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Review Article

Chronic Metabolic Acidosis in Chronic Kidney Disease

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Chronic metabolic acidosis · Bicarbonate · Chronic kidney disease · Protein metabolism · Bone density · Veverimer

Abstract
Background: Metabolic acidosis may be diagnosed as chronic (cMA) if it persists for at least 5 days, although an exact definition has not been provided by any guidelines yet. The most common cause is CKD; numerous less-known diseases can also account for cMA. ***Summary:*** In recent years, CKD-associated cMA has been proposed to induce several clinical complications. The aim of the article was to assess the current clinical evidence for complications and the respective management of CKD-associated cMA. In summary, cMA in CKD most likely promotes protein degradation and loss of bone mineral density. It aggravates CKD progression as indicated by experimental and (partly) clinical data. Therefore, cMA control must be recommended. Besides oral bicarbonate, dietary interventions potentially offer an alternative. Veverimer is a future option for cMA control; further systematic data are needed. ***Conclusions:*** The most common cause of cMA is CKD. CKD-associated cMA most likely induces a negative protein balance; the exact role on bone metabolism remains uncertain. It presumably aggravates CKD progression. cMA control is recommendable; the serum bicarbonate target level should range around 24 mEq/L. Veverimer may be established as future option for cMA control; further systematic data are needed.

Introduction

Chronic metabolic acidosis (cMA) affects many patients treated in hospitals in Europe and the USA. The term "chronic" in cMA has not exactly been defined, as opposed to "chronic" in CKD. The latter must be diagnosed if the underlying problem that affects kidney excretory

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function or induces proteinuria persists for at least 3 months [1]. The authors propose to define an acidotic state as chronic if it lasts for at least 5(–7) days or longer [2]. In acute MA, signs/symptoms of endogenous compensation may be missing. In cMA in contrast, endogenous compensation has been initiated regularly.

The most frequent cause of cMA in fact is CKD. The tubular net secretion of protons decreases, predominantly the result of diminished tubular ammoniogenesis (loss of nephron mass). In addition, the glomerular elimination of organic acid residues is impaired. The NephroTest cohort [3] revealed that most CKD stage 4 patients had positive acid balance, accompanied by a normal blood CO_2 concentration. Chronic MA in CKD is being diagnosed as normochloremic MA with increased anion gap, at least in later CKD stages [4]. It is being estimated that between 30 and 50% of all CKD subjects with a GFR of below 30 mL/min suffer from cMA [5]. The cited study also showed that the prevalence of cMA increases with decreasing m (measured) GFR: range 60–90 mL/min/1.73 m^2 2%; <20 mL/min/1.73 m^2 39% [5].

However, cMA may also evolve in other situations such as insulin-dependent diabetes mellitus or in fasting individuals. Less frequent causes of cMA include primary adrenal insufficiency, hyporeninemic hypoaldosteronism, and others.

While acute MA endangers patients mostly through hemodynamic and hyperkalemic effects [6], chronic MA significantly increases the overall morbidity in the long term. In recent years, many cMA-associated complications were discussed. Among those were protein catabolism, reduced de novo synthesis of proteins, bone demineralization, inflammation, and CKD progression. Meanwhile, not all complications have been confirmed in a controlled and prospective manner. However, there is only minor doubt that cMA promotes CKD progression. It is therefore reasonable to supply CKD subjects with MA with oral bicarbonate on a regular basis. The questions when bicarbonate therapy should be initiated and which serum bicarbonate should be targeted will be discussed in the current article. The first section focuses on cMA etiology, the second section is dedicated to cMA-associated complications, and the third section finally discusses treatment modalities of cMA including a new therapeutic.

Etiology of cMA in CKD

MA must be diagnosed if a lower pH goes in parallel with reduced serum bicarbonate. If the respective cause persists for several days or longer, the pH is increased toward the normal range, which results from endogenous (ventilatory) compensation. In this situation, the diagnosis of MA is made because of reduced serum bicarbonate. Two mechanisms potentially account for MA, reduced net proton elimination/loss of bicarbonate or accumulation of organic acids. Reduced net proton elimination and loss of bicarbonate are mentioned in conjunction since both processes do not elevate the anion gap but serum chloride (hyperchloremic, normal anion gap MA). Organic acid accumulation, however, causes an increase in the anion gap (normochloremic, high anion gap MA). As mentioned in the Introduction, the term "chronic" may be used if MA persists for at least 5 days. The proposed cutoff may appear arbitrary at first sight. However, as indicated by data published in 1960 [7], compensatory mechanisms in MA have for sure been established after this period.

The most frequent cause is CKD. The daily proton load predominantly undergoes ventilatory elimination after conversion of bicarbonate and hydrogen ions into water and carbon dioxide. Approximately 50–80 mmol of protons undergo tubular excretion, predominantly bound to either NH_3 or HPO_4^{2-} [8]. Only a small proportion is excreted freely; it determines the urine pH. Between 30 and 50% of all CKD subjects with a GFR of below 30 mL/min suffer

Table 1. Other types of cMA

Characteristics/type of cMA	Mechanism(s)
High anion gap	
Insulin-dependent diabetes mellitus	Production of beta-hydroxybutyrate and acetoacetate ↑
Fasting	Production of beta-hydroxybutyrate and acetoacetate ↑
Normal anion gap	
Diarrhea, resulting from upper GI tract infection	Intestinal loss of bicarbonate
Acetazolamide treatment	Tubular loss of bicarbonate
RTA type 1	Distal tubular proton net secretion ↓
RTA type 2	Tubular loss of bicarbonate (proximal tubule)
RTA type 4	1. Diminished aldosterone synthesis (e.g., adrenal insufficiency) 2. Diminished aldosterone activity (aldosterone receptor defect)
HDRTA	1. Distal tubular Na^+-reabsorption via ENaC ↓(pseudohypoaldosteronism type 1 – autosomal recessive) 2. Distal tubular Cl^--backleak (pseudohypoaldosteronism type 2 or pseudopseudohypoaldosteronism – Gordon syndrome)

HDRTA, hyperkalemic distal renal tubular acidosis; cMA, chronic metabolic acidosis; RTA, renal tubular acidosis.

from cMA, initially as the result of diminished tubular NH_3 synthesis [9]. In later CKD stages, reduced glomerular filtration also accounts for cMA since organic acid residues accumulate. Lately, a study by Tanemoto [4] reported on dynamic characteristics of MA in CKD. A high anion gap progressively developed during later CKD stages (stage 5), whereas in earlier stages the anion gap is normal.

Other Types of cMA

Other types of cMA shall only be mentioned briefly. All of these can occur in CKD also, without being CKD-specific or CKD-related. They should, however, be considered as differential diagnoses. Insulin-dependent diabetes mellitus can induce cMA if insulin supplementation is constantly being performed in an inadequate manner which results in the accumulation of acetoacetate and beta-hydroxybutyrate (high anion gap MA). The same disturbance can occur in individuals that fast for longer periods [10]. Normal anion gap cMA, however, can evolve in chronic (primary) adrenal insufficiency, in hyporeninemic hypoaldosteronism, and in certain types of pseudohypoaldosteronism [11]. Common hallmark is a decrease in systemic aldosterone, resulting in diminished tubular proton elimination. The current literature refers to these types of cMA as renal tubular acidosis (RTA) type 4 [12]. Harris et al. [13] showed that hyperkalemia in RTA type 4 aggravates cMA per se. In RTA types 1 and 2 in contrast, distal tubular proton secretion is either diminished (type 1) or proximal tubular bicarbonate reabsorption is impaired (type 2). Chronic diarrhea can induce cMA if the upper GI-tract including the jejunum is affected [14]. Finally, normal anion gap cMA has been reported in patients provided with a neobladder due to urothelial carcinoma [15]. Other causes of MA such as lactic acid accumulation or certain types of intoxication (methanol) rarely persist for several days or longer; they are acute in nature (Table 1). All following sections will exclusively discuss cMA in CKD.

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cMA-Associated Complications

Protein catabolism and synthesis: First clinical evidence for cMA effects on protein metabolism came from studies by Reaich et al. [16] and Ballmer et al. [17]. In the first investigation, 7 subjects without kidney disease received ammonium-chloride for 9 consecutive days. At the end of this period, serum levels of the following amino acids were increased: threonine, serine, asparagine, valin, and leucine. The findings indicated protein catabolic effects of prolonged acidosis. The second study was also designed in individuals with normal kidney function, acidosis was induced with ammonium-chloride again, and the agent was applied daily over 1 week. Two parameters were evaluated: the albumin synthesis rate (infusion of $^{2}H_{5}$phenylalanine) and the urinary excretion of urea. Both of these were compromised as reflected by lower albumin synthesis and increased urine levels of urea. In 1994, Mitch and colleagues [18] showed a loss of muscle mass in rats undergoing ammonium-chloride treatment. Acidotic animals displayed increased intramuscular ubiquitin mRNA levels, indicating the acidosis-induced activation of the so-called ubiquitin-proteasome system. Experimental evidence for protein catabolic effects cMA in kidney disease came from studies of May et al. [19]. The correction of MA in 5/6-nephrectomized rats significantly reduced urinary urea excretion. Human studies were published in 1998 [20] and 2002 [21]. The first investigation showed an increase of serum albumin in dialysis-dependent subjects receiving oral bicarbonate [20], the second trial was performed in non-dialysis-dependent CKD patients. Oral bicarbonate increased serum albumin and reduced the protein catabolic rate [21]. De Brito-Ashurst et al. [22] published a prospective, randomized (non-blinded and non-placebo containing) trial, performed in 134 CKD stage 4 patients. Oral bicarbonate was tested against standard care (SC) over a period of 2 years. After 2 years of therapy, the plasma albumin was significantly higher in bicarbonate treated individuals.

However, a 2020-published multicenter, randomized, and placebo-controlled trial [23] failed to show beneficial effects of bicarbonate on muscle function and bone mineral density. The study was performed in CKD stages 3 and 4 patients with a follow-up of 24 months.

It seems acceptable to state that cMA acts protein catabolic and most likely interferes with de novo protein synthesis. The clinical data available so far, however, do not confirm beneficial effects of oral bicarbonate on protein metabolism in a consistent manner.

Bone mineral metabolism: More than 40 years ago, McSherry and Morris [24] initiated bicarbonate treatment in 10 children with established RTA. Particularly, RTA type 1 is known to impair bone stability and thus growth in general [25]. Bicarbonate administration was associated with a normalization of the subjects' growth rate. In a 2002 published trial [26], 10 adult RTA patients received potassium citrate. Treatment increased the bone mineral density, respectively. Bergqvist et al. [27] reported about the loss of bone mass in 25 children with refractory epilepsia under a ketogenic (acidotic and antiepileptic) diet. Regarding kidney disease, Lefebvre and colleagues [28] published biopsy studies, in which bicarbonate therapy in CKD patients reduced bone resorption. In recent years, fibroblast growth factor-23 (FGF-23) has increasingly been identified as key regulator in CKD-associated bone diseases [29]. In addition, the substance most likely aggravates left ventricular hypertrophy in CKD [30]. It needs to be mentioned that FGF-23 effects on the left ventricular myocardium have also been put in question [31]. A progressive GFR loss goes in parallel with increasing FGF-23 levels [32]. The idea that FGF-23 potentially mediates deleterious effects on bone metabolism also came from studies in rarer diseases such as X-linked hypophosphatemic osteomalacia, autosomal dominant and recessive hypophosphatemic osteomalacia, and McCune-Albright syndrome, respectively. In these disorders, which share the common characteristic of hypophosphatemic osteomalacia, FGF-23 is extensively elevated [33]. In a 2012-published experimental study, metabolic but not respiratory acidosis induced substantial FGF-23 secretion

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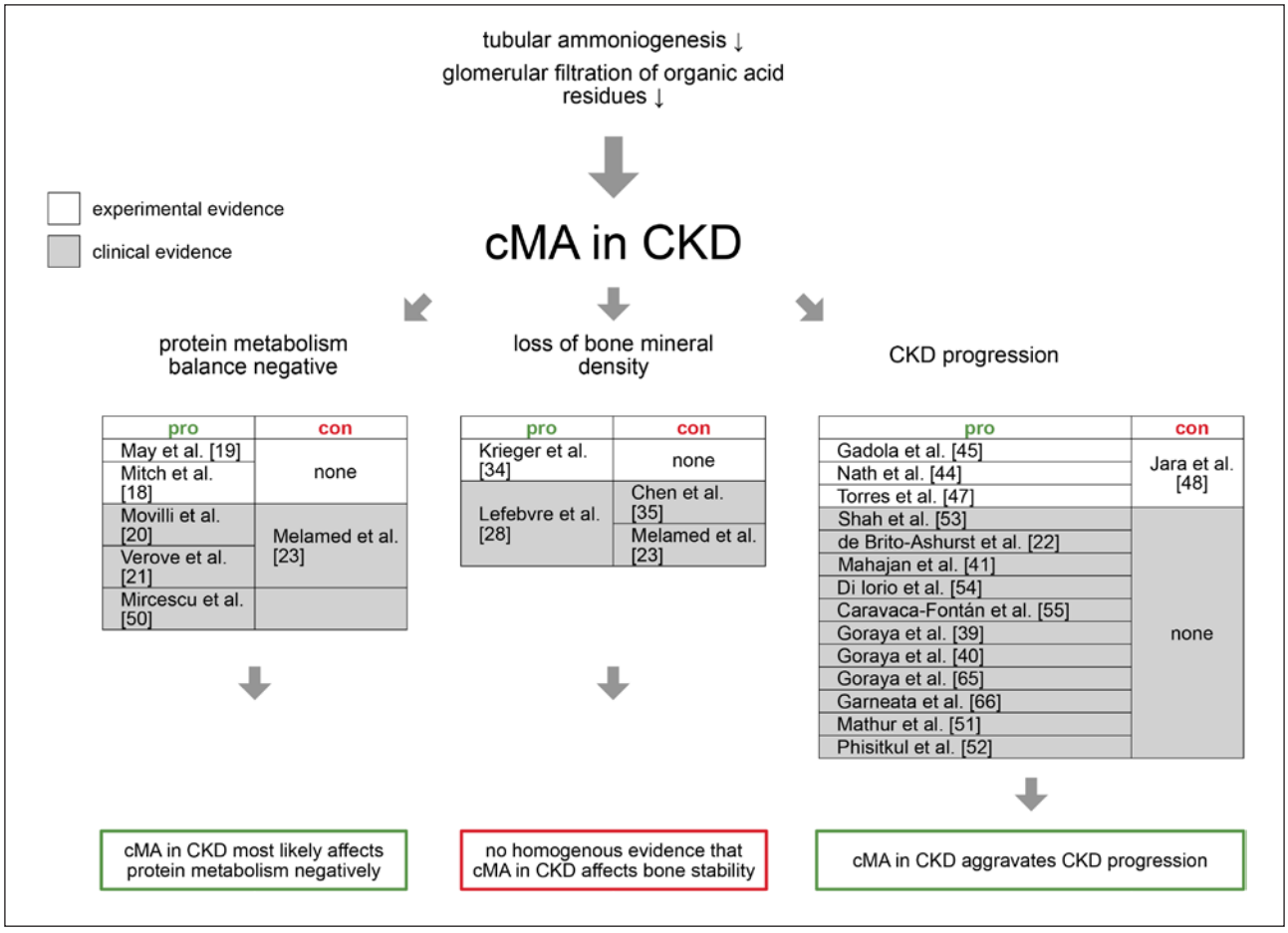

Color version available online

Fig. 1. cMA-associated complications in CKD. Three topics are covered: protein and bone metabolism, and CKD progression. The colored rectangles surround the respective conclusions. The color green was used if the literature indicates negative effects of cMA with a high degree of evidence, and the color red was applied if the current evidence is uncertain/low (pro, positive evidence; con, negative evidence). cMA, chronic metabolic acidosis.

into the medium of cultured cells, accompanied by increased FGF-23 RNA expression by the cells [34]. It needs, however, to be mentioned that a 6-months course of oral bicarbonate supplementation did not reduce but elevate serum FGF-23 in CKD subjects [35]. A very recent study by Melamed and colleagues [23] in CKD subjects (stages 3 and 4) failed to show bone stabilization under bicarbonate administration.

In summary, there is some experimental evidence for bone density loss in cMA-associated CKD. Reliable clinical data that truly prove bone stabilization under cMA treatment are missing. The exact role of FGF-23 in bone metabolism under acidotic conditions needs to be clarified also.

Inflammation: Since a long time, cMA has been regarded as pro-inflammatory stimulus. The most important mechanism, which eventually aggravates CKD progression, is an increased availability of intra-renal angiotensin II [36]. Interestingly, angiotensin-converting enzyme inhibitors do not reduce intra-renal production of the mediator [37, 38], whereas alkali supplementation in CKD subjects does. The latter measure also inhibits urinary aldosterone excretion [39–41]. Intra-renal angiotensin II on the other hand has been shown to promote interstitial

fibrosis, tubular atrophy, and interstitial inflammation [42, 43]. In 1991, Nath et al. [44] found that increased ammoniogenesis in remnant tubules stimulates complement activation and therefore inflammation. Another mechanism by which MA potentially stimulates inflammation is increased production of endothelian [45], which acts vasomodulatory, pro-apoptotic, and immunomodulatory [46]. Thus, cMA control through either dietary or pharmacological measures presumably reduces kidney inflammation. Nonetheless, biopsy studies that truly proved anti-inflammatory effects of acidosis control have not been published yet.

CKD progression. In pre-dialysis CKD, many nephrologists prescribe oral bicarbonate in order to prolong the dialysis-free period. Experimental studies from the mid-1980s and from 2004 showed that bicarbonate and citrate effectively in reduced the tubulointerstitial damage in 5/6-nephrectomized rats [47, 48]. Bicarbonate also diminished renal cyst expansion in Han:SPRD rats [49]. The mentioned study, however, failed to show comparable effects of alkali treatment in another (murine) CKD model (CD1-pcy/pcy mice) [49]. In this context, it also needs to be mentioned that in a rat CKD model, MA did not aggravate but slowed down the loss of kidney function after 5/6-nephrectomy [50]. The animals received a phosphate enriched diet. Comparable data were published by Throssell et al. [51]. Therefore, other metabolic circumstances besides the acid base metabolism apparently need to be considered as well. Human data will be discussed in the next section. Figure 1 summarizes cMA-associated complications, including additional references that were not discussed in the text [52–54].

Management of cMA

Almost all studies cited in this upcoming section analyzed kidney function-related end points in patients that underwent alkali supplementation.

Oral bicarbonate: In 2009, Shah and colleagues [55] published a retrospective cohort study in which CKD patients supplied with oral bicarbonate were evaluated for CKD progression. It became apparent that an average serum bicarbonate of 22 as opposed to 25–26 mL/min was associated with progressive loss of kidney excretory function, independently of the baseline eGFR [55]. In the same year, de Brito-Ashurst [22] published a prospective, randomized (non-blinded and non-placebo containing) trial, performed in 134 CKD stage 4 patients. Oral bicarbonate was tested against SC over a period of 2 years. Primary end point was eGFR reduction, and secondary end points were certain surrogate parameters of CKD progression including protein intake and plasma albumin. At 24 months, serum bicarbonate was higher in treated than in control patients, and the blood pressure did not differ between the 2 groups. The GFR loss, however, differed: treatment 1.88 versus control 5.93 mL/min/1.73 m^2 ($p < 0.0001$). In addition, plasma albumin significantly increased under bicarbonate therapy. Another prospective (and controlled) trial was published by Mahajan et al. [41]. All participants suffered from hypertensive nephropathy; the initial GFR was relatively preserved (mean 75 mL/min). Sodium bicarbonate (SB) was tested against sodium chloride and placebo with a follow-up period of 5 years. SB significantly stabilized the eGFR as compared to sodium chloride or placebo. Di Iorio et al. [56] published a randomized, open-labeled, controlled trial. SB was applied in CKD stages 3–5, the primary end point was Cr doubling. Other end points were all-cause mortality and time to renal replacement therapy as compared to SC; the observation period was 36 months. The following numbers of individuals were enrolled: 376 (SB) and 364 (SC). The primary end point was reached in 87 SC individuals and 25 SB subjects ($p < 0.001$). Since SB was well tolerated, the authors concluded a protective role for SB in CKD. Caravaca-Fontán et al. [57] finally performed a retrospective, observational cohort study in bicarbonate-treated adult patients with CKD stage 4–5; 969

subjects were included. The mean GFR was 14.8 ± 4.5 mL/min/1.73 m^2. Initially, 530 patients (55%) had a serum bicarbonate of <22 mEq/L, and satisfactory correction of MA was achieved in only 133 patients (25%). Nevertheless, patients in which MA was successfully corrected showed slower CKD progression. A very recent study observed protective effects of bicarbonate in children also [58].

Bicarbonate and non-CKD-related end points. Further studies showed beneficial effects of oral bicarbonate on non-CKD-related end points also: Bellasi et al. [59] (improved insulin sensitivity), Disthabanchong and Treeruttanawanich [60] (better thyroid function in non-dialysis requiring CKD), and Jeong et al. [61] (improved malnutrition). Kendrick et al. [62] convincingly demonstrated that bicarbonate treatment significantly improves vascular endothelial function in CKD patients stages 3b and 4. The question whether bicarbonate treatment results in reduced mortality of CKD subjects is difficult to answer. Until 2018, it was even hard to decide whether bicarbonate is beneficial in acute MA. The term "beneficial" stands for "reduces mortality." In 2018, however, Jaber et al. [63] published the BICAR-ICU trial, performed in critically ill subjects. Surprisingly, bicarbonate improved survival of AKI patients and reduced the dialysis incidence in affected subjects. Respective large-scale trials in CKD are missing yet.

Since oral bicarbonate is widely in use in CKD patients, one must shortly discuss to which range serum bicarbonate has to be adjusted. There is almost no doubt that alkali therapy should be initiated if bicarbonate decreases to under 22 mEq/L [64]. The latest version of the 2012 published "KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease" recommends this cutoff for treatment initiation also [1]. Most likely, the target level ranges around 24 mEq/L. Whether higher concentrations are harmful or not is still a matter of debate. In the 2013 published CRIC study, the risk for heart failure significantly increased at higher serum bicarbonate (>26 mEq/L) [65]. However, data from the Nhanes III study did not confirm this finding in a consistent manner [66]. Nevertheless, the proposed target level of 24 mEq/L is most likely a reasonable compromise. Finally, physicians need to keep in mind that bicarbonate treatment potentially increases the whole body carbon dioxide load. The amount of CO_2 production, however, depends on various circumstances, particularly on the availability of blood non-bicarbonate buffers such as albumin and hemoglobin [67]. It also needs to be mentioned that bicarbonate, which is typically applied as sodium-containing formulation, potentially increases the whole body sodium load [68].

Dietary intervention. Goraya et al. [39] performed a trial in CKD stage 4 patients with a plasma total CO_2 ($PTCO_2$) level of <22 mM. Individuals were randomly assigned to either daily oral $NaHCO_3$ at 1.0 mEq/kg or fruits and vegetables; the follow-up period was 1 year. The cystatin-based eGFR did not differ between the 2 groups, plasma bicarbonate was nevertheless higher than baseline in both groups, and plasma potassium did not increase in any of the 2 groups. Finally, fruits and vegetables were suggested as effective and safe in CKD-associated cMA. In 2014, Goraya et al. [40] reported on bicarbonate or fruits and vegetables versus SC in CKD stage 3 patients. Both interventional measures stabilized plasma TCO_2, reduced urinary angiotensinogen excretion, and prevented the loss of excretory kidney function. In 2019 [69], the same group performed a prospective, randomized trial in nondiabetic CKD patients with cMA. Interventions were usual care (UC) versus fruits and vegetables (F + V) versus bicarbonate; the follow-up was 5 years. Primary end point was eGFR reduction, and secondary end points were several cardiovascular risk (CVR) indicators. Plasma TCO_2 was higher in bicarbonate and F + V as compared to UC, respectively. In addition, eGFR loss was lower in both treatment groups without any difference between the 2. Fruits and vegetables also lowered the systolic blood pressure, serum LDL, and Lp(a) levels, and increased vitamin K. It was concluded that F + V are advantageous with regard to CVR indicators. Garneata and colleagues [70] evaluated the efficacy of a vegetarian very low-protein diet (VLPD – supplemented with

ketoanalogues of essential amino acids) for reducing the progression of CKD. The study was performed in a prospective, randomized, and controlled manner. Included subjects were nondiabetics; the baseline eGFR was defined with 30 mL/min or lower, proteinuria with <1 g daily. Primary end point was the initiation of dialysis or a 50% eGFR reduction as compared to the baseline. The authors tested VLPD against a conventional low-protein diet over 15 months. By the end of the study, eGFR was lower in conventionally treated patients (VLPD vs. conventional diet 10.8 vs. 15.1 mL/min, $p < 0.01$). In addition, VLPD improved certain metabolic parameters such as serum bicarbonate, serum phosphate, and the prescribed dose of calcium, respectively. In summary, dietary measures may potentially serve as alternative to oral bicarbonate for cMA control. An additional benefit associated with increased intake of fruits and vegetables is the supplementation with water-soluble vitamins.

Veverimer: In 2018, a completely new type of drug was introduced, veverimer [71]. The substance binds protons in the intestinal lumen, thus lowering systemic proton availability. The first reference was published in 2018 [71]. The respective study proved the drug (TRC101) to be safe and effective in correcting cMA. In 2019, 2 articles were published in LANCET [72, 73], reporting the results of trial number NCT03317444 (ClinicalTrials.gov). The study was a multicenter, randomized, placebo-controlled trial with a 40-weeks extension phase. Inclusion criteria were age 18–85 years, eGFR 20–40 mL/min, and serum bicarbonate of 12–20 mM. Patients were randomized to receive either veverimer ($n = 124$; 6 g daily) or placebo ($n = 93$), therapy duration was 12 weeks. In the short-term, veverimer corrected MA in a safe and effective manner; this observation was confirmed after the 40-weeks extension phase. In addition, the drug improved parameters of physical function, both subjectively and objectively. However, further studies must be performed before the drug can be established in the clinical management of cMA on a regular basis. Finally, the costs of the drug are without doubt higher as compared to bicarbonate or dietary interventions.

Conclusions

- The most common cause of cMA is CKD.
- CKD-associated cMA most likely induces a negative protein balance; the exact role on bone metabolism remains uncertain.
- CKD-associated cMA presumably aggravates CKD progression.
- cMA control is recommendable, the serum bicarbonate target level should range around 24 mEq/L.
- Veverimer may be established as future option for cMA control; further systematic data are needed.

Statement of Ethics

Not applicable.

Conflict of Interest Statement

The authors have nothing to disclose.

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Author Contribution

D.P. wrote the manuscript, S.P. corrected the article, and O.R. corrected the article.

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