderately decreased renal function than in patients with intact renal function when the study began. Withdrawal criteria for this study were a decrease in GFR of less than 50 mL/min, as well as a level of K^+ >5 mmol/L. In the course of observation, a slight increase in K^+ level was registered [55].

The combination of AMCRs with ACE inhibitors leads to a decrease in the proteinuria level, as well as in markers of inflammation and renal tissue fibrosis [56]. However, the use of spironolactone and eplerenone in patients with CKD is limited due to the high risk of hyperkalemia. In contrast to abovementioned drugs, a non-steroid AMCR finerenone has greater selectivity and affinity for receptors and, therefore, a lower risk of hyperkalemia developing. The ARTS-HF study demonstrated the ability of finerenone to reduce albuminuria in patients with CKD and HF combined with better drug tolerance [57]. The ARTS-DN study showed that prescribing finerenone to patients with diabetic nephropathy (GFR ≤60 mL/min/m^2) resulted in a decrease in albuminuria level, while the risk of hyperkalemia was 2.1%, 3.2%, and 1.7% at finerenone doses of 7.5, 15 and 20 mg/day, respectively [58]. In 2020-2021, we expect the results of the phase III trial on evaluating the efficacy and safety of finerenone in patients with diabetic nephropathy, FIGARO-DKD, which includes 7,437 patients [59] and of the trial on evaluating the efficacy and safety in patients with type 2 diabetes mellitus and diabetic kidney disease, FIDELIO-DKD, which includes 5,734 patients [60].

In the CRIB-II study, spironolactone added to ACE inhibitors in 112 patients with CKD of stage 2-3 for 10 weeks led to a significant decrease in the prevalence of LV hypertrophy (50%), LV mass (11.8%) and myocardial mass index (11.4%) compared with the placebo group [61]. The results correlate with the level of aldosterone in non-diabetic patients with the terminal stage of renal failure undergoing hemodialysis [62, 63].

Complications of Diuretic Therapy

The main complications of therapy with LDs and TDs are metabolic disorders: hyponatremia, hypokalemia, hypomagnesemia, hyperuricemia, hyperglycemia, and metabolic alkalosis. Hypokalemia and metabolic alkalosis become less florid when using LDs and TDs in patients with reduced renal function [13, 64]. Using a combination of ACE inhibitors, or ARBs with AMCRs leads to hyperkalemia. Spironolactone may cause the development of metabolic acidosis [65]. In addition, due to its significant affinity for progesterone and androgen receptors, spironolactone induces adverse endocrine effects, including the development of gynecomastia, decreased libido, and menstrual disorder [13].

Hyponatremia is associated with negative prognosis in patients with CKD [66], as well as in the general population [67]. Hyponatremia is more commonly found during treatment with TDs that block Na^+ transport in the distal convoluted tubule. The genetic risk factor responsible for TD-induced hyponatremia and associated with impaired prostaglandin transport and decreased water excretion was found recently [68]. In any case, if diuretic therapy should be continued in patients with CKD and hyponatremia, TD should be discontinued and replaced with LD [13].

Hyperuricemia may be a relative contraindication for using diuretics. Gout combined with the inability to use non-steroidal anti-inflammatory drugs due to the high risk of renal function failure can also be a reason for not prescribing diuretics to patients with CKD.

Hypomagnesemia can be a special problem in patients with a transplanted kidney who are receiving tacrolimus along with diuretics. Physicians should pay attention to this complication, monitor the level of serum magnesium, if necessary, use magnesium supplements and not prescribe proton pump inhibitors simultaneously [13]. Finally, diuretics can aggravate urinary incontinence, especially in elderly patients, which can also be a reason for refusing to take these drugs. Thus, a decrease in adherence to diuretic therapy was reported, which was 3-4 times more frequent among patients with urinary incontinence [69].

Using Diuretics in Patients Under Dialysis

Using diuretics in dialysis patients requires a special discussion. Questionable approaches to prescribing diuretics for this category of patients are confirmed by the results of epidemiological studies that demonstrated high variability in their use in different dialysis departments — from 0 to 83.9% [18, 36, 70]. There is a number of clinical problems typical for dialysis patients with CKD that require appropriate treatment approaches; these problems include hypertension, volume overload, edemas, high risk of cardiovascular complications (acute coronary syndrome, HF, life-threatening rhythm disorders), high level of cardiovascular mortality [18, 36, 71, 72].

Hemodialysis has no significant effect on the pharmacokinetics of LDs. Dialysis eliminates <10% of diuretics due to the close connection with plasma proteins [9, 36].

During the inter-dialysis period, a significant increase in EFV, body weight, as well as congestion in pulmonary circulation with the development of cardiac asthma / pulmonary edema are often observed. In such cases, if there is residual renal function (RRF) established with excretion of more than 200-250 mL of urine per day without diuretics, LDs are indicated.

The role of RRF in treatment approaches was studied in several large trials, and the prognostic value for dialysis patients was demonstrated. Further analysis of the CANUSA PD study revealed that the risk of death in patients undergoing peritoneal dialysis was reduced if the daily amount of urine was more than 250 mL. The CHOICE study demonstrated decreased mortality, improved quality of life, and a lower need for erythropoietins in patients on hemodialysis in the presence of RRF [73, 74].

Unfortunately, dialysis patients have a progressive decrease in RRF level, which became the reason for searching for therapeutic approaches that could prevent such a decrease [36]. Using LDs is one of them. In the DOPPS prospective study, the effects of diuretic therapy on a number of clinical parameters in 16,420 hemodialysis patients were investigated. Using diuretics was associated with a decrease in weight gain between hemodialysis sessions, a decrease in hyperkalemia development, and a twofold increase in RRF level within one year in comparison with patients who did not receive LDs [70]. J. F. Medcalf et al. noted that there was no decrease of RRF in patients on peritoneal dialysis who received furosemide at the daily dosage of 250 mg [75].

The presence of RRF (or its retaining as an effect of LDs) contributes to the maintenance of the euvolemic state which plays an important role in preventing the development of volume overload and its adverse effects (left ventricular (LV) hypertrophy, congestive HF, uncontrolled hypertension). In addition, in the presence of RRF, the excretion of medium molecules increases, plasma levels of inflammatory markers decrease, blood pressure control improves, as well as hemoglobin and phosphorus levels, and all these changes potentially improve the quality of life and increase the survival of dialysis patients [50, 76].

Using LDs reduces the risk of hypertensive episodes during hemodialysis, the incidence and severity of hyperkalemia. Dialysis patients have to adhere to a strict diet with restriction of sodium chloride, potassium, phosphates and fluid. Using LDs allows them to make their diet more diversified and increase fluid intake, which improves their adherence to treatment [18, 70]. In addition, chronic LD administration in patients undergoing peritoneal dialysis demonstrated less frequent emergence of peritonitis [36].

In another major study, the effect of LDs on the frequency of hospitalizations, deaths, and intradialysis hypotension was evaluated. A monthly assessment of weight gain, predialysis systolic BP, and ultrafiltration levels was also performed. S. Sibbel

et al. reported that continued treatment with LDs during the intradialysis period was associated with a decreased frequency of hospitalizations, intradialysis hypotension, weight gain but there were no differences in mortality between groups of patients during 1 year of dialysis treatment [77].

Aldosterone levels increase as GFR decreases. In patients with CKD of stages 3-5, serum aldosterone levels increase, which allows characterizing CKD as a state of relative hyperaldosteronism [78]. The degree of its increase is most pronounced in patients with CKD of stage 5, which makes the prescribing of AMCRs one of the main tasks for this category of dialysis patients.

There is a high risk of developing cardiovascular complications and death in dialysis patients that exceeds that in the general population by 10 or more times. In this regard, the possibility of using AMCRs spironolactone and eplerenone for reducing cardiovascular complications and mortality is being intensively studied.

One of the serious complications of taking aldosterone antagonists is a high risk of developing hyperkalemia (especially with underlying renal failure). Analysis of literature performed by W. L. Baker et al. showed that using non-natriuretic dosages of aldosterone antagonists (spironolactone 25 mg/day and eplerenone 50 mg/day) in dialysis patients was characterized by a low incidence of severe hyperkalemia, and, therefore, their use is permissible but under strict control of K^+ in plasma [79]. In prospective, double-blind RCT, S. Taheri et al. studied the efficacy and safety of spironolactone (25 mg/day) in alternate day mode, in 18 dialysis patients with chronic HF of class III-IV according to NYHA. The authors of this study found no significant differences in plasma potassium levels between subjects who received spironolactone and those who did not receive it [80].

A number of RCTs demonstrated that when spironolactone (25 mg/day) was added to ACE inhibitor, or ARB, the increase of LV mass and the development of calcification of coronary arteries slowed down along with a low risk of severe hyperkalemia in dialysis patients [81, 82]. In this category of patients, P. Flevary et al. found that low doses of spironolactone (at a rate of 25 mg per day twice a week) caused a decrease in endothelial dysfunction and improved heart rate variability [72].

Results of a three-year DONAS RCT conducted by Y. Matsumoto et al. and published in 2014 deserve a special discussion [83]. This study included 309 dialysis patients, 157 of whom received spironolactone (25 mg/day) and 152 did not receive spironolactone (control group). In the spironolactone group, cardiovascular mortality and hospitalization rate for cardiovascular complications was 5.7% vs 12.5% in the control group ($p = 0.017$), and overall mortality rate was 6.4% vs 19.7% ($p = 0.002$). Hyperkalemia, which required the withdrawal of spironolactone, was registered only in 3 patients (1.9%).

High-potential RCTs are currently being performed on the study of the use of spironolactone in patients with the terminal stage of renal failure — ALCHEMIST (**AL**dosterone Antagonist Chronic **HEM**odialysis **I**nterventional **S**urvival **T**rial), which is planned to include 825 hemodialysis patients, and ACHIEVE trial (**A**ldosterone blo**C**kade for **H**ealth **I**mprovement **EV**aluation in **E**nd-stage Renal Disease) in 2,750 patients on hemodialysis or peritoneal dialysis [23].

Thus, the abovementioned results of the efficacy and safety of aldosterone antagonists in dialysis patients allow us to recommend their use for reducing cardiovascular and general mortality under the strict control of K^+ in plasma [9, 36, 83, 84].

Conclusion

Since CKD is associated with sodium retention, which causes edema syndrome and hypertension, diuretics take an important place among therapeutic approaches for the management of patients with kidney damage. Highly effective LDs remain the basic drugs used for diuretic therapy but their proper use requires deep understanding of the pharmacokinetics and pharmacodynamics of these drugs in the presence of CKD. LDs can be administered as monotherapy, or in combination with diuretics of other classes. In addition, diuretics are prescribed for the terminal stage of renal failure with RRF, thereby helping to reduce fluid retention during the inter-dialysis period. Despite a number of side effects of diuretics, these drugs remain important elements of treatment for the most part of patients with CKD.

Author Contribution

A. I. Dyadyk: principal creation of review idea (plan, structure, issues of discussing concerns)

G. G. Taradin (ORCID ID: https://orcid.org/0000-0003-3984-8482): writing, reviewing, and approval of the final version of the manuscript

Yu. V. Suliman (ORCID ID: https://orcid.org/0000-0001-6538-9676): collection and analysis of literature data, writing of sections on pharmacokinetics and pharmacodynamics of diuretics

S. R. Zborovsky (ORCID ID: https://orcid.org/0000-0002-3754-965X): collection and analysis of literature data, writing of sections on clinical use and complications of diuretics

V. I. Merkuriev: literature search and section writing about use of diuretics in patients on dialysis treatment

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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