Differing Effects of Supplemental KCl and $KHCO_3$: Pathophysiological and Clinical Implications

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Compared to the prehistoric diet, the modern human diet contains not only excessive NaCl and deficient K^+, but also deficient precursors of HCO_3^- and sometimes excessive precursors of nonvolatile acid. The mismatch between the modern diet and the still ancient biological machinery of humans subtly but chronically disorders their internal milieu, giving rise to a prolonged state of low-grade potassium deficiency and low-grade metabolic acidosis whose severity increases with age. Supplemental KCl cannot redress this mismatch and correct this state. However, the mismatch is redressed and the state corrected by restoring intakes of K^+ and HCO_3^- to levels approaching those in the diet of our prehistoric forebearers, with either fruits and vegetables or with supplemental $KHCO_3$. So restored, $KHCO_3$ can: 1) attenuate hypertension and possibly prevent its occurrence by suppressing the phenomenon of normotensive NaCl-sensitivity, in part by its natriuretic effect; (2) prevent kidney stones by reducing urinary excretion of calcium and increasing urinary excretion of citrate; (3) ameliorate and protect against the occurrence of osteoporosis by increasing the renal retention of calcium and phosphorus, and by suppressing bone resorption and enhancing bone formation; and (4) likely prevent stroke.

POTASSIUM CHLORIDE has long been the preferred potassium salt given to correct hypokalemia in the clinical setting of hypochloremic alkalosis and persisting chloride depletion.[1] However, it is now clear that supplemental K-citrate, can readily correct the modest to moderate hypokalemia induced by hydrochlorothiazide in the relatively small dosages currently used to treat either hypertension or kidney stones,[2,3] at least in subjects in whom dietary chloride is not severely restricted. K-citrate or $KHCO_3$ can do so without inducing alkalosis.[2,3] In fact, over time, $KHCO_3$ can correct hypochloremic alkalosis and severe hypokalemia when dietary Cl^- is provided at only a modest intake of NaCl.[4]

THE QUESTION

With respect to the optimal choice of a supplemental potassium salt to correct K^+ deficiency, the major public health question today is not whether KCl should be supplemented to expeditiously correct hypokalemia and an attendent hypochloremic alkalosis. Rather, the major question is whether supplemental $KHCO_3$ can prevent or treat diseases of major public health importance by correcting the modern diet's generally unrecognized deficiencies of both potassium and bicarbonate (as bicarbonate-yielding organic anions). The deficiencies are generally unrecognized because they are not usually severe enough to cause either hypokalemia or metabolic acidosis, at least as either is traditionally characterized[5-8] (see below).

THE MISMATCH

The deficiency of K^+ and HCO_3^-, like the excess of Na^+ in the modern diet, must be considered in the context of human evolution.[9,10] The diet of our prehistoric human forebearers contained large amounts of K^+ and HCO_3^--yielding precursors, eg, citrate (from fruits and vegetables, which contain little Cl^-), but little of the then scarce NaCl, 160 to 200 and 40 to 70 mmol per day, respectively. Thus, over millions of years, humans evolved biological machinery to process this prehistoric dietary mix into an internal milieu of electrolytes and alkalinity optimally conducive to biological health. However, in modern times, the mix of minerals in the human diet has changed drastically: K^+ and HCO_3^--yielding substances are now much lower and Na^+ and Cl^- much higher (Fig). In fact, in humans, the prehistoric dietary K^+/Na^+ ratio has become reversed, and in the United States, the extent of that reversal increases with age.[11] Yet, our mineral-processing biological machinery has remained essentially unchanged, ge-

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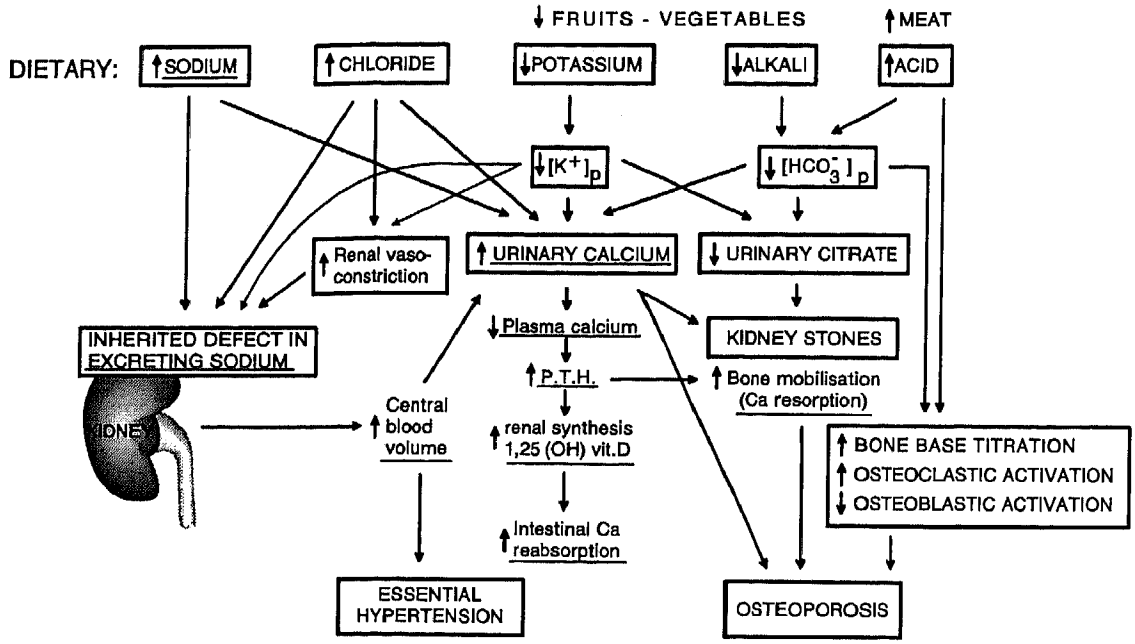

Fig. Hypothesis on the possible links between dietary electrolytes, the kidney, essential hypertension, kidney stones, and osteoporosis: possible roles of excessive dietary sodium, chloride and acid and deficient potassium and alkali. Modified and reprinted with permission from MacGregor and Cappuccio.[13] The underlined dietary determinants and pathogenetic events are those specified in the hypothesis as originally formulated and depicted by these authors. In the formulation shown here, 'osteoporosis' has replaced the original term 'bone demineralization.'

netically fixed in prehistoric time. Thus, the new mix of minerals in the modern diet is profoundly mismatched to our still ancient biological machinery. By chronically disordering the body's internal milieu, this dietary mismatch contributes critically to the expression of such "maladies of civilization"[12] as hypertension, kidney stones, osteoporosis, and stroke.

THE DISEASES

Hypertension

MacGregor and his colleagues[13] have long considered Na^+ to be the major electrolytic pathogen of the modern diet. In a recent article entitled "The Kidney and Essential Hypertension: A Link to Osteoporosis?," they propose that in "salt-replete patients with essential hypertension, a genetic defect in the ability of the kidney to excrete sodium" gives rise not only to hypertension but also to hypercalciuria and a negative calcium balance that leads to the occurrence of both kidney stones and "bone demineralization" (Fig).

In accordance with the hypothesis, MacGregor et al[14] showed some time ago that either restriction of dietary NaCl[14] or supplemental KCl attenuates essential hypertension.[15] All supplemental potassium salts can have an antihypertensive effect because they natriuretically contract extracellular fluid/blood volume,[16] an expansion of which is the only pathophysiological determinant of either hypertension or hypercalciuria identified in the formulation of MacGregor and Cappuccio.[13] (Fig). Yet, whereas supplemental $KHCO_3$ and KCl appear to be similarly natriuretic,[17] the two potassium salts have recently been found to induce opposite effects on the hypertension, stroke, nephropathy, and plasma renin activity (PRA) of the stroke-prone spontaneously hypertensive rat (SHRSP), without inducing detectable differences in urinary excretions of Na^+ or K^+ or in body weight or hematocrit.[18]

In the SHRSP fed a normal NaCl diet, supplementing dietary K^+ with KCl exacerbated hypertension, whereas supplementing either $KHCO_3$ or potassium citrate (KB/C) attenuated hypertension, when blood pressure (BP) was measured radiotelemetrically, directly, and continually. Supplemental KCl, but not KB/C, induced strokes, which

occurred in all and only those rats in the highest quartiles of both BP and PRA. The level of PRA was abnormally high with KCl but not with KB/C, and varied directly with that of systolic BP as a continuous function across all treatment groups. The severity of angiopathic nephropathy varied directly with the levels of systolic BP and PRA as a continuous function across all treatment groups.[19] These observations show that, with respect to severity of hypertension, frequency of stroke, and severity of nephropathy, the phenotypic expression of the SHRSP is: (1) either increased or not, depending on whether the anionic component of the potassium salt supplemented is or is not Cl^-; (2) increased by supplementing Cl^- without supplementing Na^+, and despite supplementing K^+; and hence (3) both selectively Cl^--sensitive and Cl^--determined. The observations suggest that in the SHRSP selectively supplemented with Cl^- the likelihood of stroke and severity of nephropathy depends on the extent to which both BP and PRA are increased by Cl^-.

These results might have been predicted. Selectively supplementing dietary Cl^- can induce and enhance renal vasoconstriction[20] that likely affects the afferent arteriole,[21] possibly by activating the tubuloglomerular feed-back response,[22] which is exaggerated in the stroke-resistant SHR,[23] the strain from which the SHRSP is derived.[24] In the SHR and presumably also in the SHRSP, narrowing of the afferent arteriole may give rise to hypertension.[25] The extent of that narrowing in the SHR varies directly with the severity of its pharmacologically attenuated hypertension.[25] Thus, by augmenting that narrowing in the SHRSP, supplemental KCl might both exacerbate hypertension and increase PRA,[18] angiotensin II, and aldosterone, and thereby induce stroke and exacerbate renal angiopathy,[18] much as might loading dietary Cl^- with NaCl.[26,27]

In a recent study of patients selected only for essential hypertension, supplementing dietary K^+ with $KHCO_3$ induced at 8 weeks a significant, persisting attenuation of hypertension compared with placebo, whereas similarly supplemented KCl did not.[28] On the basis of a recently completed study of 140 patients selected only for hypertension, we would conclude that supplemental $KHCO_3$ and KCl at 16 weeks are both effective antihypertensive agents and that $KHCO_3$ is at least as effective as KCl (unpublished observations). The question can be asked: Would the hypertension of patients selected for normal or high levels of PRA be more attenuated by supplemental $KHCO_3$ than KCl? Sealey et al[29] have pointed out that even normal levels of PRA are abnormally high in hypertensive patients because hypertension per se should suppress PRA. They have proposed that such unsuppressed levels of PRA reflect an abnormal increased renal release of renin, as might occur with pathological narrowing of only some afferent arterioles. Clearly, such narrowing can occur. Whether its extent and associated hypertension might be more susceptible to attenuation with $KHCO_3$ than with KCl remains to be determined.

Can supplemental $KHCO_3$ prevent hypertension? In 41 metabolically controlled studies of 38 healthy normotensive men (24 black men and 14 white men), we recently showed that in most of the blacks but not the whites, salt sensitivity occurred when dietary K^+ was even marginally deficient, 30 mmol per day, but not attended by hypokalemia, as judged by a fasting serum concentration of K^+ of 4.0 mmol/L. However, the pressor effect of NaCl loading was dose-dependently suppressed when dietary K^+ was increased to 70 and 120 mmol/L per day by supplemental $KHCO_3$.[8] Because normotensive salt sensitivity is a likely and possibly common precursor of hypertension,[30] such suppression might prevent or delay the occurrence of hypertension, particularly in the many blacks in whom dietary K^+ is deficient.[11] Predictably, over the mainly normal range of dietary K^+ studied, the serum concentration of K^+ remained well within the normal range, increasing only minimally when $KHCO_3$ was supplemented. However, supplemental $KHCO_3$ dose-dependently reversed and ultimately more than abolished the large hypercalciuric effect of NaCl loading. In those who are salt sensitive, and in whom dietary calcium is suboptimal as in the normotensive subjects studied, dietary replenishment of calcium may reduce BP.[31] Accordingly, a calcium-retaining effect of $KHCO_3$[32,33] might have contributed to its reversal of the pressor effect of dietary NaCl. Similarly, the abundant K^+ and HCO_3^--yielding anions (like citrate) in fruits and vegetables could mediate the hypocalciuric[34] and likely calcium-retaining effect of these foods, and thereby contribute both to their antipressor effect and its enhancement by calcium-rich dairy products.[35]

Kidney Stones

Hypercalciuria is a major risk factor for the development of kidney stones,[36] and both phenomena are reported to occur with increased frequency in patients with essential hypertension.[37] Dietary NaCl is a major determinant of urinary calcium.[38] However, in a recent epidemiological study of 51,529 men conducted prospectively over 4 years, the incidence of symptomatic kidney stones did not correlate with dietary Na^+, but did correlate strongly and negatively with dietary K^+ over a broad but normal range, and directly with the dietary intake of meat.[39] As noted, dietary K^+ is derived mainly from foods poor in Cl^- but rich in organates, which are converted in vivo to HCO_3^-. Dietary K^+ and HCO_3^- can both exert important effects on the urinary excretion of calcium (Fig). In normal humans[40-42] as well as in patients with essential hypertension,[41,43] dietary depletion of K^+ induces increased urinary excretion of calcium. This phenomenon may reflect in part the fact that even minimal dietary depletion of K^+ evokes a restricted renal capacity to excrete NaCl [44] that, combined with a continued unrestricted dietary intake of NaCl, can apparently lead to an expanded blood volume and, in consequence, an increased urinary excretion of calcium[40,41] However, like hydrochlorothiazide,[45,46] K^+ directly and strongly stimulates calcium reabsorption in the distal renal tubule, apparently by enhancing its luminal membrane transport[46] while at the same time inhibiting Na^+ transport in this membrane.[46] Such a dichotomy of effects also appears to occur with $KHCO_3$. In humans, either supplemental $KHCO_3$ or administration of chlorothiazide induces an immediate, substantial reduction in urinary excretion of calcium[32,42,47] while also inducing a natriuresis.[8,42] HCO_3^- appears to exert a hypocalciuric effect in addition to that of K^+.[48] In normal humans, $KHCO_3$ is hypocalciuric and KCl is not.[49] In a recently completed study of people selected only for essential hypertension, we observed that supplemental $KHCO_3$, but not KCl, had a significant hypocalciuric effect (unpublished data).

In addition to hypercalciuria, diminished urinary excretion of citrate is a major risk factor for the formation of kidney stones[36,50] (Fig), in part because urinary citrate normally complexes urinary calcium in a soluble form. Urinary citrate normally inhibits not only the growth of individual crystals (eg, calcium oxalate) but also crystal agglomeration, the conjoining of multiple crystals into larger masses that become clinical kidney stones.[51] Hypocitraturia occurs with even modest K^+ deficiency, presumably because it enhances the net renal tubular reabsorption of filtered citrate,[52,53] possibly by inducing intracellular acidosis in the proximal renal tubule[54] that may increase both the Na^+-coupled luminal membrane transport of citrate[55] and its mitochondrial metabolism.[52] Under normal physiological circumstances, administration of $KHCO_3$ (or K^- citrate) induces not only a reduction in the urinary excretion of calcium[42,56] but also an increase in urinary citrate[47,49,52] This citraturic effect of K^- citrate is not greater than that of $KHCO_3$.[49]

Decreases in the urinary excretion of citrate, as well as increases in urinary calcium[57] are predictably induced by high-meat diets[51] because meat and other animal proteins are rich in amino acids that are metabolized to nonvolatile acid. The typical American diet constitutes an acid load of some 1 to 2 mmol/Kg per day. Such acidogenic diets titrate the plasma HCO_3^- concentration to a value slightly lower than it would be otherwise, and even small reductions in the plasma HCO_3^- concentration can enhance renal reabsorption of citrate and reduce its excretion.[52]

Osteoporosis

The acid generated from acidogenic diets can titrate bone.[58] A metabolic bone disorder like that of osteoporosis can be induced in the rat by rendering it chronically, mildly acidotic with NH_4Cl.[59] Osteoporosis is described in patients with untreated renal tubular acidosis.[60] In infants and children with classic renal tubular acidosis (type 1), sustained correction of acidosis with alkali as either $KHCO_3$ or $NaHCO_3$ corrects osteopenia and an otherwise stunted somatic growth.[61,62] In 9 patients diagnosed with incomplete (ie, nonacidotic) renal tubular acidosis, supplement K-citrate induced an increase in bone density.[63] Reductions of extracellular pH and HCO_3^- concentration are potent and independent signals for stimulation of bone resorption and inhibition of bone formation[64] (Fig). The mammalian skeleton provides a large reservoir of basic calcium salts whose titration mitigates acid-induced reductions in blood pH and bicarbonate concentration, but at the potential cost of diminished bone mass. Even in normal

people, the renal acidification process does not completely dispatch the normal nonvolatile acid load generated endogenously from dietary precursors.[5,58] As a consequence, (1) the plasma HCO_3^- concentration is titrated to a value slightly lower than would otherwise occur, and (2) some fraction of the endogenous acid load is buffered by basic bone salts such that calcium is chronically mobilized from bone and excreted. Accordingly, over a period of years in the normally aging human, progressive bone loss might result in part from continuing low-grade metabolic acidosis and prolonged titration of alkaline skeletal calcium salts by acid generated from dietary precursors.[65]

Several observations support this formulation. In normal human subjects: (1) blood pH and plasma HCO_3^- concentration decrease slightly but significantly as endogenous acid production is increased over a normal range by dietary manipulation[5]; (2) endogenous acid production often exceeds net acid excretion[5,58]; and (3) with aging, plasma HCO_3^- decreases, and the serum concentration of Cl^- increases, reflecting the low-grade metabolic acidosis recently shown to attend the age-related decline of normal renal function and acidification capacity.[4,6] World-wide, the incidence of hip fractures correlates directly with the ingestion of meat protein,[66] which is, as noted, a major source of endogenous nonvolatile acid. These and other observations and considerations suggest the following hypothesis: In aging humans the "normal" progressive loss of bone mass will be attenuated by $KHCO_3$ supplemented in an amount sufficient to titrate the nonvolatile acid that is endogenously produced. This hypothesis predicts that this amount of supplemental $KHCO_3$ in postmenopausal women will (1) enhance the renal reclamation of calcium and phosphorus and thereby promote positive calcium and phosphorus balance, (2) prevent acid titration of calcium-containing base in bone (and plasma HCO_3^-), and thereby (3) diminish bone resorption, enhance bone formation, and increase plasma HCO_3^- concentration.

We[33] recently reported a positive test of this hypothesis in 18 healthy women (aged 51 to 77 years) all of whom were at least 5 years postmenopausal. Under controlled metabolic conditions, the subjects ate a typical whole-food diet with an endogenous acid production rate predictably productive of a positive acid balance (80 to 90 mmol per day per 60 kg body weight). After a control period of 6 days and a prior prebalance adaptation of 20 days, $KHCO_3$ (60 to 90 mmol per day per 60 kg body weight) was administered for 16 days as a liquid supplement in divided amounts with meals.

Supplemental $KHCO_3$ (1) increased the plasma HCO_3^- concentration and pH only slightly, and to values that remained well within the normal range, but virtually abolished net renal acid excretion; (2) improved external balance of calcium and phosphorus because of sustained reductions in their urinary excretion rates; (3) improved phosphorus balance sufficiently in relation to calcium so that retention of calcium as hydroxyapatite would not have been curtailed; (4) reduced the urinary excretion of hydroxyproline, a biochemical marker of the rate of bone resorption; and (5) increased the serum concentration of osteocalcin, an osteoblast-produced protein and biochemical marker of bone formation.

These conclusions were drawn: (1) In postmenopausal women, short-term supplemental $KHCO_3$ in amounts just sufficient to dissolve endogenous acid production can reduce the rate of bone resorption, increase the rate of bone formation, and reduce bone mass lost in defense of acid-base homeostasis. (2) Dietary supplements of $KHCO_3$ may be effective in the prevention and treatment of osteoporosis.

Stroke

In a 12-year prospective study of 859 upper-middle-class white subjects, all over 50 years of age, and residing in the contained community of Rancho Bernardo, California, Khaw and Barret-Connor[67] found that the incidence of stroke death varied inversely with the dietary intake of potassium independent of BP. It could be calculated that increasing dietary potassium by 10 mmol per day within the normal range would reduce the incidence of stroke death by 40%.[67] In an 8-year prospective study of 43,738 men in the United States, 40 to 75 years of age, Ascherio et al[68] recently reported a similar inverse relationship between dietary K^+ intake and the occurrence of stroke. The inverse relationship was stronger in hypertensive than in normotensive men. In those taking diuretics, the intake of K^+ as a supplement was also inversely related to risk of stroke. Tobian[10] has emphasized that the incidence of stroke world-wide varies inversely with dietary intake of K^+. If deficient dietary K^+ and HCO_3^- are major

determinants of the occurrence of both stroke and osteoporosis, one might expect that elderly women with reduced bone density might be at increased risk of stroke. In fact, Browner et al[69] have recently reported that ambulatory elderly women with low bone density are at increased risk of stroke, and the risk is substantial. Each standard deviation decrease in bone mineral density of the calcaneus and proximal radius was associated with at 1.3-fold increase in stroke. The magnitude of the increase in risk is comparable to that observed for the relation between systolic BP and stroke in the elderly.

REFERENCES

1. Schwartz WB, van Ypersele de Strihou C, Kassirer JP: Role of anions in metabolic alkalosis and potassium deficiency. N Engl J Med 279:630-639, 1968
2. Pak CYC, Peterson R, Sakhaee K, et al: Correction of hypocitraturia and prevention of stone formation by combined thiazide and potassium citrate therapy in thiazide-unresponsive hypercalciuric nephrolithiasis. Am J Med 79:284-288, 1985
3. Nicar MJ, Peterson R, Pak CYC: Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. J Urol 131:430-433, 1984
4. Garella S, Chazan JA, Cohen JJ: Saline-resistant metabolic alkalosis or "chloride-wasting nephropathy"; Report of four patients with severe potassium depletion. Ann Intern Med 73:31-38, 1970
5. Kurtz I, Maher T, Hulter HN, et al: Effect of diet on plasma acid-base composition in normal humans. Kidney Int 24:570-680, 1983
6. Frassetto LA, Morris RC Jr, Sebastian A: Effect of age on blood acid-base composition in adult humans: Role of age-related renal functional decline. Am J Physiol 271:F1114-F1122, 1996
7. Alpern RJ, Sakhaee K: The clinical spectrum of chronic metabolic acidosis: Homeostatic mechanisms produce significant morbidity. Am J Kidney Dis 29:291-302, 1997
8. Morris RC Jr, Sebastian A, Forman A, et al: Normotensive salt-sensitivity: Effects of race and dietary potassium. Hypertension 33:18-23, 1999
9. Eaton SB, Konner M: Paleolithic nutrition. A consideration of its nature and current implications. N Engl J Med 312:283-289, 1985
10. Tobian L: The Volhard lecture: Potassium and sodium in hypertension. J Hypertens 6:S12-S24, 1988
11. Frisancho AR, Leonard WR, Bollettino LA: Blood pressure in blacks and whites and its relationship to dietary sodium and potassium intake. J Chron Dis 37:515-519, 1984
12. Denton D: The Hunger for Salt. New York, NY, Springer-Verlag, 1982, pp 1-621
13. MacGregor GA, Cappuccio FP: The kidney and essential hypertension: A link to osteoporosis? J Hypertens 11:781-785, 1993
14. MacGregor GA, Best FE, Cam JM, et al: Double-blind randomised crossover trial of moderate sodium restriction in essential hypertension. Lancet 1:351-355, 1982
15. MacGregor GA, Markandu ND, Smith SJ, et al: Moderate potassium supplementation in essential hypertension. Lancet 2:567-570, 1982
16. Keith NM, Binger MW: Diuretic action of potassium salts. JAMA 105:1584-1591, 1935
17. Van Buren M, Rabelink TJ, Van Rijn HJM, et al: Effects of acute NaCl, KCl and KHCO3 loads on renal electrolyte excretion in humans. Clin Sci 83:567-574, 1992
18. Tanaka M, Schmidlin O, Yi S-L, et al: Genetically determined chloride-sensitive hypertension and stroke. Proc Natl Acad Sci U S A 94:14748-14752, 1997
19. Tanaka M, Olson J, Schmidlin O, et al: In the stroke-prone spontaneously hypertensive rats (SHRSP) the severity of renal lesions correlates with the severity of hypertension (HT) and plasma renin activity (PRA) modulated by KCl and KHCO3/K citrate. Am J Hypertens 9:37A, 1996 (abstr)
20. Passmore JC, Jimenez AE: Effect of chloride on renal blood flow in angiotensin II induced hypertension. Can J Physiol Pharmacol 69:501-511, 1991
21. Hansen PB, Jensen BL, Skøtt O: Chloride regulates afferent arteriolar contraction in response to depolarization. Hypertension 32:1066-1070, 1998
22. Briggs JP, Schnermann J: Control of renin release and glomerular vascular tone by the juxtaglomerular apparatus, in Laragh JH, Brenner BM. (eds): Hypertension: Pathophysiology, Diagnosis, and Management (ed 2). New York, NY, Raven, 1995, pp 1359-1383
23. Arendshorst WJ: Altered reactivity of tubuloglomerular feedback. Ann Rev Physiol 49:295-317, 1987
24. Okamoto K, Yamori Y, Nagaoka A: Establishment of the stroke prone hypertensive rat (SHR). Circ Res 34:I-143-I-153, 1974 (suppl 1)
25. Skov K, Fenger-Gron J, Mulvany MJ: Effects of an angiotensin-converting enzyme inhibitor, a calcium antagonist, and an endothelin receptor antagonist on renal afferent arteriolar structure. Hypertension 28:464-471, 1996
26. Volpe M, Camargo MJF, Mueller FB, et al: Relation of plasma renin to end organ damage and to protection of K^+ feeding in stroke-prone hypertensive rats. Hypertension 15:318-326, 1990
27. Rocha R, Chander PN, Khanna K, et al: Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. Hypertension 31:451-458, 1998
28. Overlack A, Maus B, Ruppert M, et al: Potassium citrate vs potassium chloride in essential hypertension: Effect on haemodynamic, hormonal and metabolic parameters [Kaliumcitrat versus Kaliumchlorid bei essentieller hypertonie]. Dtsch Med Wschr 120:631-635, 1995
29. Sealey JE, Blumenfeld JD, Bell GM, et al: On the renal basis for essential hypertension: Nephron heterogeneity with discordant renin secretion and sodium excretion causing a hypertensive vasocontriction-volume relationship. J Hypertens 6:763-777, 1988
30. Weinberger MH, Fineberg NS: Sodium and volume sensitivity of blood pressure: Age and pressure change over time. Hypertension 18:67-71, 1991
31. Weinberger MH, Wagner UL, Fineberg NS: The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. Am J Hypertens 6 :799-805, 1993
32. Lemann J Jr, Gray RW, Pleuss JA: Potassium bicarbonate, but not sodium bicarbonate, reduces urinary calcium ex-

cretion and improves calcium balance in healthy men. Kidney Int 35:688-695, 1989

33. Sebastian A, Harris ST, Ottaway JH, et al: Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med 330:1776-1781, 1994

34. Breslau NA, Brinkley L, Hill KD, et al: Relationship of animal protein-rich diet to kidney stone formation and calcium metabolism. J Clin Endocrinol Metab 66:140-146, 1988

35. Appel LJ, Moore TJ, Obarzanek E, et al: A clinical trial of the effects of dietary patterns on blood pressure. N Engl J Med 336:1117-1124, 1997

36. Coe FL, Parks JH, Asplin JR: The pathogenesis and treatment of kidney stones. N Engl J Med 327:1141-1152, 1992

37. Strazzullo P: The renal calcium leak in primary hypertension: Pathophysiological aspects and clinical implications. Nutr Metab Cardiovasc Dis 1:98-103, 1991

38. Kleeman CR, Bohannan J, Bernstein D, et al: Effect of variations in sodium intake on calcium excretion in normal humans. Proc Soc Exp Biol Med 115:29-32, 1964

39. Curhan GC, Willett WC, Rimm EB, et al: A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med 328:833-838, 1993

40. Jones JW, Sebastian A, Hulter HN, et al: Systemic and renal acid-base effects of chronic dietary potassium depletion in humans. Kidney Int 21:402-410, 1982

41. Lawton WJ, Fitz AE, Anderson EA, et al: Effect of dietary potassium on blood pressure, renal function, muscle sympathetic nerve activity, and forearm vascular resistance and flow in normotensive and borderline hypertensive humans. Circulation 81:173-184, 1990

42. Lemann J Jr, Pleuss JA, Gray RW, et al: Potassium administration reduces and potassium deprivation increases urinary calcium excretion in healthy adults. Kidney Int 39:973-983, 1991

43. Krishna GG, Kapoor SC: Potassium depletion exacerbates essential hypertension. Ann Intern Med 115:77-83, 1991

44. Krishna GG, Chusid P, Hoeldtke RD: Mild potassium depletion provokes renal sodium retention. J Lab Clin Med 109:724-730, 1987

45. Costanzo LS, Windhager EE: Calcium and sodium transport by the distal convoluted tubule of the rat. Am J Physiol 235:F492-F506, 1978

46. Brunette MG, Mailloux J, Lajeunesse D: Calcium transport through the luminal membrane of the distal tubule. I. Interrelationship with sodium. Kidney Int 41:281-288, 1992

47. Pak CYC: Citrate and renal calculi. Miner Electrolyte Metab 13:257-266, 1987

48. Sutton RAL, Wong NLM, Dirks JH: Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. Kidney Int 15:520-533, 1979

49. Sakhaee K, Alpern R, Jacobson HR, et al: Contrasting effects of various potassium salts on renal citrate excretion. J Clin Endocrinol Metab 72:396-400, 1991

50. Pak CYC, Fuller C: Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. Ann Intern Med 104:33-37, 1986

51. Kok DJ, Iestra JA, Doorenbos CJ, et al: The effects of dietary excesses in animal protein and in sodium on the composition and the crystallization kinetics of calcium oxalate monohydrate in urines of healthy men. J Clin Endocrinol Metab 71:861-867, 1990

52. Simpson DP: Citrate excretion: A window on renal metabolism. Am J Physiol 244:F223-F234, 1983

53. Hamm LL: Renal handling of citrate. Kidney Int 38:728-735, 1990

54. Adam WR, Koretsky AP, Weiner MW: 31P-NMR in vivo measurement of renal intracellular pH: Effects of acidosis and K+ depletion in rats. Am J Physiol 251:F904-F910, 1986

55. Wright SH, Kippen I, Wright EM: Effect of pH on the transport of Krebs cycle intermediates in renal brush border membranes. Biochem Biophys Res Comm 684:287-290, 1982

56. Sakhaee K, Nicar M, Hill K, et al: Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. Kidney Int 24:348-352, 1983

57. Lemann J Jr, Adams ND, Gray RW: Urinary calcium excretion in human beings. N Engl J Med 301:535-541, 1979

58. Lennon EJ, Lemann J Jr, Litzow JR: The effects of diet and stool composition on the net external acid balance of normal subjects. J Clin Invest 45:1601-1607, 1966

59. Barzel US, Jowsey J: The effects of chronic acid and alkali administration on bone turnover in adult rats. Clin Sci 36:517-524, 1969

60. Harrington TM, Bunch TW, Van Den Berg CJ: Renal tubular acidosis: A new look at treatment of musculoskeletal and renal disease. Mayo Clin Proc 58:354-360, 1983

61. McSherry E, Morris RC Jr: Attainment and maintenance of normal stature with alkali therapy in infants and children with classic renal tubular acidosis. J Clin Invest 61:509-527, 1978

62. Caldas A, Broyer M, Dechaux M, et al: Primary distal tubular acidosis in childhood: Clinical study and long-term follow-up of 28 patients. J Pediatr 121:233-241, 1992

63. Preminger GM, Sakhaee K, Pak CYC: Hypercalciuria and altered intestinal calcium absorption occurring independently of vitamin D in incomplete distal renal tubular acidosis. Metabolism 36:176-179, 1987

64. Bushinsky DA, Wolbach W, Sessler NE, et al: Physicochemical effects of acidosis on bone calcium flux and surface ion composition. J Bone Miner Res 8:93-102, 1993

65. Wachman A, Bernstein DS: Diet and osteoporosis. Lancet 2:958-959, 1968

66. Abelow BJ, Holford TR, Insogna KL: Cross-cultural association between dietary animal protein and hip fracture: a hypothesis. Calcif Tissue Int 50:14-18, 1992

67. Khaw K-T, Barrett-Connor E: Dietary potassium and stroke-associated mortality. N Engl J Med 316:235-240, 1987

68. Ascherio A, Rimm EB, Hernan MA, et al: Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 98:1198-1204, 1998

69. Browner WS, Pressman AR, Nevitt MC, et al: Association between low bone density and stroke in elderly women: The study of osteoporotic fractures. Stroke 24:940-946, 1993