Review article

The role of metabolic acidosis in chronic kidney diseases

James C. M. Chan

Department of Pediatrics, University of Vermont, The Barbara Bush Children's Hospital, Maine Medical Center, Portland, Maine 04102-3175, USA.

Background and objectives: This review focuses on three areas, basic acid-base physiology especially concerning hydrogen ion balance, development of acidosis in chronic kidney disease (CKD), and the consequences of acidosis. We highlight what is well established, what is less certain, and what is unknown.
Method and results: The literature on acidosis in CKD were searched from 2004 to 2010 utilizing PubMed, Google Scholar, and Ovid to augment the classic work on acid base physiology over the past three decades. The original research in endogenous acid production and net acid excretion were reviewed. Touching upon the development of metabolic acidosis in CKD, we focused on the consequences of chronic metabolic acidosis on growth and other important variables. Finally, we recognize the significant issue of patients' medical non-compliance and presented treatment strategy to counter this problem.
Conclusion: The correction of acidosis in chronic kidney disease needs no advocacy. The case is made conclusively. Patient non-compliance because of the medication that needs to be taken several times a day is a problem, requiring due diligence.

Keywords: Bicarbonate therapy, chronic kidney disease, growth retardation, metabolic acidosis, net acid balance, non-compliance

In this review, we focused primarily on three areas: 1) basic acid-base physiology especially concerning hydrogen ion balance, 2) development of acidosis in chronic kidney disease (CKD), and 3) the consequences of acidosis. We highlighted what is well established, what is less certain, and what is unknown. We searched the literature on acidosis in CKD, and reviewed the original research in endogenous acid production and net acid excretion. We touched upon the development of metabolic acidosis in CKD and the consequences of chronic metabolic acidosis on growth and other important variables. We recognized patient non-compliance and presented treatment strategy to counter this problem.

Acid-base physiology

It is well established that the body pH is vigorously defended [1]. Any hydrogen ions (from endogenous catabolism or exogenous consumption) are neutralized immediately by extracellular and intracellular buffers, to minimize any change in body pH and optimize enzyme functions [2].

In the plasma, the buffers are protein, phosphate, and bicarbonate [3]. Inside the erythrocytes the buffers are: hemoglobin, phosphates and bicarbonate. Because bicarbonate (HCO_3) is present in extracellular fluid and intracellular fluid, that is easily diffusible and measured as total CO_2, its plasma concentration is useful clinically to denote the acid-base status of blood.

Ketoacids and other metabolizable acids are oxidized to CO_2 and exhaled by the lungs. The non-metabolizable acids, the so called fixed acids or net acids, are excreted by the kidneys. Thus, the lungs and the kidneys are the primary organs charged with the control of acid-base balance, second only to the blood buffers.

The kidneys handle this important function by two mechanisms [4]. The first component of net acid excretion is the titratable acid (TA), which is formed by filtered phosphate combining with secreted hydrogen ions to form dihydrogen phosphate. The second component of net acid excretion is derived

Correspondence to: James C. M. Chan, M.D., The Barbara Bush Children's Hospital, Maine Medical Center, 22 Bramhall Street, Portland, Maine 04102-3175, USA. Email: chanj@ suscom-maine.net

from the action of glutaminase on glutamine to form ammonia (NH_3) that combines with secreted hydrogen ion to form ammonium (NH_4). The sum of TA plus NH_4 is the net acid excretion.

Endogenous acid production

What is well established is that subjects on a normal diet, the net acid excretion is equal to 70 mEq/day. The endogenous acid production is presumed to be 70 mEq/day to arrive at net acid balance of zero in the steady state [5]. With renal insufficiency, net acid excretion is diminished. Hence the net acid balance becomes positive leading to the development of metabolic acidosis of chronic kidney disease [6, 7].

The extensive research into endogenous acid production, from intermediary metabolism by Relman et al. is beyond the scope of this article. Interested investigators are referred to their classic papers [5-7].

Development of metabolic acidosis in chronic kidney disease

It may be crucial to know when to intervene with bicarbonate therapy by finding out at what stage of CKD metabolic acidosis is encountered [8].

To answer this question (**Fig. 1**), we studied a number of children in our practice with different degrees of impairments of glomerular filtration rate (GFR). Metabolic acidosis, defined as total CO_2 less than 21 mEq/L, is presented in the vertical axis in **Fig. 1**. It is easy to discern that at GFR of 25% or less, metabolic acidosis will be inevitably and consistently encountered. In fact, after the GFR is reduced by 50%, metabolic acidosis is encountered in many patients.

Evidence to date on the body's mechanisms of defense against disturbances of acid-base balance can be summarized as follows [3, 4]:

- First line of defense: blood buffers and exhalation of CO_2 via the lungs. Hence, the blood and the respiratory systems are the first line of defense.
- Second line of defense: renal net acid excretion. When chronic kidney disease compromises renal function to less than 25% of normal GFR, renal net acid excretion cannot adequately compensate for the endogenous acid produced and the serum CO_2 consistently drops below normal [8]. Hence, the kidneys are the second line of defense.
- Third line of defense: skeletal buffering of hydrogen ions. It has been calculated that the skeletal system contains a large reservoir of 40,000 mEq of alkali. This becomes the last line of defense but this skeletal buffering of acidosis carries considerable consequences [2].
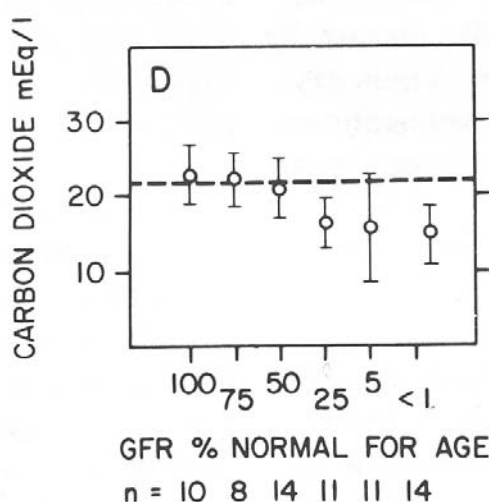

Fig. 1 The onset and progressive severity of metabolic acidosis (as represented by the serum carbon dioxide content of less than 21 mEq/L) in relationship to the fall in glomerular filtration rate (GFR) in chronic kidney disease in a number (n) of children. Metabolic acidosis becomes persistent after the GFR is at or below 25% of normal. From Chan JCM, Goplerud JM, Papadopoulou ZL, Novello AC [8]. (Data was reproduced by the author since the journal has ceased to exist).

Consequences of chronic acidosis on calcium metabolism

What are the consequences of skeletal buffering of chronic acidosis? This is best illustrated by Rodrique-Sorino's classic study [9] on children with renal tubular acidosis. While on bicarbonate treatment, the patients had serum bicarbonate at or better than 21 mEq/L and normal calcium excretion at or less than 4 mg/kg body weight per day. When bicarbonate therapy was discontinued, the plasma bicarbonate concentrations dropped to 8 mEq/L, with a corresponding rise in urinary calcium excretion to and higher than 10 mg/kg/day. Thus, the severe hypercalciuria of worsening acidosis is powerfully illustrated. To reiterate, urinary calcium excretion is normally less than 4 mg/kg/day, in untreated (or undiagnosed) renal tubular acidosis, it can go up to and beyond 10 mg/kg/day [9].

Furthermore, a few years ago, Norman et al. [10] demonstrated that renal tubular acidosis is characterized by low citrate excretion. In children with renal tubular acidosis, the hypocitratuia coupled with hypercalciuria, increase the risk of nephrocalcinosis. This risk is described in report of a four years old female who presented to our medical center [11]. At the Emergency Room where we first saw her for nausea and vomiting, her tachypnea and extreme pallor was noted. Severe nephrocalcinosis was found. Kidney biopsy showed end-stage kidney from sclerosis and interstitial nephritis. Few renal tubules were left. However, the kidney size was normal on X-ray of the abdomen. The massive microscopic calcium depositions prevented the kidney from shrinking. Short stature was noted from two years ago, which originally brought her to a local pediatrician. The dysuria and microscopic hematuria was thought to be due to urinary tract infection, for which a course of antibiotics was given. No further work up was done.

However, not all hypercalciuria gives rise to nephrocalcinosis or to this degree of destruction. As shown in the classic volume on Calcium Metabolism by Nordin [12], the highest calcium excretion in mg/day is not in renal tubular acidosis but in patients with immobilization, renal stone formers, and hyperparathyroidism. It should be recognized that without the acidosis-induced hypocitraturia as in renal tubular acidosis [11], patients with the other conditions are at lesser risk of nephrocalcinosis [12].

It is important to recognize that citrate is a calcium chelator that promotes solubility of urinary calcium. The reverse promotes nephrocalcinosis. The combination of hypercalciuria and hypocitraturia significantly increases the risk of nephrocalcinosis in renal tubular acidosis.

Hypercalciuria, calcium and vitamin D

National Aeronautics and Space Administration (NASA) has an interest on calcium and vitamin D metabolism because of the significant hypercalciuria in astronauts in zero-gravity over any period of time. They tried exercise to reduce this risk. It is unknown if the human skeletal system can last the years of travel in zero gravity on journeys to distant planets. Because of this, NASA has an interest in the hibernating animals' net acid balance and on bone buffering of endogenous acid production from intermediate metabolism.

How acidosis affects calcium and vitamin D is exceedingly complex. Early experiments by Lee et al. [13] showed a drop in serum 1,25 dihydroxyvitamin D in rats made acidotic by ammonium chloride (NH_4Cl) in their drinking water. This observation was confirmed by subsequent studies. However, in children with renal tubular acidosis, Chesney et al. [14] showed no suppression of serum 1,25 dihydroxyvitamin D. However, the degree of acidosis was rather mild in this cohort of children. Finally, Weber et al. [15] showed no suppression of 25 hydroxyvitamin D in volunteers made severely acidotic with NH_4Cl.

Interestingly, the most recent addition to this research is the study from Krapf et al. [16] showing that acidosis stimulates 1,25 dihydroxyvitamin D production. Human volunteers were made acidotic with high dose NH_4Cl resulting in serum total CO_2 dropping below 14 mEq/L. The rise of 1,25 dihydroxyvitamin D was related to the rise in urinary phosphate excretion, the fractional excretion of phosphate and the drop in serum parathyroid hormone concentrations. In contrast, with half dose NH_4Cl, the drop in serum total CO_2 was milder, and the serum 1,25 dihydroxyvitamin D was not much different from control. This latter observation, fits in well with Chesney et al's [14] earlier observation of mild acidosis. The strength of Krapf et al's innovative study [16] is to focus attention on how significant acidosis affects phosphate and parathyroid hormone activities, which were inadequately examined in previous studies on the interactions between acidosis and calcium/vitamin D metabolism. However, the question remains concerning the mechanisms by which this small degree

of difference in acidosis can so significantly bring about such big differences in phosphaturia and suppression of parathyroid hormone. Further studies are warranted.

At this point, we are dealing with somewhat contradictory results between human and animal studies, which simply remind us how complicated the relations are between acidosis, vitamin D, calcium, phosphate, and parathyroid hormone. At this time, we are certain about some aspects of skeletal buffering. However, it is impossible to make any conclusions about vitamin D metabolism in acidosis.

Acidosis on increased protein catabolism (proteolysis)

Mitch el al. [17-19] and others significantly advanced our understanding of the protein catabolism (proteolysis) in acidosis. Insulin deficiency and insulin resistance [20] in CKD result in elevated glucocorticoid production [21]. Glucocorticoids promote acidosis-induced proteolysis. Proteolysis is proportional to the degree of acidosis and blood cortisol concentrations. CKD increases muscle protein degradation [18, 19]. Children with CKD demonstrate nitrogen balance improvement with correction of acidosis. Infants with low birth weight are acidotic and treatment with bicarbonate improves their linear growth [19].

Acidosis and growth retardation

Aside from skeletal buffering and muscle wasting, pediatric nephrologists are constantly concerned with growth failure, the major consequence of acidosis in children with chronic kidney insufficiency [22]. What is well known are studies such as those of Abitbol et al. [23] regarding poor nutritional intakes inhibiting growth in children with chronic kidney disease. What is less well known are the studies that acidosis inhibits growth hormone secretion [24] and in gene expressions of insulin-like growth factor (IGF) and growth hormone receptors [25]. These key studies by Challa et al. [24, 25] and Santos et al [26] in our laboratory show control animals fed the same amount of food as the acidotic animals suffer the same inhibition of growth hormone secretion. We conclude that the lack of nutritional intakes in the anorexic animals induce inhibition of growth hormone and gene expression of IGF in plasma, kidneys, and the liver. Such changes in the growth hormone - IGF axis are

the basic mechanisms of the growth failure in children with chronic kidney disease [24-26].

Finally, chronic acidosis decreases thyroid hormone [27] and parathyroid hormone functions [28], which are normalized by correcting the acidosis with hemodialysis [28]. The effects of acidosis on the phosphaturic fibroblast growth factor 23 (FGF 23) and FGF receptors [29-31] remain to be determined.

Treatment of acidosis

The treatment options [32, 33] are bicarbonate solutions (e.g.baking soda). Shohl's solution is Bicitra, which is a bit more palatable with its sodium citrate taste. The dose is 1 to 3 mEq/kg/day, which for a 70 kg person, means 70 ml to 210 mL. Most experts recommend four divided doses per day on the rationale that bicarbonate is excreted rapidly. However, one dose every 6 hours creates a compliance problem [32]. One solution to overcome non-compliance is to prescribe the dose two to three times per day but double the doses at morning and nighttime. The large nighttime dose provides additional benefits, as growth hormone is secreted at highest level during sleep [32]. Bicarbonate (baking soda) is inexpensive and even Bicitra is not excessively expensive. Physicians need to prescribe the right amount and not increase the dose if the acidosis is not corrected. He needs to recognize patient non-compliance as a potential cause of not achieving therapeutic results. The physician may need to spend time talking to and working with the patients/parents to encourage compliance.

Summary

We start with an introduced acid-base physiology. We recognized that acidosis is inevitable in CKD after the glomerular filtration rate has fallen to or less than 25% of normal. There is no question about the significant consequences of acidosis in CKD, from the hypercalciuria to the muscle wasting, and to the acidosis induced hormonal responses affecting linear growth. The results overwhelmingly speak for themselves. Finally, we presented a treatment strategy to minimize non-compliance.

Acknowledgement

References

1. Relman AS. The acidosis of renal disease. Am J Med. 1968; 44:706-13.

2. Chan JCM. Nutrition and acid-base metabolism. Federation Proc. 40:2423-8, 1981.

3. Winters RW. The body fluids in pediatrics. Boston: Little Brown and Co, 1973.

4. Chan JCM. Acid-base disorders and the kidney. Adv Pediatr. 1983; 30:401-71.

5. Relman AS, Kurtz I. Milestones in nephrology. Feature editor: M A Knepper. J Am Soc Nephrol. 2000; 11:2155-64.

6. Goodman AD, Lemann J Jr, Lennon EJ, Relman AS. Production, excretion, and net balance of fixed acid in patients with renal acidosis. J Clin Invest. 1965; 44: 495-506.

7. Relman AR, Lennon EJ, Lemann J Jr. Endogenous production of fixed acid and the measurement of the net balance of acid in normal subjects. J Clin Invest. 1961; 40:1621-30.

8. Chan JCM, Goplerud JM, Papadopoulou ZL, Novello AC. Kidney failure in childhood. Int J Pediatr Nephrol. 1981; 2:201-22.

9. Rodriguez-Soriano J, Vallo A, Castillo G, Oliveros, R. Natural history of primary distal renal tubular acidosis treated since infancy. J Pediatr. 1982; 101:669-76.

10. Norman ME, Feldmn NI, Cohn RM, Roth KS, McCurdy DK. Urinary citrate excretion in the diagnosis of distal renal tubular acidosis. J Pediatr. 1978; 92: 394-400.

11. Chan JCM. Renal tubular acidosis: Medical progress. J Pediatr. 1983; 102:327-40.

12. Nordin BEC. Calcium, phosphate and magnesium metabolism. London: Churchill Livingston; 1976.

13. Lee SW, Russell J, Avioli LV. 25 hydroxycholecalciferol to 1, 25 dihydroxycholecalciferol: conversion impaired by systemic metabolic acidosis. Science. 1977; 195: 994-6.

14. Chesney RW, Kaplan BS, Phelps M, DeLuca HP. Renal tubular acidosis does not alter circulating values of calcitriol. J Pediatr. 1984; 104:51-5.

15. Weber HP, Gray RW, Dominguez JH, Lemann J Jr. The lack of effect of chronic metabolic acidosis on 25-hydroxyvitamin D metabolism and serum parathyroid hormone in humans. J Clin Endocrinol Metab. 1976; 43:1047-55.

16. Krapf R, Vetsch R, Vetsch W, Hulter HN. Chronic metabolic acidosis increases the serum concentration of 1, 25 dihydroxyvitamin D in humans by stimulating its production rate. Critical role of acidosis-induced renal hypophosphatemia. J Clin Invest. 1992; 90: 2456-63.

17. Mitch WE, Medina R, Grieber S, May RC, England BK, Price SR, et al. Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. J Clin Invest. 1994; 93:2127-33.

18. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome system. N Engl J Med. 1996; 335:1897-905.

19. Rajan VR, Mitch WE. Muscle wasting in chronic kidney disease: the role of the ubiquitin proteasome system and its clinical impact. Pediatr Nephrol. 2008; 23:527-35.

20. Mak RH. Effect of metabolic acidosis on insulin action and secretion in uremia. Kidney Int. 1998; 54:603-7.

21. Schambelan M, Sebastian A, Katuna A, Arteaga E. Adrenocortical hormone secretory response to chronic NH_4Cl-induced metabolic acidosis. Am J Physiol. 2001; 252:E454-60.

22. Salusky IB, Kuizon BG, Juppner H. Special aspects of renal osteodystrophy in children. Sem Nephrol. 2004; 24:69-77.

23. Abitbol CL, Warady BA, Massie MD, Baluarte JH, Fleischman LE, Geary DF, et al. Linear growth and anthropometric and nutritional measurements in children with mild to moderate renal insufficiency: a report of the growth failure in children with renal diseases study. J Pediatr. 1990; 116:S46-54.

24. Challa A, Krieg RJ Jr, Thabet MA, Veldhuis JD, Chan JCM. Metabolic acidosis inhibits growth hormone secretion in rats: mechanism of growth retardation. Am J Physiol. 1993; 265:E547-53.

25. Challa A, Chan W, Krieg RJ Jr, Thabet MA, Liu F, Hintz RL, et al. Effect of metabolic acidosis on the expression of insulin-like growth factor and growth hormone receptor. Kidney Int. 1993; 44:1224-7.

26. Santos F, Chan JCM, Krieg RJ, Niimi K, Hanna JD, Wellons MD, et al. Growth hormone secretion from pituitary cells in chronic renal insufficiency. Kidney Int. 1992; 41:356-60.

27. Brungger M, Hulter HN, Krapf R. Effect of chronic metabolic acidosis on thyroid hormone homeostasis in humans. Am J Physiol. 1997; 272:E648-53.

28. Graham KA, Reaich D, Channon SM, Downie S, Goodship TH. Correction of acidosis in hemodialysis patients increases the sensitivity of the parathyroid glands to calcium. J Am Soc Nephrol. 1997; 8:627-31.

29. Gattineni J, Bates C, Twombley K, Dwarakanath V, Robinson ML, Goetz RM, et al. FGF23 decreases

renal NaPi-2a and NaPi-2c expression and induces hypophosphatemia in vivo predominantly via FGF Receptor 1. Am J Physiol. 2009; 297:F282-91.

30. Gutierrez OM, Mannstadt M, Isakova T, Rauh-Hain JA, Tamez H, Shah A, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. New Engl J Med. 2008; 359:584-92.

31. Hsu C. FGF-23 and outcomes research - when physiology meets epidemiology. New Engl J Med. 2008; 359: 640-2.

32. Chan JCM, Scheinman JI, Roth KS. Renal tubular acidosis. Pediatr Rev. 2001; 22:277-86.

33. Futrakul N, Sila-asna M, Futrakul P. Therapeutic strategy towards renal restoration in chronic kidney disease. Asian Biomed. 2007; 1:33-44.