

Alkali Therapy In Renal Tubular Acidosis: Who Needs It?

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Pines and Mudge (1) coined the term “renal tubular acidosis” (RTA) to denote a renal tubular disorder that causes acidosis by restricting the reduction of urinary pH and thereby the titration of urinary buffers and excretion of acid. In extensive earlier studies of this “specific form of renal acidosis,” which is now termed “classic” or “type I RTA,” Albright *et al.* (2) demonstrated that metabolic acidosis induces hypercalciuria and consequent negative calcium balance and recognized that over time these are critical and alkali-reversible pathogenic determinants of nephrocalcinosis and nephrolithiasis and of “osteomalacia and late rickets.” The acidosis of type I RTA may also give rise to osteoporosis (3) and to other disorders of bone demineralization (4). In children with classic RTA, alkali therapy can heal osteopenia and induce normal somatic growth, even after severe stunting (5–7), but apparently only when given in amounts that sustain full correction of acidosis. These amounts must be great enough not only to titrate endogenously produced nonvolatile acid but also to offset renal bicarbonate wasting that characterizes the classic RTA of children in whom bicarbonate therapy has induced rapid growth (6,8). Lesser amounts of alkali and the consequent plasma bicarbonate concentrations of low-grade metabolic acidosis have been found to be unavailing with respect both to the attainment of normal growth and the correction of hypercalciuria (5).

These observations prompt a series of questions about the pathogenic potential of chronic low-grade metabolic acidosis in adults, their possible benefit from its treatment with alkali, and the kind of alkali that is most availing. In adults with type I RTA that is not fully expressed, can low-grade metabolic acidosis be a pathogenic determinant of clinically important metabolic disease? Nonvolatile acid is endogenously produced at a rate that can exceed the capacity of the normal kidney to excrete it (9,10), and such excessive acid is buffered by bone at the cost of its resorption and demineralization (11,12); can alkali therapy therefore prevent, delay, or reverse either metabolic bone disease or calcium-containing kidney stone formation in those with diet-induced, low-grade metabolic acidosis but neither a recognized form of RTA nor renal failure? If so is alkali therapy best provided to these patients as KHCO_3 because it: induces in normal humans a hypocalciuric effect greater than that induced by NaHCO_3 (13) and one that more

than offsets the hypercalciuric effect of dietary NaCl (14); induces an improved external calcium balance in normal men (13) and women (15); occurs naturally and plentifully in precursory form in fruits and vegetables, *e.g.*, as potassium citrate in which organate *in vivo* is completely converted to bicarbonate? Can realization of the therapeutic potential of alkali therapy depend on the attaining of a metabolically optimal range of plasma bicarbonate that is higher than that comprising its lower “normal” range (5,15,16)?

Metabolic bone disease and hypercalciuric nephrolithiasis would seem to occur frequently in adults with the incomplete syndrome of RTA (iRTA) (17,18), in which a modest impairment of renal acidification like that of type I RTA does not cause frank metabolic acidosis but can give rise to chronic low-grade metabolic acidosis (19,20). The severity and even the occurrence of that acidosis presumably depend not only on the extent to which renal excretion of acid is impaired but also on the rate at which nonvolatile acid is (or is not) generated from the diet. In adult patients with iRTA in whom acidosis was demonstrably absent, Pak *et al.* (21,22) found that alkali therapy with potassium citrate that increased plasma bicarbonate only slightly still corrected hypercalciuria and hypocitraturia, reduced the rate at which kidney stones were formed, increased fractional intestinal calcium absorption, and increased mineral density in the radius. Subsequently, Osther *et al.* (19) reported that biochemical markers of bone formation (serum osteocalcin) and bone resorption (urinary hydroxyproline) were significantly decreased and increased, respectively, in ten kidney stone formers with iRTA but not in 10 without. More recently, Weger *et al.* (20) reported the occurrence of iRTA in 20 or 48 patients referred for evaluation of DXA-documented osteoporosis, only two of whom had either kidney stones or nephrocalcinosis. In each of these two groups of adult patients with iRTA, “mild” acidosis was documented and proposed as a pathogenic determinant of metabolic bone disease; however, a trial of alkali therapy was not reported in either group.

Acidosis enhances osteoclastic activity and inhibits osteoblastic function and hence bone formation (11,12,23–28). Conversely, metabolic alkalosis decreases bone calcium efflux by suppressing osteoclasts and stimulating osteoblasts (29). A third of a century ago, Wachman and Bernstein (30) proposed that acid generated by the modern diet demineralizes bone. Recently, Sebastian *et al.* (15) reported a positive test of this hypothesis. In metabolically controlled studies of healthy postmenopausal women, supplemental KHCO_3 , which increased plasma bicarbonate only slightly to values remaining well within the normal range, immediately and reversibly induced a near abolition of net renal acid excretion. Concomitantly, (1)

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the external balance of calcium and phosphorus improved because of sustained and substantial reductions in their urinary excretion rates, and (2) the urinary excretion of hydroxyproline decreased and the serum concentration of osteocalcin increased. From these observations, the following were concluded: (1) a state of low-grade metabolic acidosis existed immediately before and after KHCO_3 was supplemented; (2) the acidosis resulted from the endogenous generation of non-volatile acid at a rate greater than that at which the kidney could excrete it; (3) the acidosis induced bone resorption and reduced bone formation; (4) the acidosis induced an increased renal loss of calcium and phosphate and thereby negative balances of both; and (5) supplemental KHCO_3 reversed each of these metabolic derangements by fully titrating endogenous nonvolatile acid.

In addition to inducing a reduction in ammonia nitrogen excretion, supplemental KHCO_3 induced a sustained and similar reduction in urea nitrogen excretion in these postmenopausal women (31). These findings suggest that the higher nitrogen excretion rates that occurred before KHCO_3 was supplemented reflect an acidosis-induced nitrogen wasting. Metabolic acidosis induces nitrogen wasting in part by directly increasing the rate of protein degradation in skeletal muscle, which occurs without a commensurate increase in its rate of protein synthesis (32,33).

These experimental observations accord with recent epidemiologic observations that support both “a positive influence of alkaline-forming foods on bone health” and a negative influence of a high net-acid dietary load on the likelihood of fractures (34–37). Accordingly, it seems likely that an increased dietary intake of fruits and vegetables (or supplemental KHCO_3 or both) may prevent or delay the expression of osteoporosis, muscle wasting, and calcium-containing kidney stones by preventing or correcting the chronic, low-grade metabolic acidosis that occurs in older people (38) consequent to some combination of the high net acid-load of the modern diet and the modest non-azotemic impairment of renal acid excretion that attends increasing age (38–41). Such an acidosis-causing impairment might be well-designated “presbynephric” RTA to connote the therapeutic potential of alkali in the increasingly large number of elderly people who are likely to be so impaired by such RTA (39). With the scope of its recognized expression so expanded, the frequency of its consequent occurrence so increasing, and the potential societal benefits of its treatment so enormous (and so inexpensively achieved), RTA may be coming of age as a disorder of public health importance.

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