Chapter 6
Pathophysiologic Approach to Metabolic Acidosis

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Introduction

Metabolic acidosis is a process whereby (1) an excess nonvolatile acid load is placed on the body due to excess acid generation or diminished acid removal by normal homeostatic mechanisms; or (2) bicarbonate is lost from the body [1–4]. While metabolic acidosis is usually suspected when plasma bicarbonate is reduced, the clinician must be aware that metabolic acidosis might be present in a patient with normal or even increased plasma bicarbonate if the metabolic acidosis is part of a mixed acid–base disorder. In addition, subclinical metabolic acidosis can occur when plasma bicarbonate is normal or minimally reduced. This type of metabolic acidosis is known as eubicarbonatemic metabolic acidosis [1]. It can be viewed as a subclinical form of acidosis that nonetheless has potential morbidity in terms of disturbed bone and/or protein metabolism and possibly enhances progression of chronic kidney disease (CKD).

Plasma Chloride and the Plasma Anion Gap

The presence or absence of hyperchloremia is useful in the evaluation of metabolic acidosis. When plasma chloride is increased and plasma sodium normal, either a chronic respiratory alkalosis or a hyperchloremic metabolic acidosis is present [2]. An arterial blood gas is usually needed to distinguish with certainty between a metabolic acidosis and a chronic respiratory alkalosis. The clinical setting coupled with

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the use of urinary anion gap (UAG) is often sufficient for the proper diagnosis while avoiding the invasive blood gas measurement [3]. Calculation of the plasma anion gap and evaluation of urinary acid excretion complete the evaluation of metabolic acidosis. The specific types of high and normal anion gap acidosis are discussed in detail elsewhere in this book.

The type of metabolic acidosis present can be initially approached by assessing whether plasma anion gap (AG) is normal or elevated and helps differentiate hyperchloremic metabolic acidosis (normal AG) from high AG metabolic acidosis. Although these categories can overlap the classification is nevertheless very useful to clinicians [3–5]. In a pure hyperchloremic metabolic acidosis, there is an increase in plasma chloride equivalent to the fall in plasma bicarbonate, so that the sum of these two anions remains unchanged [1–3, 5]. An increase in plasma chloride proportional to an increase in plasma sodium usually reflects dehydration. In this case plasma anion gap does not change appreciably [2, 3].

A clinical setting in which the AG may be misleadingly low is hypoalbuminemic states [6–8]. Albumin is negatively charged and makes up a significant portion of unmeasured anions [7]. Therefore, hypoalbuminemia will lead to an underestimation of the size of the AG and potentially to a failure to recognize a clinically important high AG metabolic acidosis. To circumvent this issue, the effect of serum albumin on the plasma AG must be taken into account in the analysis of acid–base disturbances. Figge et al. derived a formula for the plasma AG that takes into account serum albumin, which is based on a mathematical model that has been verified by experiments in vitro [6]. This formula is as follows:

$$\text{Albumin-corrected AG} = \text{AG} + 2.5 \times (4.4 - \text{albumin in g/dl})$$

For each 1-g/dl decrease in serum albumin below 4.4 g/dl, the observed AG underestimates the actual concentration of unmeasured anions by about 2.5 mEq/l. This estimation has been shown to correlate more or less with other formulas that take into account the effect of plasma albumin on the anion gap [3, 7]. An alternative would be to simply accept that hypoalbuminemia leads to a low anion gap and to use this "baseline" anion gap as the basis for comparison with the observed anion gap in an acid–base disorder. For example, if a patient with nephrotic syndrome chronically has an albumin of 2.5 g/dl and the anion gap is typically low around 7 mEq/l, then a current anion gap of 12, though seemingly normal, would constitute an elevated anion gap of 5 units for this patient and should trigger a search for the cause [3].

A low plasma AG is seen in certain IgG myelomas in which the cationic nature of the paraprotein causes a rise in chloride anions in order to balance the protein's cationic charge [8]. In contrast, the plasma anion gap is normal or even increased in multiple myeloma associated with IgA and IgG paraproteins [8]. IgG paraproteins have isoelectric points that are higher than physiologic pH and are positively charged. The converse takes place with IgA paraproteins, which have isoelectric points below physiologic pH. They behave like anions and when present in large concentrations, the anion gap should increase. In IgA myeloma, however, the AG is usually normal as a result of co-existing hypoalbuminemia, which may reduce an

otherwise elevated AG to a normal level. Thus, the interpretation of the plasma AG requires a careful review of all the possible variables that may affect it [3].

An additional limitation with the use of plasma AG occurs in the detection of mixed metabolic acid–base disturbances [9]. The relationship between the increase in the anion gap above normal (ΔAG) and the decrease in serum bicarbonate concentration below normal (ΔHCO_3^-) helps uncover the presence of a mixed acid–base disorders (typically a high AG metabolic acidosis accompanied by either a metabolic alkalosis or a normal AG metabolic acidosis).

Deviations from the presumed 1:1 ratio in this relationship ($\Delta AG/\Delta HCO_3^-$) that is present in a high AG metabolic acidosis have been used to diagnose these complex acid–base disturbances [6, 9]. When the ΔHCO_3^- (using a mean normal value for bicarbonate of 24 mEq/l) exceeds the ΔAG, a normal AG metabolic acidosis co-exists. Conversely, when the ΔAG exceeds the ΔHCO_3^-, a metabolic alkalosis is present in addition to the high AG metabolic acidosis. Several studies, however, have indicated that there is variability in this ratio, such that a deviation from a 1:1 ratio may not necessarily indicate the presence of a co-existing normal AG acidosis or metabolic alkalosis. This is due to the fact that this 1:1 ratio may be transient and/or dependent on the type of metabolic acidosis present [6, 8, 10–12]. Studies involving ketoacidosis or lactic acidosis, as well as rarer causes of organic acid accumulation such as toluene poisoning, showed that ratios either greater than 1 or less than 0.8 (the latter being less common) were observed in the absence of an apparent co-existing metabolic alkalosis or normal AG acidosis [8, 10, 13–18]. This underscores the importance of considering patient history, physical examination, or other laboratory data in accurately defining an acid–base disorder. Nonetheless, the plasma AG, with all the previously mentioned caveats, provides a convenient "starting point" in the evaluation of metabolic acidosis and helps to monitor over time the presumed changes in unmeasured anions responsible for the anion gap such as lactate during therapy for metabolic acidosis in the acute setting.

Acid Excretion by the Kidney in Metabolic Acidosis

Two major components of acid excretion are stimulated as part of the homeostatic response to chronic metabolic acidosis: excretion of acids collectively referred to as "titratable acids" and excretion of ammonium. Excretion of both leads to the formation of "new" bicarbonate [3]. In addition, bicarbonate is also formed from the metabolism of retained organic anions such as citrate which represents potential alkali [19].

Titratable Acids

Metabolic acidosis typically increases acid excretion which prevents further and sustained acidosis and contributes to recovery from this acid–base disorder. Titratable acids are urine solutes that buffer secreted protons (H^+), enabling H^+

excretion without substantial decreases in urine pH (or equivalently, increases in urine free H^+ concentration) [20]. Multiple solutes such as phosphoric acid, sulfuric acid, and creatinine contribute to what is collectively referred to as titratable acid excretion. Phosphate is the predominant component, typically accounting for more than 50 % of total titratable acid [20, 21]. At a typical serum pH of 7.4, approximately 80 % of filtered phosphate is HPO_4^{2-} and 20 % is $H_2PO_4^-$.

Titratable acid excretion in the form of phosphate reflects the amount of filtered HPO_4^{2-} that buffers H^+ secreted in the proximal tubule, loop of Henle, distal tubule, and collecting duct. The proximal tubule is the primary site of phosphate reabsorption and is the nephron location where metabolic acidosis and other acid–base disorders regulate phosphate transport [19]. Acute and chronic metabolic acidosis decrease proximal tubule phosphate reabsorption through a variety of mechanisms including decreased apical plasma membrane Na^+-dependent phosphate transport [22, 23]. Metabolic acidosis decreases luminal pH as a result of decreased filtered bicarbonate load and increased H^+ secretion. Luminal acidification then independently inhibits proximal tubule phosphate uptake causing phosphaturia [24, 25]. Metabolic acidosis also increases PTH release and PTH inhibits proximal tubule phosphate reabsorption, increasing luminal phosphate availability as a titratable acid and thereby promoting urine net acid excretion in response to metabolic acidosis. The effect of metabolic acidosis on FGF 23, another potent phosphaturic hormone, is unclear. A reduction in plasma FGF 23 levels has been reported during chronic metabolic acidosis [26]. This somewhat unexpected finding would lead to decrease in phosphate in urine and less titratable acid excretion. Further research in this area will help clarify the role of FGF 23 with respect to titratable acid excretion.

Acidosis-induced changes in phosphate excretion depend on systemic phosphate availability. When dietary phosphate is restricted, basal phosphate excretion is greatly reduced and the typical increase in urinary phosphate excretion in response to metabolic acidosis is greatly blunted [27]. Changes in extra kidney phosphate metabolism could contribute to increased phosphate availability for excretion as titratable acid. Metabolic acidosis increases small intestine Na^+-dependent phosphate uptake and this is associated with increased expression of both protein and mRNA for the primary small intestinal apical plasma membrane phosphate transporter NaPi-IIb [28]. There is also increased phosphate release from bone in response to both acute and chronic metabolic acidosis [29]. The net effect of these extra kidney effects is to enable changes in urinary phosphate excretion for buffering protons without causing a change in systemic phosphate concentration in response to changes in systemic acid–base status. Nevertheless, the ability to enhance net acid excretion by increasing phosphate and thus titratable acidity is limited. Importantly, increased NH_4^+ excretion provides the major adaptive increase in net acid excretion in response to a chronic acid challenge to systemic acid–base status.

Ammonium (NH_4^+)

Ammonia is produced by almost all kidney epithelial cells but the proximal tubule is quantitatively the primary site for ammoniagenesis. Glutamine is the primary metabolic substrate for ammoniagenesis. An essential initial adaptive response to metabolic acidosis is increased extraction and catabolism of plasma glutamine that occurs predominately in the proximal convoluted tubule [19]. The resulting increase in kidney ammoniagenesis and NH_4^+ transport into the urine accomplish the final excretion of acid by trapping secreted hydrogen ions with NH_3 and forming NH_4^+. Acute onset of metabolic acidosis produces a rapid and pronounced increase in renal catabolism of glutamine [30]. Within 1–3 h, arterial plasma glutamine concentration increases twofold [31] due to increased release of glutamine from muscle and liver [32]. Uptake of glutamine through the basolateral membrane of proximal tubule cell occurs by reversal of the neutral amino acid exchanger LAT 2 and through increased expression of a basolateral glutamine transporter SNAT3. In addition, the transport of glutamine into the mitochondria may be acutely activated [33]. Acidosis enhances gene expression of enzymes involved in glutamine metabolism and gluconeogenesis that leads to production of ammonium and bicarbonate, respectively. Additional responses include acute activation of NHE3 [34]. This process facilitates rapid removal of cellular NH_4^+ and ensures that the bulk of NH_4^+ generated from the amide and amine nitrogens of glutamine is excreted in the urine [35]. Finally, cellular concentrations of glutamate and α-ketoglutarate are significantly decreased within the rat renal cortex [36]. The latter compounds are products and inhibitors of the glutaminase and glutamate dehydrogenase reactions, respectively. The acute increase in renal ammoniagenesis results from a rapid activation of key transport processes, an increased availability of glutamine, and a decrease in product inhibition of the enzymes of ammoniagenesis. Several transport proteins mediate medullary NH_4^+ reabsorption by the thick ascending loop of Henle [37]. The mechanisms that maintain high interstitial NH_4^+ concentrations in the medulla and papilla, thereby limiting NH_4^+ backflux into the systemic circulation, remain elusive. A role of sulfatides in kidney NH_4^+ handling, urinary acidification, and acid–base homeostasis has been recently proposed [38]. In mammals, sulfatides accumulate in the kidney with particularly high concentrations in distal nephron segments and the renal medulla [39]. The major renal sulfatide in humans and rodents is the galactosylceramide(GalCer)-derived SM4s. Sulfatides, most probably by their anionic extracellular charge, are required to maintain high interstitial NH_4^+ concentration in the papilla. This high interstitial NH_4^+ concentration is needed for urine NH_4^+ excretion under basal conditions and during metabolic acidosis [38].

The net effect is that NH_4^+ excretion can increase from its basal level of 30–40 mEq/day to more than 200–300 mEq/day with severe and persistent metabolic acidosis [40–42]. This marked ability to increase in NH_4^+ excretion contrasts with the more limited ability to increase titratable acid by increasing phosphate excretion due to lack of an increase in plasma phosphate levels with attendant increased phosphaturia.

Citrate

Citrate is an organic anion and serves a dual purpose in the urine. For humans ingesting Western diets that are typically acid-producing, urine in their basal state has a negligible amount of HCO_3^- whereas citrate is the main urine base under these basal conditions (~500 mg/day) [19]. In addition to base excretion, the 1:1 Ca^{2+}:$Citrate^{3-}$ complex has a very high association constant and solubility. These properties make citrate the most effective Ca^{2+} chelator in the urine under basal conditions, thereby preventing Ca^{2+} precipitation with phosphate and oxalate [43, 44]. Consequently, low urine citrate excretion (hypocitraturia) is a major underlying cause of human kidney stones [43].

Urine citrate is in millimolar quantities under basal conditions and regulation of its kidney handling is entirely by the proximal tubule (Fig. 6.1). Reabsorption of filtered citrate occurs in the proximal tubule apical membrane by NaDC1 (SLC13A2), an Na1-dependent dicarboxylic acid co-transporter [45]. Although citrate is in equilibrium between its divalent and trivalent forms in the proximal tubule lumen, its divalent form ($citrate^{2-}$) is the transported species. Once it is absorbed from the proximal tubule lumen, citrate can be metabolized by cytoplasmic ATP citrate lyase to oxaloacetate and acetyl-CoA or shuttled into the mitochondria to enter the citric acid cycle [46]. When $citrate^{2-/3-}$ is converted to CO_2 and H_2O, 2 or 3 H^+ are consumed. Therefore, each milliequivalent of citrate excreted in the urine is tantamount to 2 or 3 OH^- loss [44].

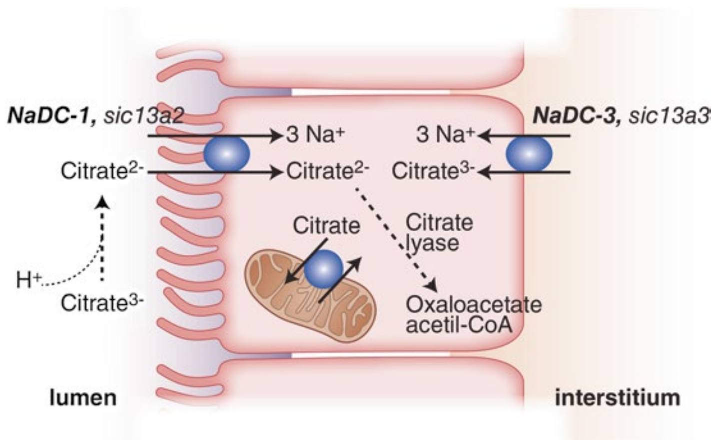

Fig. 6.1 Scheme for the metabolism of citrate in a proximal tubule cell. The carrier NADC-1 of apical membrane reabsorbs the bivalent citrate. In conditions of acidosis the presence of H^+ in the proximal tubule fluid stimulates the formation of citrate bivalent from trivalent. The divalent citrate is reabsorbed and metabolized by citrate lyase or through the tricarboxylic acid cycle in the mitochondria of proximal tubular cells. NADC-1 (SLC13A2) = Na-dependent low affinity carrier of dicarboxylic acids. NADC-3 (SLC13A3) = Na-dependent high affinity carrier of dicarboxylic acids. Modified from Dogliotti et al. *Journal of Translational Medicine* 2013 11:109. doi:10.1186/1479-5876-11-109

With metabolic acidosis there is an adaptative increase in citrate uptake and metabolism within the proximal tubule, reducing urine base excretion. In this way citrate retention provides a compensatory mechanism for metabolic acidosis. This adaptative increase in citrate reabsorption occurs by multiple mechanisms [19]. Acidification of lumen pH titrates citrate^{3-} to citrate^{2-}, the latter being the preferred substrate for transport across the proximal tubule as discussed. In addition, low pH directly activates NaDC1 to increase transport independent of divalent citrate [47, 48]. In addition to enhanced citrate transport, increased cellular metabolism also drives citrate reabsorption. After cellular uptake, citrate is metabolized through one of two pathways: a cytoplasmic pathway involving citrate lyase or a mitochondrial pathway involving the citric acid cycle [46] (Fig. 6.1).

During metabolic acidosis, the cytoplasmic citrate lyase and mitochondrial aconitase activities also increase [49]. Because both pathways generate HCO_3^-, increased citrate reabsorption is equivalent to a decreased base excretion that leads to decreased urine citrate concentration and pH, the latter being a tubular milieu favoring kidney stone formation [19, 50]. Consequently, this adaptive response to mitigate metabolic acidosis comes at the cost of increased risk for kidney stones and helps explain the increased stone risk in states characterized by chronic metabolic acidosis such as renal tubular acidosis [51, 52].

Net Acid Excretion

The traditional formula for net acid excretion is as follows:

$$\text{Net acid excretion} = U_{NH_4^+} + U_{\text{Titratable acid}} - U_{HCO_3^-}$$

To more comprehensively describe the kidney role in acid–base balance using the urine net acid excretion formula, it is necessary to include the portion of daily dietary alkali load that is excreted in the form of organic anions which can be metabolized to HCO_3^-. Thus, urine excretion of organic anions represents loss of potential HCO_3^- [53]. A formula for net acid excretion that would take this into account is as follows:

$$\text{Revised net acid excretion} = (U_{NH_4^+} + U_{\text{Titrated acid}}) - (U_{HCO_3^-} + U_{\text{Potential } HCO_3^-})$$

In normal subjects urine pH is approximately 6.0 for the majority of measurements performed during a 24-h period [54]. This suggests that the urine contains little HCO_3^- and therefore $U_{HCO_3^-}$ can be considered negligible at this urine pH. Rather than increasing HCO_3^- excretion, dietary alkali is converted initially to HCO_3^- in the liver and is then titrated through the production of organic acids such as citrate. Under normal conditions, approximately 40 % of NAE is in the form of TA and 60 % is in the form of ammonia; urine HCO_3^- is essentially zero and urinary organic anions such as citrate represent the main mode of base excretion. During metabolic acidosis and with chronic acid loads there is also a decrease in the base excretion

such as citrate and other organic anions [55, 56]. It should therefore be noted that a low level of citrate excretion may be a clue to the presence of subclinical or eubicarbonatemic metabolic acidosis. Since urine HCO_3^- is typically low under most basal conditions, low urine citrate might better reflect adaptation to subtle metabolic acidosis than urine HCO_3^-. Ideally, all components of net acid excretion should be part of the evaluation of metabolic acidosis.

Implications for Alkali Therapy

Traditionally, alkali therapy has been reserved for patients with acute or chronic metabolic acidosis. The primary purpose in treating chronic metabolic acidosis associated with CKD has been to prevent morbidities related to bone disease, improve the nutritional status, and prevent muscle protein breakdown [1–4, 57]. These goals are themselves very good reasons to use alkali therapy in the CKD population with chronic metabolic acidosis. Data from animal and observational studies in patients with non-dialysis dependent CKD also suggest that lower serum HCO_3^- concentrations are associated with a higher risk of progressive kidney function loss [58–60]. Additionally, data from non-dialysis CKD patients has shown association of higher HCO_3^- levels (>22–24 mmol/l) with lower mortality and improved kidney and overall survival outcomes [60–62]. The reason for the association between metabolic acidosis and more rapid progression of CKD is not clear but it seems logical to postulate that the need to excrete the daily dietary acid load in CKD promotes an adaptive increase in NH_4^+ excreted per nephron. This may be associated with activation of the complement system, the renin–angiotensin system, and with increased renal production of endothelin-1, all of which may produce tubulointerstitial inflammation and chronic kidney damage [63, 64]. Small randomized trials have hence been conducted and have shown benefits of alkali therapy on slowing CKD progression [61–64]. Dietary acid reduction and alkali-based diets of fruits and vegetables also hold promise as a kidney-protective strategy in CKD management [64].

These recent findings will hopefully foster more research on the potential of alkali-based therapies, the optimal dose, and the time of initiation in the management of the various stages of CKD [65]. Clearly, proper attention to metabolic acidosis and its recognition even in subclinical stages offer opportunities for therapeutic intervention for CKD.

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