

Expert Opinion

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Diuretics in clinical practice. Part II: electrolyte and acid-base disorders complicating diuretic therapy

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Importance of the field: As with all potent therapeutic agents, the use of diuretic compounds has been linked with several adverse effects that may reduce quality of life and patient compliance and, in some cases, may be associated with considerable morbidity and mortality. Among the various types of adverse effects, disturbances of electrolyte and acid–base balance are perhaps the most common, and some of them are the aetiological factors of other side effects (i.e., hypokalaemia causing ventricular arrhythmias or glucose intolerance). The mechanism and site of action and, therefore, the pharmacological effects of each diuretic class largely determine the specific electrolyte or acid–base abnormalities that will accompany the use of each diuretic agent.

Areas covered in the review: This article reviews the major electrolyte disturbances (hypokalaemia, hyperkalaemia, hyponatraemia, disorders of magnesium and calcium balance), as well as the acid–base abnormalities complicating the use of the various diuretic agents.

What the reader will gain: The reader will gain insights into the pathogenesis of the diuretic-induced electrolyte and acid–base disorders together with considerations for their prevention and treatment.

Take home message: Knowledge of the pharmacologic properties of each diuretic class and appropriate monitoring of patients under diuretic treatment represent the most important strategies to prevent the development of diuretic-related adverse events and their consequences.

Keywords: diuretics, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia

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1. Introduction

Diuretics are potent therapeutic tools that have been used broadly for > 50 years in the treatment of major diseases of internal medicine, such as hypertension and common oedematous disorders (cardiac failure, nephrotic syndrome, hepatic cirrhosis). Certain diuretics have been also used for years in the treatment of more specific conditions, such as glaucoma, cerebral oedema, hypercalcaemia, hypercalciuria and diabetes insipidus [1–3]. Although providing important help in the treatment of many diseases, as in the case of all potent therapeutic agents, the clinical use of diuretics has the potential to cause several adverse effects. These may reduce quality of life and patient compliance and, in some cases, may be associated with considerable morbidity and mortality [4]. Among the various types of adverse effects, disturbances of electrolyte and acid–base balance are perhaps the most common, and some of them are the aetiological factors of other side effects (i.e., hypokalaemia being responsible for the genesis of ventricular arrhythmias or glucose intolerance).

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Article highlights.

- The specific electrolyte or acid–base abnormalities that characterise each diuretic class can be largely anticipated from the pharmacologic mechanism of action and the nephron segment where each class of diuretics acts.
- Hypokalaemia is the most common electrolyte disorder linked to diuretic use and is associated with a number of serious cardiac adverse consequences (arrhythmias, sudden death); the lower doses at which thiazides and related agents are prescribed for hypertension treatment in the last years seem to have helped towards reduction in the incidence of diuretic-induced hypokalaemia.
- Hyperkalaemia is a side effect of potassium-sparing diuretics. The increase in the use of aldosterone-blockers for conditions other than their traditional indications (i.e., heart failure) was associated with important increase of the incidence of diuretic-induced hyperkalaemia; thus, careful use and appropriate dosing of these agents is required, especially in patients with additional risk factors for hyperkalaemia.
- Diuretic-induced hyponatraemia is a very common electrolyte disorder, occurring mainly in out-patients under thiazide treatment. Severe hyponatraemia can have serious consequences. Adequate monitoring of serum Na^+ levels, especially in predisposed patients, is the most appropriate strategy to prevent the development of this side effect during diuretic treatment.
- Chronic treatment with thiazide and loop diuretics can produce small reductions in serum Mg^{2+} levels; as Mg^{2+} homeostasis plays a major role in several actions at cellular level, attention needs to be paid to the detection and appropriate correction of Mg^{2+} depletion during diuretic treatment.
- Thiazides and loop diuretics have contrasting well-described effects on Ca^{2+} renal handling; thiazides reduce urinary Ca^{2+} excretion by a large percentage and are indicated for the treatment of nephrolithiasis with increased urinary Ca^{2+} excretion, whereas loop diuretics increase Ca^{2+} loss and are used to treat hypercalcaemia.
- Carbonic anhydrase inhibitors typically increase renal HCO_3^- excretion resulting in metabolic acidosis, especially in elderly patients. Potassium-sparing diuretics can also induce metabolic acidosis. Mild metabolic alkalosis develops commonly during thiazide or loop diuretic treatment but is usually without important consequences.

This box summarises key points contained in the article.

In the renal tubules, reabsorption of NaCl is driven by the electrochemical Na^+ gradient generated by the Na^+/K^+ -ATPase pump of the basolateral membrane, which is present in practically all tubular epithelial cells; however, the Na^+ transport pathways of the luminal tubular membrane, as well as the amount of Na^+ reabsorbed, differ between the various segments of the nephron [3]. With the exception of osmotic agents, all other diuretics act by interfering with a specific transport system of the luminal membrane; in fact, the most common classification of diuretic agents in carbonic anhydrase inhibitors, osmotic agents, loop diuretics, thiazides and related sulfonamide compounds, and potassium sparing diuretics is

largely based on their mechanism of action. The mechanism and site of action of each diuretic class determine their pharmacological effects, natriuretic efficacy and specific clinical indications, as well as several of their side effects [1,3]. Therefore, as in the case of pharmacological actions, the specific electrolyte or acid–base abnormalities for each class of diuretics can be largely anticipated from the pharmacologic mechanism of action and the nephron segment where a class of diuretics acts (Table 1) [5]. Based on this, strategies of adequate monitoring of diuretic treatment, appropriate dose adjustment and electrolyte replacement, when necessary, can prevent the development and the consequences of electrolyte or acid–base disorders and ensure patients' safety.

This article represents the second part of a work on the clinical use of diuretics that reports on the disturbances of electrolyte and acid–base balance complicating the use of diuretic agents and discusses strategies for their prevention and treatment.

2. Hypokalaemia

The secretion of K^+ into the tubular lumen occurs mainly in the cortical collecting duct and to a lesser extent at the final segment of the distal convoluted tubule and the connecting tubule, following the lumen negative electric gradient due to Na^+ reabsorption [3,6]. A number of different factors can participate in increased K^+ secretion and consequently K^+ depletion and hypokalaemia during diuretic therapy. First, increased flow-dependent Na^+ delivery to these regions of the distal nephron: all of carbonic anhydrase inhibitors, osmotic diuretics, loop diuretics, and thiazides and related agents promote K^+ secretion by inhibiting Na^+ reabsorption in their site of action and increasing Na^+ delivery to the collecting duct [4,5,7,8]. The second factor is diuretic-induced volume depletion, which stimulates the renin–angiotensin system (RAS) resulting, among others, in secondary hyperaldosteronism; aldosterone stimulates Na^+ reabsorption and, therefore, K^+ secretion in the collecting duct [4,5,7,8]. With the exception of carbonic anhydrase inhibitors, all the above agents induce Cl^- depletion which independently promotes urinary K^+ loss [9], whereas loop and thiazide diuretics promote Mg^{2+} depletion which also induce kaliuresis, through unknown mechanisms [3,10]. Further, as K^+ loss is also a function of dietary NaCl , when NaCl intake is high, distal delivery of Na^+ remains also high and K^+ secretion is promoted [5]. Finally, the risk of hypokalaemia would be greater in patients with low total body potassium, as in many elderly patients [11].

Several studies on the prevalence and severity of hypokalaemia in patients receiving diuretics suggest that they differ between the various diuretic classes and that they are dose-related. Long-acting agents, such as chlorthalidone, produce more pronounced K^+ losses, while thiazides with intermediate duration of activity have shorter effect [4,5,8,12]. In a previous study of 447 hypertensive patients receiving 50 mg

Table 1. Electrolyte, acid-base and other disturbances and side effects related to the use of diuretics.

Diuretic agents	Major pharmacologic renal actions	Electrolyte and water disturbances	Acid-base disturbances	Other side effects	Contra-indications
Carbonic anhydrase inhibitors	Inhibition of proximal Na ⁺ , HCO ₃ ⁻ and water reabsorption. Increased distal exchange of Na ⁺ with K ⁺	Volume depletion Hypokalaemia	Hyperchloraemic metabolic acidosis	Light-headedness, circumoral paresthesias, weakness, confusion	Hypersensitivity in sulfonamides, metabolic acidosis, pregnancy, hepatic failure, renal failure
Osmotic agents	Impairment of Na ⁺ , Cl ⁻ , HCO ₃ ⁻ and water reabsorption. Increased distal exchange of Na ⁺ with K ⁺	Volume depletion Hypokalaemia	Hypochloraemic metabolic alkalosis	Congestive heart failure, headache, nausea, vomit, fever, confusion, lethargic state	Congestive heart failure, volume depletion, non-reversible anuria
Loop diuretics	Inhibition of Na ⁺ , K ⁺ and Cl ⁻ reabsorption at the loop of Henle. Increased distal exchange of Na ⁺ with K ⁺ . Inhibition of Ca ²⁺ and Mg ²⁺ reabsorption. Impairment of kidney maximum urine concentrating and diluting capacity	Volume depletion Hypokalaemia Hyponatraemia Hypomagnesaemia	Hypochloraemic metabolic alkalosis	Hyperglycaemia, dyslipidaemia, hyperuricaemia, nausea, ototoxicity, allergic interstitial nephritis	Hypersensitivity in sulfonamides, gout, pregnancy, non-reversible anuria
Thiazides and related agents	Inhibition of Na ⁺ and Cl ⁻ reabsorption at the distal tubule. Increased distal exchange of Na ⁺ with K ⁺ . Inhibition and Mg ²⁺ reabsorption. Increase of Ca ²⁺ reabsorption. Impairment of kidney maximum urine diluting capacity	Volume depletion Hypokalaemia Hyponatraemia Slight hypercalcaemia	Hypochloraemic metabolic alkalosis	Hyperuricaemia, glucose intolerance, (insulin resistance and decreased insulin secretion), increased total and LDL-cholesterol, increased triglycerides, erectile dysfunction, impotence, orthostatic hypotension, lithium accumulation	Hypersensitivity in sulfonamides, gout, hepatic failure, renal failure
Potassium-sparing agents	Inhibition of Na ⁺ reabsorption at the collecting tubule. Impairment of K ⁺ (and H ⁺) secretion in the collecting tubule. Inhibition of Mg ²⁺ tubular secretion	Hyperkalaemia	Hyperchloraemic metabolic acidosis	Nausea, flatulence and skin rash with amiloride or triamterene, nephrolithiasis with triamterene ynecomastia and libido decrease in men, galactorrhoea with spironolactone	Hyperkalaemia, renal failure, hepatic failure. Triamterene should not be used during pregnancy

LDL-cholesterol: Low-density lipoprotein-cholesterol.

of hydrochlorothiazide daily, the serum K^+ fell to 3.0 – 3.5 mmol/l in 56% and to <3.0 mmol/l in only 2.4% of the patients [13]. In another study in 193 hypertensive patients taking 5 mg of bendrofluzide, a dose equivalent to 100 mg of hydrochlorothiazide, serum K^+ between 3.0 and 3.5 mmol/l occurred in only 19% of the study population [14]. Loop diuretics are less likely to cause hypokalaemia when used to treat essential hypertension than thiazides [3,5,8]. During the first several days of thiazide diuretic therapy, plasma K^+ falls an average of 0.6 mmol/l (in a dose-dependent manner) as compared with a 0.3 mmol/l drop in patients taking furosemide [15]. The latter could be either due to the short duration of action an intermittent NaCl retention with loop diuretics or only a matter of doses used. Carbonic anhydrase inhibitors do not seem to be responsible for major hypokalaemia, although they are kaliuretic. In a study of 92 glaucoma patients receiving acetazolamide or methazolamide, only 8 developed hypokalaemia, all of whom were also receiving thiazides for hypertension [16]. Needless to say, patients with refractory edema treated with high-dose synergistic combinations (i.e., loop diuretics and metolazone) are at higher risk for hypokalaemia [5].

The degree of hypokalaemia is strictly dose-dependent. Luckily, due to the rather shallow dose–response curve of the thiazide diuretics [1] their antihypertensive efficacy does not greatly increase with dose [17]; this enabled the use of lower doses of these agents in recent years which has helped to reduce hypokalaemia incidence. With higher doses previously used in hypertension (i.e., hydrochlorothiazide 50 – 100 mg), the reduction in serum potassium ranged from 0.1 to 1.4 mmol/l (average 0.7 mmol/l) [18]; with hydrochlorothiazide 25 mg, the fall ranged between 0.2 and 0.7 mmol/l; whereas with hydrochlorothiazide 12.5 mg, reductions <0.3 mmol/l have been reported [19]. Similar changes of serum potassium with increasing dose have been reported with other thiazides, that is, bendrofluzide [20]. The above reductions would translate into an incidence of hypokalaemia (serum potassium <3.5 mmol/l) of 20% or more with higher doses and about 5 – 10% with hydrochlorothiazide or chlorthalidone 12.5 – 25 mg [21,22]. In the Systolic Hypertension in the Elderly Program (SHEP), 7.2% of the patients developed hypokalaemia after 1 year of treatment with chlorthalidone up to 25 mg. [23]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), use of chlorthalidone (12.5 and 25 mg/day) produced hypokalaemia in 12.7% of patients at 2 years and 8.5% at 4 years [24]. The use of diuretics in combination with ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs) or β -blockers, minimises the incidence of hypokalaemia, as the last drugs tend to reduce the renal excretion of K^+ . In the recently published Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study, in patients receiving combination of the ACEI benazepril with hydrochlorothiazide 12.5 or 25 mg, only 0.3% presented hypokalaemia during 3 years of follow-up [25].

Diuretic-induced hypokalaemia has several adverse consequences. A number of previous clinical trials using large doses of thiazide diuretics has shown an association between hypokalaemia and ventricular arrhythmias, particularly premature ventricular contractions [26,27], whereas other studies suggest an increase in sudden cardiac death with nonpotassium-sparing diuretics [28,29]. In the SHEP study, the 7.2% of chlorthalidone-treated patients who developed hypokalaemia did not show the treatment benefits on coronary events and stroke presented in similarly-treated, but normokalaemic patients [23]. These cardiac implications of diuretic-induced hypokalaemia remain controversial, as the issue is confused by several factors, including the inconstant relationship between serum K^+ concentrations and total body K^+ deficits during diuretic therapy and the fact that in most relevant studies serum K^+ values have not been measured frequently enough or under standardised conditions to allow sufficient knowledge of ‘average’ K^+ value at the time of an event [8]. However, the consequences of diuretic-related hypokalaemia are more pronounced in predisposed patients, that is, those with left ventricular hypertrophy, congestive heart failure, myocardial ischaemia or under digitalis treatment. The association between diuretic-related hypokalaemia and digitalis toxicity is well documented in clinical studies showing that patients under concomitant treatment with diuretics and digitalis had an ~1.5-fold higher risk of digitalis toxicity compared to those treated with digitalis alone [8,30]. Based on these observations, it seems reasonable to propose closer monitoring of serum K^+ levels in these patients and restoration of K^+ deficits especially when patients develop arrhythmias and need hospitalisation [31,32]. Thiazide-induced hypokalaemia may also contribute to glucose intolerance with this class of diuretics, as it reduces both insulin secretion and insulin sensitivity [33,34]. In a recent quantitative analysis of such as trials containing 83 thiazide diuretic study arms, a significant inverse relationship between serum potassium and glucose levels was noted; however, it appeared that the glucose intolerance with diuretic therapy could not be totally explained by hypokalaemia [35]. Finally, hypokalaemia may interfere with blood pressure (BP) reduction, through various mechanisms [36]. Dietary potassium depletion was associated with BP increase [37], while in a small study K^+ supplementation (average increase in serum K^+ of 0.56 mmol/l) to correct hypokalaemia in diuretic-treated patients was followed by a 5.5 mmHg average fall in mean BP [38].

Prevention of hypokalaemia should be an additional goal in all patients treated with diuretics. Serum Na^+ and K^+ levels should be regularly monitored in such patients. Use of the lowest effective dose (especially for hypertension), intake of a diet low in sodium and rich in potassium, and combination with agents with potassium sparing properties (i.e., ACEIs, ARBs or β -blockers) as needed may be effective measures to prevent or reverse hypokalaemia [3,21]. If the above measures are not capable of correcting K^+ levels (especially in the presence of additional morbid factors, such as congestive heart

Table 2. Risk factors for development of hyperkalaemia with potassium sparing diuretics.

Impaired renal function
Hyporeninaemic hypoaldosteronism
Diabetes mellitus with high glucose levels or hyporeninaemic hypoaldosteronism
Advanced stages of heart failure with accompanying reductions in renal function
Increased doses of potassium sparing agents
Pre-therapy serum $K^+ > 4.5$ mEq/l
Concurrent high potassium diet, potassium supplements or salt substitutes
Volume depletion
Loop and/or thiazide diuretic-related
Intercurrent illnesses (typically gastrointestinal)
Older age (related to level of renal function)
Caucasian race
Commonly used drugs that modify potassium homeostasis
Non-steroidal anti-inflammatory drugs or COX inhibitors
ACE inhibitors
Angiotensin-receptor blockers
Renin inhibitors
β -Blockers
Heparin
Trimethoprim
Pentamidine
Cyclosporine
Tacrolimus

failure, digitalis treatment, cirrhosis), reorganization of the diuretic regimen with an addition of a potassium-sparing diuretic or oral K^+ supplementation may be required [3,21]. Potassium-sparing agents should be prescribed cautiously, as the combined effects cannot be directly predicted and the risk of hyperkalaemia exists (see below) [5,8]. When K^+ supplementation is indicated, potassium chloride is preferred, as it corrects metabolic alkalosis and intracellular K^+ deficiency better than other salts (included in organic fruits) [5,39]. Exceptions are use of a carbonic anhydrase inhibitors or patients with renal stones or osteoporosis in need of reducing urinary Ca^{2+} loss, where an alkaline salt such as potassium citrate or bicarbonate is more appropriate [5,40]. Of note, the addition of K^+ supplements to thiazide therapy had little effect on the risk of sudden cardiac death, whereas this risk was substantially reduced in patients receiving a thiazide and K^+ -sparing diuretic in combination [28]. This difference could not be explained by differences in serum K^+ concentrations, suggesting that other properties of K^+ -sparing diuretics were involved; decreasing urinary losses of magnesium is one hypothesis, but relevant studies were not sufficient to test it [8].

3. Hyperkalaemia

Hyperkalaemia is a potentially life-threatening condition due to the risk of ventricular arrhythmias and cardiac arrest when serum K^+ is severely elevated [41]. Hyperkalaemia can only be a side effect of potassium-sparing diuretics, all of which increase serum K^+ concentrations in a dose-dependent manner [41,42]. This property along with their poor natriuretic efficacy resulted in use of potassium-sparing mostly in the treatment of hypertension in combination with other agents to correct potassium deficiency in patients with (spironolactone and eplerenone) or without (amiloride and triamterene) mineralocorticoid excess. However, previous data suggested that hyperkalaemia developed in 8.6% of patients receiving spironolactone and in up to 23% of patients on a kaliuretic diuretic given potassium-sparing agents alone or with potassium supplements to treat or prevent hypokalaemia [5,22]. Consequently, potassium-sparing agents were a contributing factor in ~ 5 – 15% of hospital-acquired hyperkalaemia [43].

Although hyperkalaemia (serum $K^+ > 5.5$ mmol/l) may occur with any of the potassium-sparing agents, current knowledge suggests that this is rather uncommon in the absence of additional predisposing factors [21,44] listed in Table 2. Among these factors, the most common in clinical practice seems to be impaired renal function (especially in older individuals) or use of medications interfering with potassium secretion such as ACEIs, ARBs, β -blockers and non-steroidal anti-inflammatory agents [1,5,8]. The recently demonstrated beneficial effects of spironolactone and eplerenone in patients with heart failure [45,46] along with the current evidence for their efficacy in resistant hypertension [47,48] resulted in increase in the use of these agents in daily clinical practice; thus, it seems reasonable that clinical problems related to hyperkalaemia would be exaggerated, as a degree of renal failure and concomitant use of ACEIs, ARBs and β -blockers are very common among patients with heart failure or resistant hypertension [8,49]. Data from both clinical studies and clinical practice support this hypothesis. The Randomized Aldactone Evaluation Study (RALES) of spironolactone in heart failure [45] was preceded by a short, dose-finding study in which hyperkalaemia (serum $K^+ \geq 5.5$ mEq/l) occurred more commonly than in previous studies, that is, in 13, 20 and 24% of heart failure patients treated with spironolactone 25, 50, and 75 mg/d, respectively [50]. Thus, in the main RALES trial, investigators selected the dose of 25 mg. Further, a report from a Toronto health provider has shown that the much greater use in the community patients with heart failure of spironolactone following the publication of the RALES trial has largely increased the complications of hyperkalaemia; hospitalisations for hyperkalaemia rose from 2.4/1000 admitted patients in 1994 to 11/1000 admitted patients in 2001 and in-hospital death from hyperkalaemia rose from 0.3/1000 to 2/1000 over the same period [51]. Specific recommendations exist regarding appropriate administration and contraindications for the use of

Table 3. Risk factors for development of hyponatraemia with diuretics.

Older age
Female gender
Low body mass
Low sodium diet
Behavioral disturbances that may increase water intake
Psychogenic polydipsia
Psychosis
Volume depletion with excess sodium loss (i.e., after stimulation of thirst leading to increased water intake and ADH secretion leading to water retention)
Diminished capacity to excrete free water (i.e., impaired renal function)
Coexisting potassium or magnesium depletion
Coexisting glucocorticoid deficiency or hypothyroidism
Concurrent use of other medications that alter water homeostasis
Antidepressants
Antiepileptic drugs
Antipsychotic drugs
Non-steroidal anti-inflammatory drugs or opiates
Anticancer agents (vinca alkaloids, cisplatin, cyclophosphamide)
Chlorpropamide

ADH: Antidiuretic hormone.

aldosterone antagonists in an attempt to minimise the risk of hyperkalaemia in patients with heart failure [52]. Aldosterone antagonists are contraindicated in patients with baseline serum K^+ levels above 5 mEq/l; concomitant use of non-steroid anti-inflammatory drugs, COX-2 inhibitors and potassium supplements should be avoided. The initial doses recommended are 12.5 mg for spironolactone and 25 mg for eplerenone, with close monitoring of serum K^+ levels and renal function for at least the first 3 months after initiating therapy [52]. Elevation of serum K^+ levels above 5.5 mEq/l during treatment requires discontinuation or dose reduction of the aldosterone antagonist, unless patients have been receiving potassium supplementation, which should then be stopped [52]. Thus, the use of potassium-sparing agents must be very cautious when any of the factors of Table 2 are present and treatment decisions should be guided by detailed evaluation of treatment benefits and costs for the patient.

4. Hyponatraemia

Hyponatraemia can be either a result of water retention or loss of effective solute (Na^+ and K^+) in excess of water [53]. The capacity of normal kidney to excrete water is great, but for maximal renal excretion of electrolyte-free water, three conditions must be met: the delivery of tubular fluid to the diluting sites (the loop of Henle and the distal convoluted tubule) must be normal, the ability of the diluting sites to

reabsorb solute must be normal and antidiuretic hormone (ADH) must be suppressed so that water is not reabsorbed in the collecting duct [5]. Thiazides and thiazide-related diuretics act by blocking $NaCl$ reabsorption at the distal convoluted tubule, which is the major diluting site, thereby, significantly impairing the renal diluting capacity [1-3]. Loop diuretics impair Na^+ , K^+ and Cl^- reabsorption in the thick ascending limb of the loop of Henle (a less important diluting site), which on one hand blunts renal diluting capacity, but on the other decreases the osmolality of medullary interstitium, providing the driving force for ADH-induced water absorption at the collecting duct, impairing also renal concentrating capacity [1-3]. Therefore, the major impairment of free water clearance and achievement of maximally dilute urine results from thiazide treatment, whereas loop diuretics have a lesser effect. Carbonic anhydrase inhibitors and osmotic agents do not interfere with the kidney diluting capacity, as their site of action is distinct from the renal diluting sites. Potassium-sparing diuretics also act in a site that does not play a major role in production of diluted urine. However, addition of a potassium-sparing diuretic to a thiazide treatment may deteriorate hyponatraemia, as it further reduces the total amount the amount of Na^+ that is reabsorbed; this has been shown for the combination of hydrochlorothiazide with amiloride [53,54].

Diuretic-induced volume depletion also causes a relative decrease of glomerular filtration rate and more avid proximal tubular Na^+ reabsorption, which both reduce solute delivery to the diluting sites [5]. The underlying disease of the patient (i.e., congestive heart failure, hepatic cirrhosis) may itself decrease effective intravascular volume and enlarge this effect. Further, volume and sodium depletion from excessive diuretic effect leads to a volume stimulus to ADH release. Overall, diuretics can interfere with all three requirements for production of maximum diluted urine.

Diuretics are a very common cause of hyponatraemia, especially in the out-patient setting [55-57]. Thiazides and thiazide-related agents (chlorthalidone, indapamide) are implicated most often, but furosemide, metolazone, spironolactone, and combinations of thiazides with amiloride or triamterene may also be responsible [5,53,56,58,59]. A previous review suggested that 73% of cases were associated with use of thiazide-related agents, 6% with furosemide and only 1% with spironolactone [56]. Thus, thiazides and related-agents are > 10-fold more likely than loop diuretics to produce hyponatraemia [60]. Thiazide-induced hyponatraemia usually develops within 2 weeks after initiation of therapy, whereas furosemide-induced hyponatraemia occurs after a longer interval [56,60]; however, thiazide-related hyponatraemia can occur on a delayed basis even after several years of therapy, when additional factors are added [61], as those shown in Table 3. The elderly seem to carry the greatest risk for diuretic-induced hyponatraemia, with incidence rising up to 11% among geriatric patients [60,62,63]; interestingly, the majority of affected individuals are female [56,58,62]. Concurrent use of other medications that impair water

excretion, low body mass, as well as psychosis or other behavioral disturbances that may increase water intake also enhance the risk of hyponatraemia during thiazide treatment [5,58,64]. Although the apparent female predominance in thiazide-induced hyponatraemia could be related to overrepresentation of females in thiazide-treated cohorts, a real intrinsic susceptibility of females may also be the case, due to factors such as older age, reduced body mass, exaggerated natriuretic response to a thiazide diuretic, diminished capacity to excrete free water and self-imposed water intake [61,65].

Several studies have tried to explore the underlying pathophysiologic mechanisms for diuretic-related hyponatraemia. Although the overall picture is not totally clear, these mechanisms have been recently summarised [53] and include the following, in order of possible relative prevalence and/or importance: i) direct inhibition of urinary dilution capacity by diminishing NaCl reabsorption in the diluting segments [1-3,58]; ii) excess renal loss of effective solutes (Na⁺ and K⁺) compared to water loss resulting both from diuretic action and ADH-induced water retention [58]; iii) appropriate stimulation of ADH secretion due to diuretic-induced volume depletion [2,66]; iv) stimulation of thirst [5,56]; v) the coexisting hypokalaemia that lead to small transcellular cation exchange with K⁺ moving intracellularly and Na⁺ moving intracellularly to preserve electroneutrality [67]; vi) excessive ADH secretion, due to osmostat reset with normal diluting capacity at low serum Na⁺ concentrations, an effect probably occurring from thiazide-induced intracellular potassium depletion [5,55,58,68]; vii) impaired renal function leading to reduced free-water clearance in the presence of normal ADH suppression [5,63]; and viii) magnesium depletion [69].

Prevention of diuretic-induced hyponatraemia involves adequate monitoring of serum Na⁺; this should be within the first few weeks of thiazide treatment (particularly in elderly women) and in regular intervals afterwards [5]. In patients with a previous episode of hyponatraemia, thiazides should be used with greater caution, if at all; loop agents may be a better choice in this setting when diuretic treatment is needed [5]. Mild diuretic-related hyponatraemia (typically between 125 – 135 mmol/l) is usually asymptomatic and can be treated with several actions (which are not necessarily mutually exclusive). These include withdrawing the diuretic agent (or switching thiazide to loop diuretic if diuretic therapy remains necessary), restricting free-water intake, replacing K⁺ and Mg²⁺ losses, and replenishing NaCl if the patient is volume depleted [2,58,70]. Severe hyponatraemia (generally < 125 mmol/l) is presented with CNS symptoms, due mainly to oedema of brain cells: headache, nausea, vomiting, aggressiveness, disorientation, and in heavier cases (usually < 115 – 120 mmol/l) lethargic state, coma and seizures. Severe hyponatraemia with heavy neurologic symptoms represents a true medical emergency and needs intensive treatment, which is still surrounded by controversy [2,70]. The major problem in this setting is that rapid correction or overcorrection of hyponatraemia is associated with the osmotic demyelinating

syndrome, which leads to permanent brain damage [56,71,72]. Thus, the risks of ongoing hyponatraemia must be balanced against those of too rapid correction. Observations suggest that no neurologic complications present in patients in whom hyponatraemia is corrected with a rate < 12 mmol/l in the first 24 h, a rate < 18 mmol/l in the first 48 h, or an average rate < 0.55 mmol/(l h) [73]. Thus, recommendations are that plasma Na⁺ should be corrected by no > 0.5 mmol/(l h) during the first 24 h, a rate that should be slowed once mild hyponatraemia (125 – 130 mmol/l) has been reached or symptoms have abated [2,65,74].

5. Disorders of magnesium homeostasis

The major part of the filtered Mg²⁺ (50 – 70%) is reabsorbed in the thick ascending limb of the loop of Henle driven by the lumen positive voltage at this segment created by Na⁺ transport through the Na⁺-K⁺-2Cl⁻ co-transporter; another 25 – 35% of Mg²⁺ is reabsorbed at the proximal tubule and 10% is reabsorbed in the distal convoluted tubule [75]. Loop diuretics have been consistently reported to inhibit Mg²⁺ reabsorption and cause magnesium depletion and probably hypomagnesaemia with either intensive short-term or moderate long-term treatment [5,75,76]. The effects of thiazides on renal Mg²⁺ excretion are more difficult to reconcile with their known transport effects. It seems that thiazides have little acute effect on Mg²⁺ homeostasis, whereas, chronic administration tends to increase Mg²⁺ excretion [4,75-77]. The mechanisms involved in thiazide-induced hypomagnesaemia are not totally clear but seem to include several conditions that independently induce urinary Mg²⁺ loss, such as induction of hypokalaemia, suppression of parathyroid hormone secretion (caused by the thiazide anticalciuric effect) and secondary hyperaldosteronism due to volume depletion, as elevated aldosterone levels were shown to enhance renal Mg²⁺ excretion in animal studies [4,5,78]. In addition, experimental studies have shown that chronic thiazide treatment reduces the renal mRNA expression and protein abundance of an epithelial Mg²⁺ channel, named transient receptor potential subfamily M, members 6 (Trpm6), suggesting that Trpm6 downregulation may represent a general mechanism involved in the pathogenesis of hypomagnesaemia accompanying Na⁺-K⁺-2Cl⁻ co-transporter inhibition or inactivation [79].

Severe hypomagnesaemia can be associated with several electrocardiographic changes up to supraventricular and ventricular tachyarrhythmias, as well as neurological changes, which are usually nonspecific and include mental status changes and/or neuromuscular irritability [65,80]. As with hypokalaemia, the clinical significance of hypomagnesaemia during diuretic treatment is not fully elucidated [5]. Magnesium depletion and hypomagnesaemia when the above diuretics are used is usually mild, possibly because of increased proximal tubular reabsorption of Mg²⁺ induced by the volume depletion [5,7]. Prolonged therapy with thiazide and loop diuretics can be related to average reductions in serum

Mg²⁺ concentration by 5 – 10% [5,81]. Thus, routine monitoring and treatment of hypomagnesaemia in all patients receiving loop diuretics or thiazides is rather not indicated [5,82]. However, cellular Mg²⁺ depletion may occur in up to 50% of patients receiving diuretics and can be present despite normal serum Mg²⁺ concentrations [65,83]. Further, patients with congestive heart failure, and/or secondary hyperaldosteronism who receive high doses of loop diuretics on a chronic basis, as well as the elderly patients with poor dietary magnesium intake or high alcohol intake may be at increased risk of severe hypomagnesaemia [5,65,84] and seem to need closer Mg²⁺ surveillance. Several issues also arise concerning the treatment of diuretic-related hypomagnesaemia. In the presence of tachyarrhythmias, hypomagnesaemia should rather be rapidly treated; this should rather be the case in hypomagnesaemia with neuromuscular manifestations [65]. With regards to BP control, however, there appears to be little additional reduction in BP when Mg²⁺ deficiency is corrected, a case that differs from BP reduction seen in some studies when Mg²⁺ supplementation takes place in a non-deficient state [65,85]. Of note, as discussed above, Mg²⁺ is an important factor for K⁺ homeostasis. Many patients with hypokalaemia (up to about 40% in some studies) have also low serum Mg²⁺ concentrations, and it has been shown that this hypomagnesaemia could lead to refractory potassium repletion [65,86,87]. Thus, presence of hypokalaemia should prompt for measurement of serum Mg²⁺ and correction of the Mg²⁺ depletion, if present [86]. Parenteral Mg²⁺ is the most effective way of correcting hypomagnesaemia but should be withheld for emergency conditions [65]. Several oral Mg²⁺ salts are available for the treatment of less severe Mg²⁺ depletion [65,88]; this could be accompanied by foods rich in Mg²⁺, such as whole-grain cereals, green vegetables, nuts, cocoa and seafood [4,65].

Potassium-sparing diuretics reduce Mg²⁺ excretion; this action may take part in the collecting duct, where only a small amount of Mg²⁺ is reabsorbed, but also at the distal convoluted tubule [75,78]. Aldosterone antagonists may also inhibit renal Mg²⁺ excretion caused by elevated aldosterone levels [4]. Due to this effect, potassium-sparing diuretics can be used to correct Mg²⁺ loss associated with the use of more proximally active diuretics [5,78]. Amiloride in particular has been used effectively to treat idiopathic renal magnesium wasting [78,89].

6. Disorders of calcium homeostasis

Thiazide and thiazide-related diuretics stimulate Ca²⁺ reabsorption and reduce Ca²⁺ excretion by 40 – 50%, an effect useful for the treatment of nephrolithiasis from idiopathically increased urinary Ca²⁺ excretion [90]. Distinct mechanisms can be responsible for this action. First, thiazides inhibit Na⁺ reabsorption without inhibiting Ca²⁺ reabsorption in the distal convoluted tubule, as this is a site where natriuresis and calciuresis are separated; this results in volume depletion

which, in turn, increases both proximal Na⁺ and Ca²⁺ reabsorption making net renal Ca²⁺ secretion to fall. This mechanism is supported by the fact that the decrease in renal Ca²⁺ excretion can be abolished when thiazide-induced Na⁺ losses are replaced [5]. On the other hand, thiazides increase distal Ca²⁺ reabsorption. These agents were shown to stimulate Ca²⁺ reabsorption in isolated distal tubule cell luminal membrane vesicle preparations, an effect lost when luminal Na⁺ concentration is increased [91]. At the cellular level, this effect may take place through opening of voltage-dependent transient cation channels due to electrically negative tubular cell interior, which results from Cl⁻ re-entry from the interstitium, through increased 3Na⁺-Ca²⁺ exchange at the basolateral membrane following thiazide-induced reductions in intracellular Na⁺ and other, less known mechanisms [3]. Other factors possibly involved in an increase in serum calcium during thiazide treatment are direct stimulation of bone reabsorption from thiazides or the relative hyperproteinaemia resulting from volume contraction, which can increase the bound calcium concentration [4,5].

Thiazides produce only a mild elevation in serum calcium levels (usually 0.1 – 0.2 mg/dl) in healthy individuals [21]. The fact that serum calcium does not continue to rise in the face of continuing increased Ca²⁺ reabsorption is practically the result of parathyroid hormone suppression resulting in retention of bone calcium [92] and reduced vitamin D synthesis followed by reduced intestinal Ca²⁺ absorption [93]. In this context, evidence deriving from clinical studies suggests that thiazides may exert beneficial effects on prevention and treatment of age-related osteoporosis [94]. In particular, observational studies have associated long-term thiazide use with fewer fractures and lower rates of bone loss [94], whereas recently published randomised controlled trials have shown that hydrochlorothiazide treatment preserved cortical mineral bone density at the hip and spine in normal postmenopausal women, suggesting that thiazides may represent an additional tool in the prevention and treatment of osteoporosis [95,96]. Discontinuation of thiazides leads to rapid restoration of the serum calcium levels [97]. Modest and severe hypercalcaemia (> 12 mg/dl) during thiazide therapy will only occur in individuals with another underlying cause, that is, those with immobilization hypercalciuria, primary hyperparathyroidism or vitamin D treated hypoparathyroidism who cannot reduce parathyroid hormone in response to a subclinical rise in serum calcium level. Thus, when hypercalcaemia develops during thiazide treatment, an underlying disorder of calcium homeostasis should be suspected [97]. The potassium-sparing diuretic amiloride was also reported in some animal studies to directly increase distal Ca²⁺ reabsorption, thus, causing mild hypercalcaemia [98,99], but this effect is not extensively studied in humans.

Loop diuretics cause urine Ca²⁺ loss as they impair electric voltage positive to the lumen that is responsible for Ca²⁺ and Mg²⁺ reabsorption at the thick ascending limb [1,3,100]. Treatment with loop diuretics is not usually accompanied

by important hypocalcaemia, due to the calcium homeostatic mechanisms discussed above. However, this calciuretic action has been successfully used to treat hypercalcaemia following the correction of associated volume depletion [97,101]. It has to be noted that hypomagnesaemia of any cause, including therapy with loop or thiazide diuretics, can independently cause hypocalcaemia because of either decreased release or decreased action of parathyroid hormone [84]. Importantly, this Mg^{2+} depletion can make hypocalcaemia refractory to treatment [65]. Thus, when hypocalcaemia is present in patients receiving diuretics, Mg^{2+} depletion should be suspected and corrected.

7. Acid–base disorders

Inhibition of carbonic anhydrase in the proximal tubule results in impaired Na^+ and HCO_3^- reabsorption [1,3]. Carbonic anhydrase-induced HCO_3^- renal excretion may be beneficial in the treatment of metabolic alkalosis in patients with reduced respiratory drive and to protect against acute altitude sickness [1,3]. However, this loss of HCO_3^- may often result in modest to severe metabolic acidosis, which is not without problems. A previous study comparing elderly patients with glaucoma patients receiving 250 – 1000 mg of acetazolamide daily with patients not receiving carbonic anhydrase inhibitors showed that 55% of acetazolamide-treated patients developed metabolic acidosis, with 41% of them exhibiting a venous pH below 7.29. The mean tCO_2 of acetazolamide-treated patients was significantly lower than that of controls (19.6 ± 4.1 versus 24.3 ± 5.2 mEq/l) [102]. Another study suggested that this metabolic acidosis could have important symptoms, as 44% of patients receiving acetazolamide or methazolamide developed malaise, fatigue and anorexia that resolved with bicarbonate supplementation; again, the tCO_2 level of symptomatic patients was significantly lower than that of patients who remained asymptomatic [16]. The elderly are at the greatest risk for acetazolamide-related metabolic acidosis, not only because they are most likely to be receiving glaucoma treatment but also because of the age-associated decline in renal function that may result in acetazolamide accumulation in plasma [103].

Potassium-sparing diuretics also produce metabolic acidosis. Inhibition of the Na^+ movement through the apical membrane of the principal cells impairs the creation of the lumen-negative voltage gradient and, therefore, inhibits (apart from K^+ secretion) electrogenic H^+ secretion into the tubular lumen [104,105]. Coexisting hyperkalaemia impairs renal ammoniogenesis and, thus, reduces the amount of urinary buffer available [5]. Taken together, the above two effects reduce net acid excretion; patients may have an acid urine, but they also are unable to acidify maximally [1]. Hyperkalaemia also promotes the maintenance of metabolic acidosis through increased K^+ transport from the extracellular to the intracellular compartment in exchange with H^+ . The characteristic presentation of a hyperchloraemic metabolic acidosis with hyperkalaemia in patients treated with potassium-sparing

diuretics resembles type IV renal tubular acidosis [106]. Patients with renal insufficiency, congestive heart failure, as well as the elderly are particularly susceptible to developing severe metabolic acidosis when treated with potassium-sparing diuretics [65,107]; thus, particular attention should be paid to monitoring pH levels in such patients. Correction of metabolic acidosis may take place (depending on the severity and the co-existing morbidities of each case) by reduction or discontinuation of acetazolamide or potassium-sparing agents, addition of a thiazide or a loop diuretic, correction of hyperkalaemia, treatment of co-morbid conditions and HCO_3^- supplementation.

Mild metabolic alkalosis is a frequent feature of loop or thiazide diuretic therapy, particularly at higher doses. Severe metabolic alkalosis is much less common and, when it occurs, is a manifestation of overly aggressive therapy, usually with loop diuretics [3,65]. Metabolic alkalosis induced by these agents is an adverse factor in patients with cirrhosis and ascites, in whom it may provoke hepatic coma by partitioning ammonia into the brain and in patients with chronic obstructive pulmonary disease, in whom it may further reduce ventilation [2]. Metabolic alkalosis also impairs the natriuretic response to loop diuretics and may play a role in the diuretic resistance to these agents [108]. The generation of metabolic alkalosis with loop or thiazide diuretic therapy is due to urinary losses of Na^+ and Cl^- , without respective losses of HCO_3^- , that is, production of a relatively HCO_3^- free urine [3,5,65]. With regard to mannitol, the osmotic effect in the proximal tubule causes some excretion of HCO_3^- , but the effect at the loop of Henle predominates, so that Na^+ and Cl^- are mainly excreted with the urine, producing also metabolic alkalosis [1]. Maintenance of metabolic alkalosis is promoted by various factors. Secondary hyperaldosteronism resulting from volume depletion directly stimulates distal nephron H^+ secretion in exchange with Na^+ . Volume depletion is also responsible for increase in the proximal tubular Na^+ reabsorption in exchange with H^+ by the Na^+-H^+ co-transporter. Lack of Cl^- is very important in the maintenance of metabolic alkalosis as it may also impair HCO_3^- secretion or promote H^+ secretion in the distal tubule [5,109]. Coexisting hypokalaemia also promotes the maintenance of metabolic alkalosis through increased K^+ transport from the interior of every body cell in exchange with H^+ in an attempt to restore serum K^+ levels. Diuretic-induced metabolic alkalosis is best managed by administration of Cl^- as KCl and/or NaCl (although NaCl administration may be cumbersome in patients intolerant to intravenous saline, such as those with congestive heart failure). In several cases, a potassium-sparing diuretic or a carbonic anhydrase inhibitor should be also considered [2].

8. Conclusion

The extensive use of diuretic agents have provided an important hold towards treatment of major medical disorders but was also associated with a number of adverse effects, among

which disorders of electrolyte and acid–base balance are of major importance. The long research on the diuretic compounds has provided detailed insight into their mechanism of action and pharmacologic properties, which is of great help towards understanding of the development of electrolyte and acid–base abnormalities for each diuretic class. Further, accumulating evidence from relevant clinical studies provides us with extended information on the relative frequency and associated risks of the above diuretic-related disturbances. All this knowledge, along with future research findings, should be carefully translated by clinicians into prompt monitoring, adequate prevention and effective treatment of electrolyte and acid–base abnormalities, in order to achieve the maximum benefits of diuretic therapy for their patients.

9. Expert opinion

Electrolyte and acid–base abnormalities are very important side effects of the various diuretic agents, and can be associated with considerable morbidity and mortality. Loss of K^+ leading to hypokalaemia seems to be the most common electrolyte disorder linked to diuretic use. Previous clinical studies have shown that the frequency of hypokalaemia differs between the various diuretic classes. Thiazides and related agents are more often associated with hypokalaemia than loop diuretics, when the latter are used in equivalent doses. Further, the possibility of thiazide-related hypokalaemia is increasing with dose. Similarly, clinical experience suggests that when high doses of loop agents are used to ensure adequate diuresis in hospitalised patients, the risk of hypokalaemia is importantly elevated. Older clinicians can also argue that the shift in hypertension treatment towards use of lower doses of thiazides and the increasingly common use of diuretic-RAS blocker combinations for hypertension and heart failure during the last 20 years have greatly helped towards reduction of hypokalaemia in the community.

Diuretic-induced hypokalaemia is associated with a number of adverse consequences. An association of hypokalaemia with ventricular arrhythmias and sudden cardiac death was noted in several clinical trials of diuretics and several factors predisposing to these cardiac complications of hypokalaemia are described. However, because the documented associations of hypokalaemia and cardiac risk are confounded by several issues, future research is needed to delineate issues including the exact cardiac risk in relation to the level of serum K^+ and the type of co-morbid conditions, the level of serum K^+ requiring intervention given the characteristics of the patient, the optimum type of intervention (dose adjustment or discontinuation of the diuretic, combination treatment with potassium-sparing agents, use of potassium supplements) and others. Background and clinical evidence also suggests that thiazide-induced hypokalaemia contributes to glucose intolerance of thiazides. This is a very important observation, at a time when the effects of the various antihypertensive classes on glucose tolerance is a field of great research interest

and a debate is active on whether new-onset diabetes during diuretic treatment carries similar cardiovascular risk with pre-existing diabetes [110]. Finally, population data and small clinical studies suggest that hypokalaemia may interfere with BP reduction; however, further research is again needed in order to clarify the exact degree of BP increase for each level of serum K^+ or total body potassium and the exact benefits of K^+ supplementation towards BP control.

Hyperkalaemia is a side effect of potassium-sparing diuretics with well-established associations with arrhythmias and cardiac death. A number of factors elevate the risk of hyperkalaemia, several of which become increasingly common, that is, chronic kidney disease (CKD), uncontrolled diabetes mellitus, or use of ACEIs, ARBs and β -blockers for concomitant conditions. Further, in the past few years a new aldosterone-blocker, eplerenone, was released in the market and the class gained new possible indications, including heart failure and resistant hypertension. As expected, and quickly captured from relevant studies [51], this increase in aldosterone-blocker use resulted in a burst in the incidence of hyperkalaemia and related complications. We must note that depending on the frequency of clinical use of aldosterone-blockers in the next years, the whole field of the diuretic-related side effects may change considerably and hyperkalaemia may become the most important clinical problem. In every case, the above observations represent a clear example on the possible risks that may appear when a therapeutic intervention proven successful in clinical studies is used in the real world, and highlights the importance of the responsibility of the medical community and the need for continuous, post-marketing surveillance studies. Performance of several such studies (including different patient and ethnic populations) in the near future seems currently the most important research direction in the field of diuretic side effects; the findings of these studies should complement existing data on the benefits of aldosterone-blockers, in order to fully elucidate the benefit:risk ratio of their clinical use.

Thiazides and thiazide-related diuretics are the agents most possible to impair the renal diluting capacity and thus produce hyponatraemia, followed by loop diuretics. In everyday clinical practice hyponatraemia seems also to be an increasing problem, mainly due to the increased number of elderly individuals with multiple underlying disorders who are chronically treated with diuretics and often receive other medications affecting water homeostasis, have diminished sodium intake and suffer from impaired renal function leading to reduced free-water clearance. Given this increasing importance of hyponatraemia, a number of questions in the field should be further clarified by future research. One such question relates to the exact factors predisposing to hyponatraemia, especially with regard to the apparent greater susceptibility of female individuals, in order to establish clear monitoring and prevention recommendations for every patient category. Perhaps even more important for clinical practice is the clarification of the questions around the risks

and benefits of hyponatraemia treatment; although current recommendations seem quite reasonable in relation to available information, the existing clinical data on the field are limited and need to be complemented by future studies clarifying the exact indications and the optimal way to correct this important disorder.

The effects of the various diuretic classes on magnesium homeostasis, as well as the clinical significance of related alterations in Mg^{2+} levels, are less well studied. Chronic treatment with thiazide and loop diuretics produces small reductions of serum Mg^{2+} concentration but in several patient categories (elderly, alcoholic and those with secondary hyperaldosteronism), severe hypomagnesaemia may be noted; most importantly, cellular Mg^{2+} depletion may occur even in patients with normal serum Mg^{2+} concentrations. As the intracellular Mg^{2+} levels are important for many cellular processes, future research should elucidate the relation between serum and intracellular Mg^{2+} levels during diuretic treatment and the consequences of intracellular Mg^{2+} depletion. Moreover, future studies should better identify the patient categories at risk for hypomagnesaemia to establish detailed monitoring recommendations and delineate the indications and the optimal strategy of hypomagnesaemia correction.

Thiazides and loop diuretics have contrasting well-described effects on Ca^{2+} renal handling that have been quite useful in the treatment of calcium-related disorders. Evidence suggests that treatment with either thiazide or loop agents is not accompanied by important alterations of serum Ca^{2+} due to the homeostatic circuits that keep serum Ca^{2+} levels within narrow limits. However, at a time when research on bone and

mineral metabolism in renal disease is greatly extended and many patients with stages 4 and 5 CKD are treated with loop diuretics, an interesting question to be clarified from future research is whether and to what extent the calciuretic action of loop diuretics could be an additional factor for parathyroid hormone elevation in these patients.

Carbonic anhydrase inhibitors typically increase renal HCO_3^- loss and previous studies suggest that use of these agents may result in symptomatic metabolic acidosis, especially in elderly individuals. This effect is often neglected by both treating physicians (who are mainly ophthalmologists prescribing these agents for glaucoma) and other clinicians called to examine such a patient with nonspecific symptoms of metabolic acidosis. Again, these important older data should be followed by more detailed studies, so that clear monitoring recommendations and treatment indications could be generated. Mild metabolic alkalosis develops commonly during thiazide or loop diuretic treatment but is usually without important consequences. However, in some patients with multiple underlying conditions requiring aggressive diuretic treatment, severe metabolic alkalosis may occur and produce further problems. Correction of metabolic alkalosis in such patients requires careful handling; NaCl administration may be difficult in many cases and addition of acetazolamide or potassium-sparing agent could be an important help.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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