

Metabolic Acidosis of Chronic Kidney Disease and Cardiovascular Disorders

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ABSTRACT

The burden of chronic diseases, which include both cardiovascular diseases (CVD) and chronic kidney disease (CKD), is constantly growing worldwide. Moreover, bidirectional links between kidney and heart disorders are commonly recognized and the pathogenesis of these interactions is a matter of current interest in medicine. One remarkable aspect, extensively showed by epidemiological studies, is the very high prevalence of CVD in patients with CKD, up to thirty times higher than in the general population. Since the traditional cardiovascular risk factors cannot solely account for this difference, numerous abnormalities due to the decline in glomerular filtration rate were hypothesized to be involved as non-traditional risk factors for CVD. Among them, the metabolic acidosis frequently seen in advanced CKD was studied, but conflicting results were reported. Therefore, we intend to briefly summarize the current knowledge and points of controversy regarding the possible influence of CKD-related chronic metabolic acidosis on cardiovascular diseases.

Keywords: acidosis, bicarbonate, cardiovascular disease, chronic kidney disease, vascular calcifications.

INTRODUCTION

Metabolic acidosis is one of the most common consequences of chronic kidney disease (CKD), and its prevalence increases with the decline in glomerular filtration rate (GFR). The kidney has a central role in maintaining bicarbonate homeostasis by reabsorbing the filtered bicarbonate in the proximal

tubule and synthesizing enough base to neutralize a net acid load (1). The latest allows renal excretion of hydrogen ions either as ammonium or titratable acidity. Thus, the kidney contributes to a normal acid-base homeostasis. When the functional renal mass is reduced, as in CKD, impairment of renal acid handling occurs, leading to acidemia and consumption of bicarbonate in order to buffer the retained acid.

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Recently, the consequences of abnormal acid handling by the kidney in CKD were described as “metabolic acidosis of CKD (MAC)”, which seems to be more fitted than the previously used label of “uremic acidosis”, as metabolic acidosis is not typically accompanied by the clinical manifestation of uremia (1).

Metabolic acidosis of CKD is usually mild to moderate, with a serum bicarbonate (HCO_3^-) level ranging between 12 and 23 mEq/L (2). However, despite its relative lack of severity, it can have an adverse impact on different organs and systems, leading to increased morbidity and mortality (3). For instance, acidosis was involved in the pathogenesis of CKD-related bone disease, aggravation of secondary hyperparathyroidism, protein catabolism, chronic inflammation, resistance to insulin and growth hormone, impaired myocardial contractility and accumulation of β_2 microglobulin (2). In addition, metabolic acidosis was linked to worsening kidney function and CKD progression through multiple mechanisms, like ammonia-induced activation of the alternative complement system due to the increased ammonia generation per nephron, increased endothelin-1 and aldosterone production, all of which can cause tubulointerstitial fibrosis (4). More important, some of these disorders were proved to be alleviated by treating acidosis (Figure 1).

Less straight forward are the relations between metabolic acidosis and cardiac and vascular pa-

thology. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in CKD patients (5). Moreover, CVD begins before end-stage renal disease (ESRD), and patients with reduced renal function are more likely to die of CVD than to develop ESRD (6). There are three CVD conditions which should be considered in patients with CKD: alterations in cardiac geometry, including left ventricular “eccentric” hypertrophy, arteriosclerosis and atherosclerosis (6).

Although the risk of death increases with MAC aggravation, the effect of MAC on cardiovascular disease is subject of debate (7). Thus, in some studies MAC was associated to factors that could induce CVD, like hypertension and chronic inflammation, while in others study, serum bicarbonate was not related to cardiac structural and functional abnormalities (8-10).

It is important to highlight that the type of onset, duration and severity of metabolic acidosis can differently impact on the systemic actions of acid overload, thus explaining the distinct effects that MAC was associated with.

Acute versus chronic metabolic acidosis

The difference between acute and chronic metabolic acidosis is imprecise. In some studies acute metabolic acidosis was defined according to duration, as lasting between minutes to several days (7), while chronic metabolic acidosis has a duration of at least three days or more, though some experts expand the period to weeks and even years (7). On the other hand, the metabolic acidosis could be defined by severity: the acute one is more severe, with a blood pH as low as 6.8, in contrast to the chronic one, where the blood pH is usually above 7.3 and never below 7.2 (11).

Acute metabolic acidosis is quite common among critically ill patients admitted in intensive care units, in one study the disorder affected approximately 64% of these patients (12). In contrast, chronic metabolic acidosis is less common; thus, only 1.9% of more than 15,000 subjects in the NHANES III study had serum bicarbonate concentration below 22 mEq/L, but its prevalence increased to 19% when only the patients with an eGFR in the range of 15 to 29 mL/min were considered (7, 13).

The causes of acute and chronic metabolic acidosis are different. Diabetic ketoacidosis and lactic acidosis are the most frequent causes of

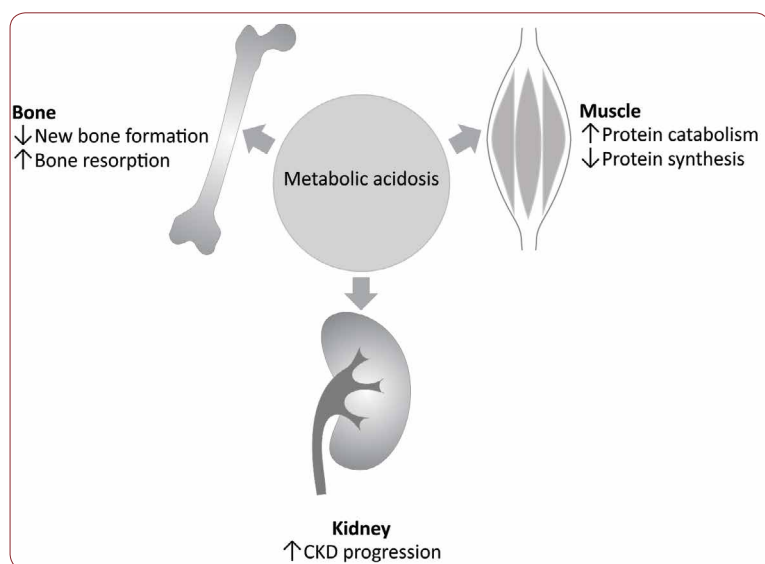


FIGURE 1. Proved consequences of metabolic acidosis in chronic kidney disease. CKD: chronic kidney disease; ↑: increase; ↓: decrease

acute metabolic acidosis, being responsible of more than 85% of cases of severe metabolic acidosis (*i.e.*, blood pH <7.1) (14). Other causes of acute metabolic acidosis include alcoholic ketoacidosis, administration of large amounts of chlorine rich solutions and acute diarrhea (7). In contrast, the most common causes of chronic metabolic acidosis are CKD and different forms of renal tubular acidosis (11). Less frequent encountered disorders that can lead to chronic metabolic acidosis are chronic diarrhea and loss of bicarbonate rich fluids from intestinal fistulae (7).

The severity of acidemia and the length of tissue exposure to a low pH could explain the difference in consequences of acute and chronic acidosis. While acute metabolic acidosis primarily harms the cardiovascular system, chronic metabolic acidosis affects mainly musculoskeletal system and bone (7). Therefore, categorizing metabolic acidosis into acute and chronic may be valuable both to predict the consequences and to guide the management. However, chronic metabolic acidosis was also associated with some factors related to cardiovascular disease, like hypertension and chronic inflammation (8, 15).

Cardiovascular effects of acute metabolic acidosis

Some studies suggest that myocardial depression, decreased catecholamine efficacy, and arrhythmias are favored by acute metabolic acidosis. However, these observations came mainly from experimental studies and were not entirely confirmed in clinical studies.

Decreased cardiac contractility and cardiac output when the pH falls below 7.1 have been shown mostly in experimental models (16). The impairment in cardiac output seems to be pH dependent: when pH is experimentally reduced from 7.4 to 7.2, a catecholamines-induced increase in cardiac output was actually reported. But when the systemic pH is reduced under 7.1, the cardiac output falls (17, 18), as a result of sympathetic system inhibition and of the increased vagal activation by this pH threshold (17). Also, acute metabolic acidosis could reduce contractility by altering intercellular calcium disposition. Interestingly, transient decreases in pH to 6.8 in patients with diabetic ketoacidosis were not associated with depressed cardiac function (19).

Metabolic acidosis might affect vascular smooth muscle cells (VSMC) and endothelial cells. Intracellular metabolic acidosis can transiently alter intracellular calcium disposition and reduce the number of adrenoreceptors on the cell surface (20-21). Furthermore, it can relax VSMC by opening the ATP-sensitive potassium channels (22). Also, acute metabolic acidosis can up-regulate the inducible nitric oxide synthase in endothelium and VSMC, the resulting overproduction of nitric oxide having a direct vasodilator effect (23-24).

Acute metabolic acidosis was involved in the genesis of cardiac arrhythmias. A decrease in systemic pH induces various changes of the cardiac rhythm, globally or in atrial isolated areas. Abnormal repolarization or transient depolarizations in the cardiac Purkinje fibers and depolarization of isolated ventricular myocytes have been also reported. Therefore, ventricular arrhythmias are common in this setting and can lead to sudden cardiac death (25).

Besides the decrease in the systemic pH, acute metabolic acidosis also lowers the interstitial and intracellular pH. Table 1 summarizes the effects of

Receptor/ion channel	Comments
Beta-adrenergic receptor	pH<7.1 decreases catecholamines binding to their receptor (27)
Ca ²⁺ -sensing receptor (CaSR)	The sensitivity of CaSR to Ca ²⁺ is reduced by acidosis (28)
Acid sensing ion channels (ASIC)	ASIC are pH-sensitive channels permeable to Ca ²⁺ and Na ⁺ , expressed on dorsal root sensory neurons ganglion of the heart, implicated in transmission of ischemic pain (29)
Transient receptor potential vanilloid 1 (TRPV1)	TRPV1 are Ca ²⁺ -permeable channels activated at a pH<6; might contribute to myocardial cell death and cardiac arrhythmias (30)
Proton-sensing G-protein coupled receptors	Present in the vascular tissue, half maximal activation at pH of 7.17 releases Ca ²⁺ from intracellular deposits (31)
pH sensitive K ⁺ channels	Alters K ⁺ flux, which contributes to cardiac arrhythmias and hypotension (32)
Na ⁺ -H ⁺ exchanger (NHE1)	Activation by acidosis might contribute to cardiac dysfunction and development of cardiac arrhythmias (33)
Ca ²⁺ : Calcium; Na ⁺ : Sodium; K ⁺ : Potassium; H ⁺ : Hydrogen	

TABLE 1. The effects of acute metabolic acidosis on cardiovascular receptors and ion channels (26)

interstitial and intracellular acidosis on different cardiovascular receptors and ion channels.

Acidosis can also modify hemoglobin delivery of oxygen to tissues, an effect which depends on its duration. As acidosis reduces the affinity of hemoglobin for oxygen (Bohr effect), metabolic acidosis can increase oxygen delivery to tissues. However, a decrease in 2,3-diphosphoglycerate production by the red blood cells also occurs, which increases the affinity of hemoglobin for oxygen. Given that the time-dependent changes in pH and in 2,3-diphosphoglycerate have different effects on the affinity of hemoglobin for oxygen, the final effect will depend on the duration of acidosis (7).

Cardiovascular effects of chronic metabolic acidosis

In contrast to acute metabolic acidosis, the impact of chronic metabolic acidosis on cardiovascular disease has been less studied. Although there is an increased risk of mortality associated with chronic metabolic acidosis, there is no compelling evidence that cardiovascular function is significantly affected. Probably because the acidosis is less severe, the cardiovascular consequences are less pronounced. Furthermore, experimental studies in partially nephrectomized rats suggest that chronic metabolic acidosis might have a protective effect on vascular calcifications.

β_2 -microglobulin accumulation in patients with ESRD contributes to the development of amyloidosis. Most of the amyloid infiltration is seen in the muscle-skeletal system – causing carpal tunnel syndrome, bone cysts and disruptive spondyloarthropathy – and, rarely, even infiltrative cardiomyopathy. Since there is an inverse relationship between serum bicarbonate and β_2 -microglobulin levels in patients with ESRD, metabolic acidosis has been suggested as a potential factor of β_2 -microglobulin amyloid accumulation (34).

Some observational studies reported that metabolic acidosis is a risk factor for hypertension, while one large study found no relationship between acid load and the risk of hypertension. Subjects from the 1999–2000 and 2001–2002 NHANES cohorts in the highest quintile of anion gap had systolic blood pressure higher than participants in the lowest quintile (35). Furthermore, a direct association between the serum anion

gap and blood pressure was reported in non-diabetic patients followed in a multispecialty group practice: every 1 mEq/L higher serum anion gap was associated with a 0.27 and 0.20 mm Hg higher systolic blood and diastolic blood pressure (36). Additionally, a cross-sectional study in Japan showed that the dietary acid load was positively and independently associated with systolic and diastolic blood pressure (37). However, in the Rotterdam study, Engberink *et al* found no evidence of an association between dietary acid load and the risk of hypertension in adults over ≥ 55 years (38).

Inflammation is considered to have an important role in the development and progression of ischemic cardiovascular disease. Interestingly, the production of tumor necrosis factor α by macrophages increased after exposure to a low pH (39). Furthermore, the correction of metabolic acidosis in a small number of peritoneal dialysis patients was associated with a reduction in tumor necrosis factor α levels (40). However, no significant difference was observed in serum levels of C-reactive protein and interleukin-6 in three separate groups of hemodialysis patients with a mean serum bicarbonate of 19.2, 24.4, and 27.5 mEq/L (41).

Recently, Kendrik *et al*, using a randomized crossover design, examined the effect of sodium bicarbonate administration on endothelial function, measured by the brachial artery flow-mediated dilation (FMD). Patients received sodium bicarbonate and usual care for six weeks each, with a two-week washout period in between. FMD was assessed at the beginning and the end of each six-week interval. FMD improved after treatment with sodium bicarbonate, suggesting that the correction of MAC could improve endothelial function (42). However, the mechanism by which sodium bicarbonate treatment improves endothelial function is unclear. Regardless of the reported relationship between metabolic acidosis and increased inflammation, which results in endothelial dysfunction, the authors did not find any significant changes in inflammation during treatment (42). Moreover, the authors found no relation between the markers of bone turnover or bone formation and FMD (42).

Metabolic acidosis enhances the production of catecholamines, endothelin-1 and aldosterone, all of which can contribute to changes in left ventricular mass and geometry (43). The as-

sociation between serum bicarbonate and left ventricular hypertrophy, left ventricular mass indexed to height, left ventricular geometry, ejection fraction and diastolic dysfunction were assessed in 3,483 participants without NYHA class III/IV heart failure, enrolled in the Chronic Renal Insufficiency Cohort study (9). In univariate analysis, patients with low serum bicarbonate were more likely to have left ventricular hypertrophy and abnormal left ventricular geometry. However, in multivariate analysis this association vanished after adjustment for clinical factors (9). Thus, the association between serum bicarbonate and heart disease could be either confounded or mediated by other traditional cardiovascular risk factors (9).

CKD patients develop arterial media calcification, a process in which a serum phosphate-driven phenotypic conversion of VSMC to osteoblasts, mediated by the sodium-dependent phosphate co-transporter Pit-1 (essential for vascular smooth muscle cells transdifferentiation into osteoblasts), was claimed. Because metabolic acidosis promotes bone dissolution by rising hydroxyapatite solubility, increases osteoclasts activity and suppresses the bone formation by osteoblasts, it could have similar effect on VSMC. Metabolic acidosis seems to inhibit the trans-differentiation of VSMC by preventing the up-regulation of Pit-1 (44). Furthermore, metabolic acidosis has been reported, in cultured rat osteoblasts, to inhibit the production of collagen, to down-regulate alkaline phosphatase and to up-regulate matrix-Gla protein (an inhibitory protein of vascular calcification) (45-46). Thus, even if VSMC trans-differentiate into osteoblast, the ability to produce bone-like tissue is hampered.

In line with these considerations, our group reported some potential beneficial effects of metabolic acidosis on vascular calcifications in non-dialysis CKD patients. We conducted a prospective cross-sectional study on 95 clinically stable stage 3b+ CKD patients (median age 61 (58, 65) years, 60% male, median eGFR 27 (22, 32) mL/min) in which we evaluated the relationship between serum bicarbonate and non-invasive markers of CVD. In univariate

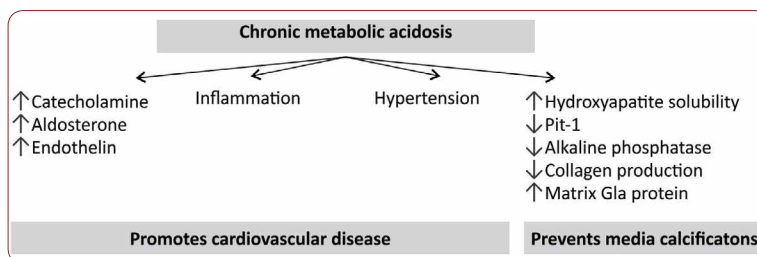


FIGURE 2. The ambivalent effect of chronic metabolic acidosis on cardiovascular disease (explanations in text). Pit-1: sodium-dependent phosphate co-transporter 1; ↑: increase; ↓: decrease

analysis, acidotic patients had lower intima-media thickness, cardio-ankle vascular index, abdominal aortic calcification score (Kauppila score) and higher ankle brachial index. Moreover, the absence of MAC was retained as an independent predictor of abdominal aortic calcifications after adjustments for traditional and non-traditional cardiovascular risk factors (47). Accordingly, MAC seems related to the extent of medial calcifications in CKD patients.

Therefore, chronic metabolic acidosis effect on cardiovascular disease seems to be ambivalent: it could promote cardiovascular disease through increased production of key hormones and aggravation of inflammation and hypertension, while on the other hand it could prevent vascular disease acting as a vascular calcification inhibitor, since the process of arteriosclerosis recapitulates osteogenesis (Figure 2).

Metabolic acidosis of CKD contributes to several important complications of CKD, and studies favoring its therapy are steadily increasing. However, a conclusive randomized multicentric clinical trial is still lacking. Furthermore, given the significant burden of cardiovascular disease in the CKD population, most of it incompletely understood, the relationship between chronic metabolic acidosis — and its treatment — to cardiovascular disease risk is of great interest. Therefore, a randomized trial with cardiovascular endpoints would be an important step forward in clarifying the relationship between metabolic acidosis and cardiovascular disease in patients with CKD. □

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