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IMPACTS OF NUTRITIONAL INVOLVEMENTS FOR METABOLIC ACIDOSIS IN PATIENTS WITH CHRONIC RENAL ILLNESS: ARTICLE REVIEW

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ABSTRACT

Chronic kidney disease represents the predominant etiology of chronic metabolic acidosis. Reduced tubular ammoniogenesis, or the loss of nephron mass, is the main cause of the decrease in the tubular net secretion of protons. Numerous problems related to cMA have been explored recently. These included the breakdown of proteins, decreased production of new proteins, demineralization of bone, inflammation, and the advancement of chronic kidney disease. Foods like cheese, meat, eggs, and grains often increase the amount of acid in the diet, whereas fruits and vegetables (F+V) are thought to produce bases. The most common cause of chronic metabolic acidosis is chronic renal illness. Chronic metabolic acidosis linked to CKD most likely worsens the course of chronic kidney disease. Rather than metabolic acidosis, insufficient hemodialysis is the cause of malnutrition in chronic hemodialysis patients. Patients with kidney disorders can effectively manage metabolic acidosis by increasing their fruit and vegetable consumption and taking oral alkali supplements.

INTRODUCTION

Many people are treated for chronic metabolic acidosis (cMA) in hospitals in the USA and Europe. In contrast to "chronic" in CKD, "chronic" in cMA lacks a clear definition. According to Levin & Stevens (2014), proteinuria must be diagnosed if the underlying problem that affects renal excretory function or results in it lasts for three months or longer. Actually, the most frequent cause of cMA is CKD. The primary reason for the decline in tubular net secretion of protons is decreased tubular ammoniogenesis, or the loss of nephron mass. Furthermore, there is a reduction in the glomerular clearance of organic acid residues.

The cohort of NephroTest showed that the majority of patients with stage 4 CKD had normal blood CO2 content and a positive acid balance. At least in the latter stages of CKD, chronic MA is characterized as normochloremic MA with an increasing anion gap (Vallet et al., 2015; Shawkat et al., 2023). Between 30 and 50% of all CKD patients with a GFR of less than 30 mL/min are thought to be affected by cMA. However, cMA may also develop as a result of other conditions including fasting or insulin-dependent diabetic mellitus. cMA is also linked to primary adrenal

insufficiency, hyporeninemic hypoaldosteronism, and other less frequent causes (Moranne et al., 2009).

Acute MA primarily puts patients at risk for hemodynamic and hyperkalemic consequences, while chronic MA dramatically raises total morbidity over time. Numerous problems related to cMA have been explored recently. These included the breakdown of proteins, decreased production of new proteins, demineralization of bone, inflammation, and the advancement of chronic kidney disease. Not every difficulty has, however, been verified in a planned and prospective way. There is, however, very little question that cMA accelerates the course of CKD. Therefore, it makes sense to regularly give oral bicarbonate to CKD people who have MA (Hamad & Abdulrahman, 2024).

Oral bicarbonate supplements have been used for many years to treat metabolic acidosis and have been proposed as a means of delaying the onset of renal failure. Oral alkali therapy was beneficial in maintaining kidney function and postponing renal failure, according to a recent meta-analysis including 3695 participants. Shi et al. (2022) said that, it had no effect on cardiovascular (CV) events, proteinuria, or all-cause mortality. Notwithstanding these positive outcomes, alkali therapy has been linked to a number of noteworthy adverse effects, such as flatulence, belching, and stomach discomfort, according to clinical trials (Łoniewski & Wesson, 2014).

Acid-base equilibrium is known to be significantly influenced by diet. Foods like cheese, meat, eggs, and grains often increase the amount of acid in the diet, whereas fruits and vegetables (F+V) are thought to produce bases. Prior single-center studies have demonstrated that, in comparison to bicarbonate therapy and standard care, adding base—that is, including F+V into the diet—improves metabolic acidosis, preserves renal function, and lowers indicators of cardiovascular disease (CVD) (Goraya et al., 2013; Goraya et al., 2019).

A 2019 meta-analysis found that there is low to moderate assurance that taking oral alkali or reducing dietary acid can both slow the progression of chronic kidney disease (CKD). Oral alkali, however, has been connected to worse hypertension or requiring antihypertensive medication (Navaneethan et al., 2019). A thorough analysis of the studies on the impact of dietary interventions is still required. The effects of nutritional interventions for metabolic acidosis in patients with chronic renal illness are compiled in this review. The investigation ought to contrast how renal outcomes, acid-base balance, and the associated safety and compliance are affected by increasing dietary base versus decreasing dietary acid.

Chronic Renal Disease Patients' Acidosis in Metabolism

The renal paracrine hormones angiotensin II, aldosterone, and ET-1 are activated in chronic metabolic acidosis, increasing net acid excretion (Wesson et al., 2020). In addition to the ascending limb of the loop of Henle, the distal tubule, the connecting tubule, and the collecting duct (NHE3/NHE2, H+-ATPase, and the proton-potassium (K+) exchange ATPase [H+/K+-ATPase]), these hormones also increase the activity of H+ transporters in the proximal tubule (NHE3 and the proton-translocating ATPase [H+-ATPase]). Ammoniagenesis is accelerated by chronic metabolic acidosis, resulting in ammonia that is titrated to ammonium and removed as net acid. Serum bicarbonate rises as a result of increased urine acid excretion over hours to days, which lowers stored acid (Remer, 2001).

In people with chronic kidney disease (CKD), metabolic acidosis is linked to a quicker deterioration in renal function. Numerous single-center clinical trials have demonstrated that reducing dietary acid or taking oral alkali to treat metabolic acidosis and CKD slows the disease's progression. Some of these studies included measurements of renal hormones and biomarkers, which reveal underlying adaptive mechanisms to correct acidosis. These results lend credence to the theory that acid retention leads to persistently high levels of angiotensin II, aldosterone, and ET-1, all of which exacerbate inflammation and fibrosis. By stimulating complement, ongoing

ammoniagenesis exacerbates this process and can harm renal tissue. Types of metabolic acidosis in CKD are depicted in Figure 1.

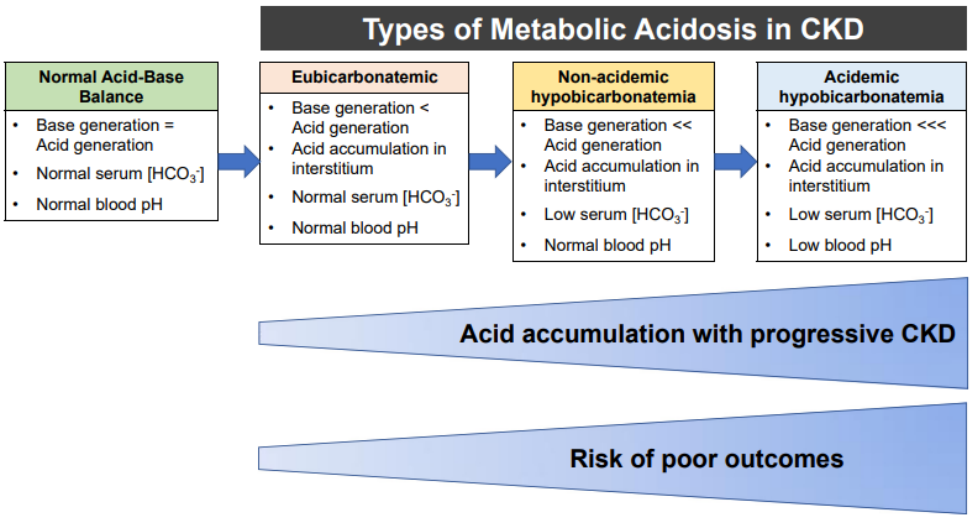

Figure 1. Types of metabolic acidosis in CKD (23)

Complications of Chronic Metabolic Acidosis

Protein catabolism and synthesis: Research by Reaich *et al*. and Ballmer *et al*. provided the first clinical proof of cMA's effects on protein metabolism (Reaich et al., 1992; Ballmer et al., 1995). In the first study, ammonium chloride was given to seven participants who were healthy kidneys for nine days in a row. The following amino acids showed increases in serum levels at the conclusion of this period: leucine, valin, asparagine, serine, and threonine. The results showed that chronic acidosis has catabolic effects on proteins. The second trial used the same methodology but used participants with normal renal function; ammonium chloride was used to induce acidosis once more, and the drug was applied every day for a week.

The rate of albumin production (infusion of 2H5phenylalanine) and the excretion of urea in the urine were the two parameters that were assessed. Both of these were impaired, as seen by elevated urea levels in the urine and decreased albumin production. Rats treated with ammonium chloride displayed a decrease in muscle mass in 1994, according to Mitch and colleagues. Increased intramuscular ubiquitin mRNA levels were seen in acidotic mice, suggesting that the so-called ubiquitin-proteasome system was activated as a result of acidosis (Mitch et al., 1994). In a prospective, randomized, non-blinded, and placebo-free trial involving 134 patients with stage 4 CKD, De Brito-Ashurst *et al*. published their findings. Over the course of two years, oral bicarbonate was assessed against standard care (SC). Following two years of treatment, those receiving bicarbonate had much greater plasma albumin levels.

Nevertheless, a multicenter, randomised, placebo-controlled trial that was published in 2020 was unable to demonstrate that bicarbonate had any positive benefits on bone mineral density or muscle function. Patients in stages 3 and 4 of CKD participated in the trial, which had a 24-month follow-up (Melamed, et al., 2020). According to Bergqvist *et al*., 25 children with refractory epilepsia who were fed an acidotic and antiepileptic ketogenic diet experienced a loss in bone mass. Lefebvre and colleagues conducted biopsy investigations on renal disease, showing that bicarbonate therapy decreased bone resorption in CKD patients.

In recent years, fibroblast growth factor-23 (FGF-23) has gained increased recognition as a crucial regulator in bone abnormalities associated with chronic kidney disease (Silver & Naveh-Many, 2013). Additionally, the medication most likely exacerbates left ventricular hypertrophy in CKD. It should be mentioned that the impact of FGF-23 on the left ventricular myocardium has been questioned. A consistent drop in GFR is associated with rising FGF-23 levels. The idea that FGF-

23 may have detrimental effects on bone metabolism was further supported by research on less frequent disorders such as McCune-Albright syndrome, autosomal dominant and recessive hypophosphatemic osteomalacia, and X-linked hypophosphatemic osteomalacia, respectively. In conclusion, there is some experimental evidence involving CKD linked with cMA to a reduction of bone density. There are no trustworthy clinical studies that genuinely demonstrate bone stability during cMA treatment. It is also necessary to elucidate the precise function of FGF-23 in bone metabolism in acidotic environments.

Dietary Strategies for Treating Metabolic Acidosis in Chronic Kidney Disease

Changing the kind and quality of food is essential for treating chronic kidney disease. The CKD patients have impaired nitrogen waste product and toxin elimination as a result of renal impairment. Dietary protein restriction is the cornerstone of nutritional therapy for CKD patients on conservative therapy. The low-protein diet (LPD) is defined as consuming less than 0.8 g of protein per kilogram of body weight each day and 25–35 kcal of energy per kilogram of body weight per day. LPDs work on the basis that a reduced intake of protein will produce fewer waste products formed from protein and retain fixed acids for a shorter period of timeThe surviving nephron's decreased proteinuria and hyperfiltration slows the course of CKD and, ideally, postpones the initiation of RRT.

An LPD can slow the progression of chronic kidney disease (CKD) by lowering proteinuria, lowering blood pressure, and reversing metabolic acidosis, according to a study conducted in Italy by Bellizzi et al. (2016). There are various types of LPDs. The vegan LPD, for instance, provides 0.6 to 0.7 g/kg of b.w. daily. In order to give patients who are unable or unwilling to ingest protein-free foods the needed amino acids, Cupisti et al. developed the vegan LPD, a low-phosphorus diet based on certain grain and legume combinations. Plant-based foods like grains, legumes, vegetables, and tubers should be a part of a vegan diet.

One must avoid the toxic phosphate additives found in ultra-processed foods made from animals and consume vitamins, fiber, and natural bioactive substances such as antioxidants found in plant-based foods and minor polar compounds (MPCs) found in extra virgin olive oil (EVOO) in order to follow a vegan lifestyle. There are advantages to treating comorbidities linked to chronic kidney disease (CKD), such as metabolic acidosis, arterial hypertension, dyslipidemia, and hyperphosphatemia. Utilizing the alkalinizing properties of a plant-based diet can help minimize metabolic acidosis and its negative effects, especially in people with chronic kidney disease.

Research on How Dietary Factors Affect Metabolic Acidosis in Renal Disease Patients

According to a study done in Basrah, Iraq, 14.5% of 117 patients with metabolic acidosis and CKD stages 3-5 also had severe metabolic acidosis. It was more prevalent in stage 5 CKD (64.7% vs. 35.3%) than in stage 4 CKD. The following conditions were statistically substantially associated with severe metabolic acidosis: glomerular diseases, urinary tract obstruction, anemia, hyperkalemia, hypocalcemia, hyperphosphatemia, and decreased cortical thickness on ultrasonography. Using multivariate analysis, the development of severe metabolic acidosis was predicted by female sex, glomerular abnormalities, and urinary tract obstruction. In another study conducted in Baghdad, Iraq, they concluded that the number, length, and sufficiency of hemodialysis sessions were significantly correlated with the albumin level, and that patients with metabolic acidosis had lower serum albumin concentrations (Razak et al., 2018).

In case-control study done in the University of Al-Qadisiyah, Iraq they established that there is a substantial body of research suggesting that untreated metabolic acidosis is harmful to general health. Patients on maintained hemodialysis (MHD) have an adverse influence on their nutritional status due to metabolic acidosis, as evidenced by an independent and significant association with hypoalbuminemia. In a study conducted in Mosul, Iraq, they found that malnutrition in chronic hemodialysis patients is caused by inadequate hemodialysis rather than metabolic acidosis. In a Korean study they noticed that in Korean predialysis CKD patients, metabolic acidosis was

substantially linked to a rise in renal events and a fast reduction in renal function (Kim et al., 2021).

In another Korean study they stated that oral alkali supplements and increased fruit and vegetable consumption are effective treatments for metabolic acidosis. Previous studies have shown that oral sodium bicarbonate treatment may preserve renal function without significantly increasing blood pressure or body weight. There is currently no research on Veverimer, a polymeric drug that is non-absorbed and counterion-free and is being developed to treat metabolic acidosis. Further research is also necessary to comprehend the target therapeutic range of serum bicarbonate and the drugs used to treat metabolic acidosis.

CONCLUSION

The most common cause of chronic metabolic acidosis is chronic renal illness. Chronic metabolic acidosis linked to CKD most likely worsens the course of chronic kidney disease. Rather than metabolic acidosis, insufficient hemodialysis is the cause of malnutrition in chronic hemodialysis patients. Patients with kidney disorders can effectively manage metabolic acidosis by increasing their fruit and vegetable consumption and taking oral alkali supplements.

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