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Potassium administration increases and potassium deprivation reduces urinary calcium excretion in healthy adults

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Potassium administration increases and potassium deprivation reduces urinary calcium excretion in healthy adults. This study was undertaken to evaluate the effects of dietary K intake, independent of whether the accompanying anion is Cl^- or HCO_3^-, on urinary Ca excretion in healthy adults. The effects of KCl, $KHCO_3$, NaCl and $NaHCO_3$ supplements, 90 mmol/day for four days, were compared in ten subjects fed normal constant diets. Using synthetic diets, the effects of dietary KCl-deprivation for five days followed by recovery were assessed in four subjects and of $KHCO_3$-deprivation for five days followed by recovery were assessed in four subjects. On the fourth day of salt administration, daily urinary Ca excretion and fasting $U_{Ca}V/GFR$ were lower during the administration of KCl than during NaCl supplements ($\Delta = -1.11 \pm 0.28$ SEM mmol/day; $P < 0.005$ and -0.0077 ± 0.0022 mmol/liter GFR; $P < 0.01$), and lower during $KHCO_3$ than during control (-1.26 ± 0.29 mmol/day; $P < 0.005$ and -0.0069 ± 0.0019 mmol/liter GFR; $P = 0.005$). Both dietary KCl and $KHCO_3$ deprivation (mean reduction in dietary K intake -67 ± 8 mmol/day) were accompanied by an increase in daily urinary Ca excretion and fasting $U_{Ca}V/GFR$ that averaged on the fifth day $+1.31 \pm 0.25$ mmol/day ($P < 0.005$) and $+0.0069 \pm 0.0012$ mmol/liter GFR ($P < 0.005$) above control. Both daily urinary Ca excretion and fasting $U_{Ca}V/GFR$ returned toward or to control at the end of recovery. These observations indicate that: 1) $KHCO_3$ decreases fasting and 24-hour urinary Ca excretion; 2) KCl nor $NaHCO_3$, unlike NaCl, do not increase fasting or 24-hour Ca excretion and 3) K deprivation increases both fasting and 24-hour urinary Ca excretion whether the accompanying anion is Cl^- or HCO_3^-. The mechanisms for this effect of K may be mediated by: 1) alterations in ECF volume, since transient increases in urinary Na and Cl excretion and weight loss accompanied KCl or $KHCO_3$ administration, while persistent reductions in urinary Na and Cl excretion and a trend for weight gain accompanied K deprivation; 2) K mediated alterations in renal tubular phosphate transport and renal synthesis of 1,25-$(OH)_2$-vitamin D, since KCl or $KHCO_3$ administration tended to be accompanied by a rise in fasting serum PO_4 and $TmPO_4$ and a fall in fasting $U_{PO_4}V/GFR$, a fall in serum 1,25-$(OH)_2$-D and a decrease in fasting $U_{Ca}V/GFR$, while dietary KCl or $KHCO_3$ deprivation were accompanied by a reverse sequence.

Increased rates of acid production produced by the ingestion of high protein diets or the experimental administration of NH_4Cl augment urinary calcium (Ca) excretion rates in human beings and cause Ca balances to become negative as a consequence of enhanced bone resorption [1–4]. Conversely, the administration of $NaHCO_3$ inhibits the increase in urinary Ca excretion induced by increasing dietary protein intake [5]. However, we recently reported that the administration of $NaHCO_3$, 60 mmol/day, had no effect on either urinary Ca excretion rates, intestinal Ca absorption or Ca balances, whereas the administration of $KHCO_3$ in the same quantity reduced urinary Ca excretion rates without affecting intestinal Ca absorption, and thus caused Ca balances to become equivalently more positive [6]. Other studies have also demonstrated that the administration of potassium citrate reduced urinary Ca excretion but that equal doses of sodium citrate were less effective [7]. Those observations suggested that K might have an effect to reduce urinary Ca excretion. Earlier studies in rats have demonstrated that K augments distal tubular phosphate (PO_4) reabsorption, an effect that was only detectable when basal serum PO_4 concentrations were normal (such as, when PTH was present) [8]. Furthermore, a recent study has shown that the administration of either KCl or $KHCO_3$, 90 mmol/day, to healthy men is accompanied by a fall in urinary PO_4 excretion and a rise in serum PO_4 concentrations together with small decrements in serum 1,25-$(OH)_2$-D concentrations [9]. Neither serum PTH levels nor urinary excretion rates of cAMP were affected by K [9]. However, neither that comparison of the effects of KCl and $KHCO_3$ administration [9] nor earlier studies of experimental K deprivation [10–13] provide information about the effects of potassium on Ca excretion, although urinary Ca excretion has been found to increase when K depletion was produced by substituting Na for dietary K without changing the intake of inorganic anions [14].

The present studies were, therefore, undertaken to: 1) compare the effects of KCl and of $KHCO_3$ administration to the effects of NaCl and of $NaHCO_3$ administration; and 2) to assess the effects of brief dietary K deprivation, achieved by the removal of either KCl or $KHCO_3$ from the diet, on urine and blood composition in healthy adults. The results demonstrate that K loading reduces and K deprivation increases urinary calcium excretion. Preliminary reports of the results have been published in abstracts [15–19].

Methods

We studied thirteen healthy adults, four women and nine men, in the Medical College of Wisconsin Clinical Research Center with their consent under protocols approved by the Medical College of Wisconsin Human Research Review Committee. The subjects ranged in age from 21 to 41 years and

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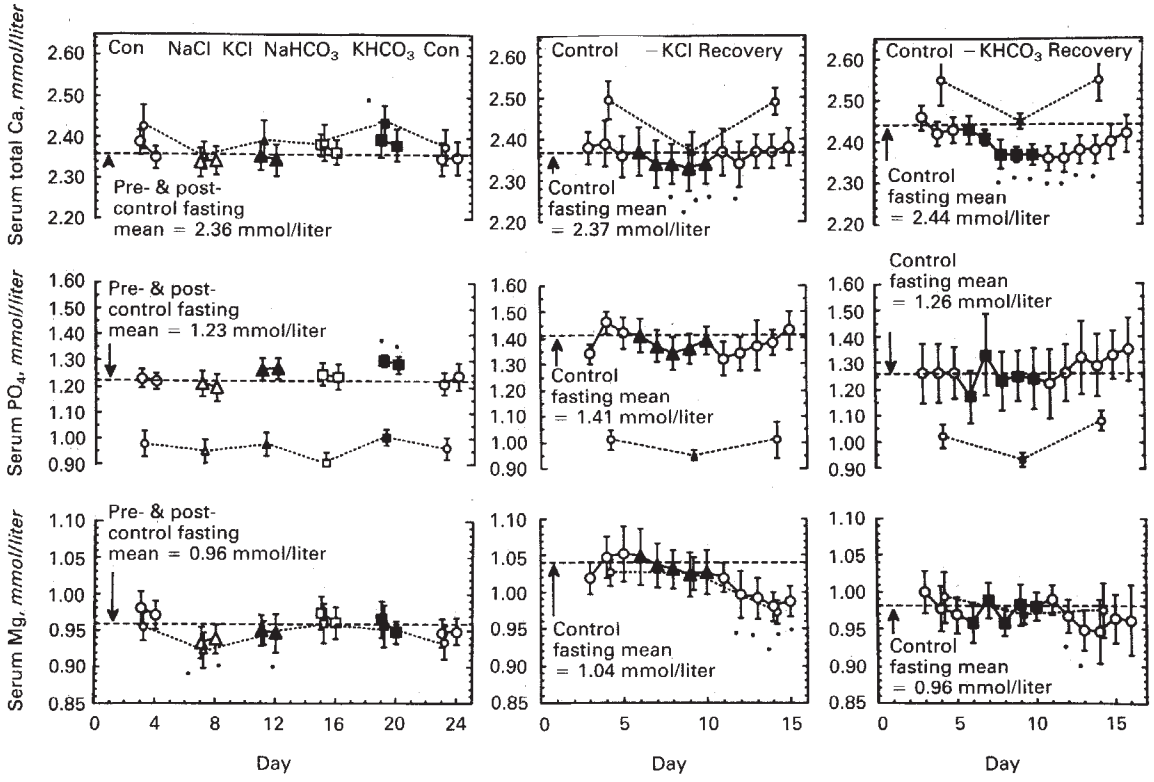

Fig. 1. *Mean serum Ca, PO_4 and Mg concentrations during pre- and post-control and during administration of NaCl, KCl, $NaHCO_3$ and $KHCO_3$ in 10 subjects (**left**); during control, KCl deprivation and recovery in 4 subjects (**middle**); and during control, $KHCO_3$ deprivation and recovery in 4 subjects (**right**).* Data for control or recovery periods are shown by (○), for NaCl administration by (△), for KCl administration or deprivation by (▲), for $NaHCO_3$ administration by (□) and for $KHCO_3$ administration or deprivation by (■). The large symbols show fasting means while the small symbols connected by dashed lines show means for measurements 90 minutes after breakfast alone or breakfast + 30 mmol salt (**left**) or ingestion of 25% of formula diets (**middle, right**). The vertical lines through each symbol represent SEM. Statistically significant changes, by repeated measures of analysis of variance, from pre- and post-control during salt administration (**left**) and from control during KCl deprivation and recovery (**middle**) or from control during $KHCO_3$ deprivation and recovery (**right**) are shown by the solid dots above or below the vertical standard error lines.

averaged 31 ± 2 SEM years. Their body weights ranged from 54.58 to 95.30 kg and averaged 70.59 ± 3.97 kg. The women were studied at random times with respect to their menstrual cycles; one of the women was taking an oral contraceptive. The subjects continued their usual daily activities but were asked to avoid strenuous exercise. All subjects were weighed and their blood pressure measured while fasting each morning.

The effects of KCl, $KHCO_3$, NaCl and $NaHCO_3$ administration were compared in ten subjects (two women and eight men). Each of these subjects ate, on alternate days, two constant whole food diets of similar composition that were individually designed to maintain body weight. These diets provided an average of: Ca 21.6 ± 0.9, Mg 17.1 ± 1.5, P 55.5 ± 4.1, Na 165 ± 14, K 85 ± 6 and Cl 151 ± 12 mmol/day. Estimated caloric intake ranged from 1830 to 3750 kcal/day in individual subjects and averaged 38.4 ± 1.1 kcal/kg/day. Tap water was used to prepare diet beverages. In addition, the subjects drank deionized water as they desired. Eight of these subjects were observed during an initial four-day control period followed by four subsequent four-day periods, during which each subject was given 90 mmol/day of NaCl, KCl, $NaHCO_3$ and $KHCO_3$ and then a final four-day control period. For two of the subjects, additional four-day control periods were observed after the administration of each salt. The sequence of administration of each salt was different for each subject. The salts were administered by giving 30 mmol dissolved in 50 ml of cherry syrup t.i.d. with meals. During the control periods, the subjects were given 50 ml of plain cherry syrup vehicle t.i.d. with meals. These subjects collected daily 24-hour urines preserved with thymol and phenylmercuric nitrate and under a layer of mineral oil. However, on the third day of each study phase, the urine was preserved during collection with 20 ml 6 mol/liter HCl in order to permit comparisons of measurements of oxalate when urine was preserved with acid during collection to measurements when urine was collected at ambient pH. Those results were reported separately [20]. Fasting morning urines were collected at the end of the fourth day of each study phase. Fasting blood specimens were obtained at the end of the third and fourth days of each study phase. Another blood specimen was obtained 90 minutes after breakfast and ingestion of the vehicle or salt on the fourth day of each study phase in eight subjects. In addition, four of these eight subjects also collected a two-hour urine following breakfast on the fourth day of each study phase.

The effects of dietary K deprivation were evaluated in eight subjects (two women and six men; five of these subjects had

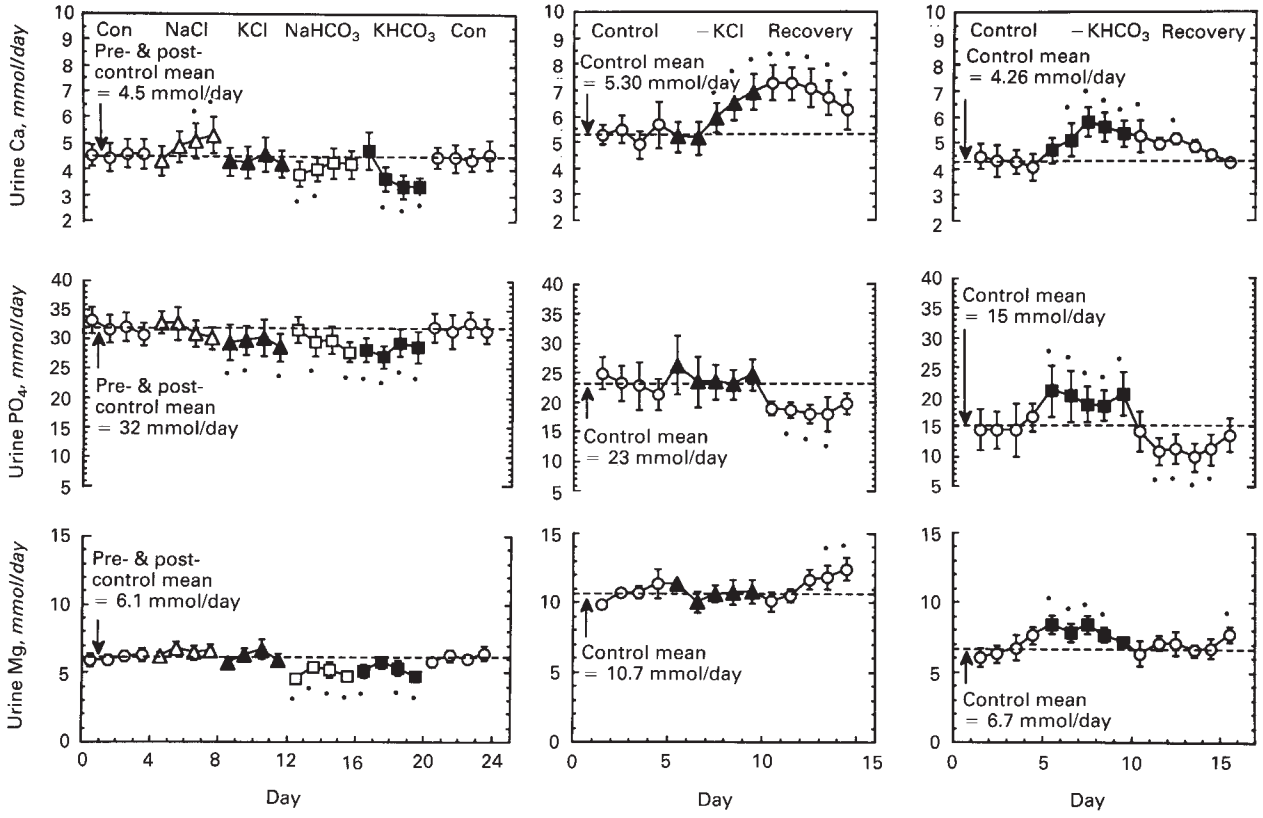

Fig. 2. *Mean daily urinary excretion of Ca, PO_4 and Mg during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).* Symbols as in Fig. 1.

previously been studied during salt administration). These subjects were fed a liquid formula diet in proportion to their body weights. This formula provided 45 kcal/kg/day using 1.0 g soy protein/kg/day, 2.0 g corn oil/kg/day, 4.6 g cornstarch hydrolysate and 1.15 g sucrose/kg/day. The diet also contained NaCl 1.4 mmol/kg/day, $Ca(OH)_2$ 0.234 mmol/kg/day, $Mg(OH)_2$ 0.234 mmol/kg/day, Na_2HPO_4 0.2 mmol/kg/day and $NaH_2PO_4 \cdot H_2O$ 0.05 mmol/kg/day. The formulas were also supplemented with L-methionine 15 mg/kg/day because the soy protein is deficient in that amino acid. The basal formula eaten by four subjects (four men) contained KCl 1.0 mmol/kg/day (74 ± 1 mmol/day) while the formula eaten by the other four subjects (two women and two men) contained $KHCO_3$ 1.0 mmol/kg/day (60 ± 7 mmol/day). The formulas were prepared with tap water. In addition, the subjects drank deionized water as they desired. Each subject was also given one multiple vitamin capsule daily that contained iron and folic acid. These subjects were observed during five-day control periods, followed by five days of K deprivation when either KCl or $KHCO_3$ were omitted from the formulas (diet K 2 ± 1 mmol/day) and then during a recovery period of five days when control quantities of KCl were restored to the formulas or six days when control quantities of $KHCO_3$ were restored to the formulas. These subjects also collected daily urines preserved with thymol and phenyl mercuric nitrate. Fasting morning blood samples were collected on the last three control days and all subsequent days. Another blood specimen was obtained 90 minutes after ingestion of the initial 25% of each subjects' liquid diet ("breakfast") on the last day of control, the last day of K deprivation and the last recovery day. Fasting morning urine specimens were collected on the last two days of each study phase and a two-hour urine was collected after "breakfast" on the last day of each study phase.

Urine volume, creatinine, Na, K, Cl, Ca, Mg, PO_4, pH, total CO_2 content, ammonium and hydroxyproline were measured by previously described methods [6]. Blood pH and serum CO_2 content and the concentrations of Na, K, Cl, Ca, Mg, PO_4 and 1,25-$(OH)_2$-vitamin D were also measured as described previously [6]. The interassay coefficient of variation for 1,25-$(OH)_2$-D in 50 assays performed during the period of these studies averaged 19%. In two assays, in which the sample was measured twelve times, the intraassay coefficient of variation averaged 13%. All samples from a given subject were analyzed in a single assay. Serum immunoreactive intact PTH was measured using kits (Allegro) obtained from Nichols Institute (San Juan, Capistrano, California, USA) [21]. The interassay coefficient of variation in nine assays averaged 9.4%. Fasting $TmPO_4$/GFR was estimated from the nomogram of Walton and Bivjoet [22]. Serum immunoreactive osteocalcin was measured in four subjects deprived of potassium using kits obtained from Incstar (Stillwater, Minnesota, USA).

The slopes of the individual body weights versus time on the constant diets, estimated from the weights on days 2 to 5 of the initial control period and the last two days of the final control or recovery period, were used to estimate weight changes attributable to caloric imbalance and thus to estimate Δ weight attributable to the changes in electrolyte intake.

Results are presented as group means ± SEM. The signifi-

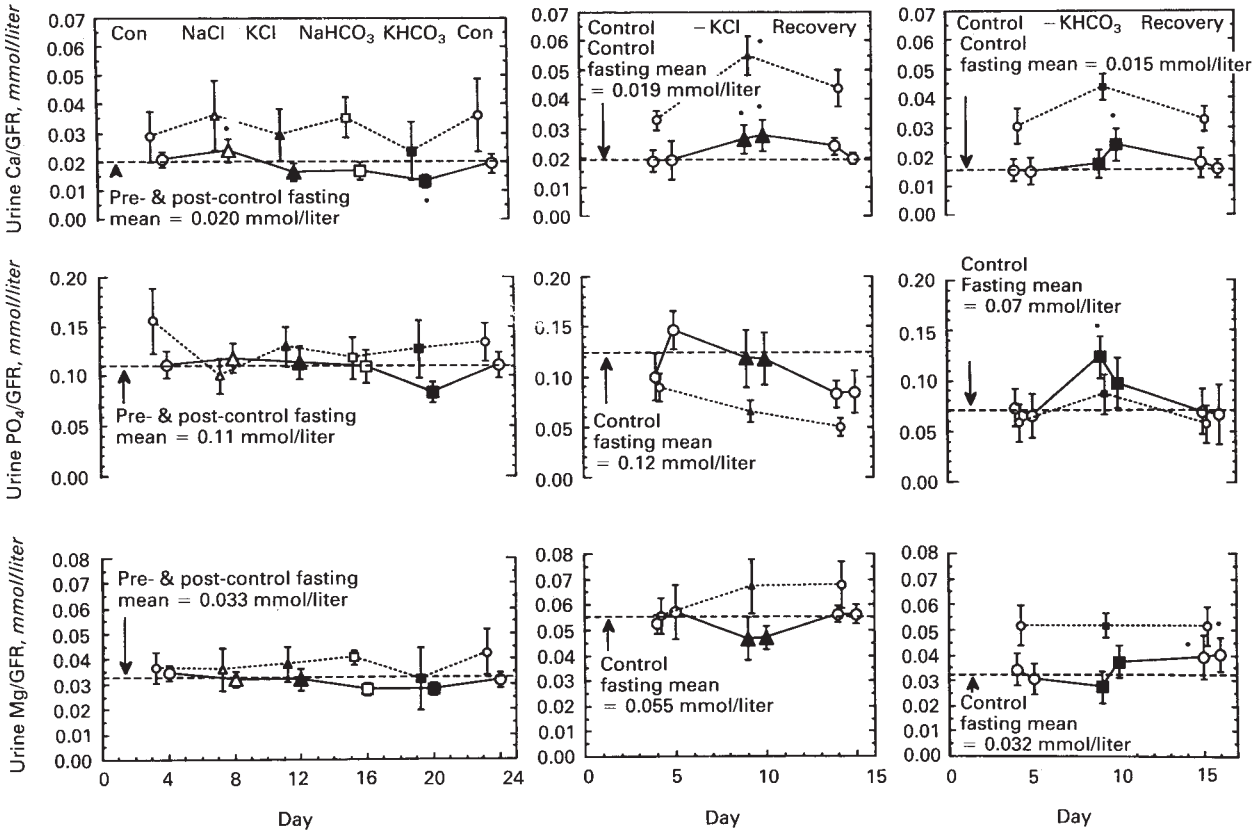

Fig. 3. *Mean fasting urine Ca/GFR, PO_4/GFR and Mg/GFR during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).* The large symbols show fasting means. The small symbols connected by dashed lines show means for urines collected 2 hours after breakfast or breakfast + 30 mmol salt in 4 subjects (**left**) or ingestion of 25% of daily formula diet (**middle, right**). Symbols as in Fig. 1.

cance of changes from control were evaluated by repeated measures of analysis of variance with adjustment for multiple comparisons [23] using SAS. Although the subjects given salt supplements received the salts in individually varying sequences, all of the results are, for clarity, presented in the sequence NaCl, KCl, $NaHCO_3$, $KHCO_3$. Since the directional changes were similar in the two subjects observed during control periods after each salt, the data for those intervening periods are not shown. Feces were not collected but the times of defecation were recorded. The subjects defecated every 1.2 ± 0.1 days; none had diarrhea.

Results

The detailed results are summarized in Figures 1 through 5.

Effects of NaCl, KCl, $NaHCO_3$ and $KHCO_3$ administration and of KCl and $KHCO_3$ deprivation on serum and urine Ca, PO_4 and Mg

As shown in Figure 1, the administration of $KHCO_3$ was accompanied by significant increases in serum total Ca concentration after breakfast as well as increases in fasting serum PO_4 concentrations. Conversely, during both dietary KCl and $KHCO_3$ deprivation fasting serum total Ca concentrations decreased, returning to control during recovery. In addition, KCl deprivation was accompanied by an insignificant trend toward lower serum PO_4 concentrations. Fasting serum Mg concentrations fell during the administration of NaCl and of KCl and during recovery from K deprivation.

As shown in Figure 2, the administration of $KHCO_3$ was accompanied by reduced daily urinary Ca excretion rates, as observed previously [6]. Deprivation of either KCl or $KHCO_3$ was accompanied, after a delay of one or two days, by increased daily rates of Ca excretion, that returned toward or to control during recovery when the K salts were restored to the diets. NaCl administration was accompanied by increased urinary Ca excretion, as expected. In contrast to $KHCO_3$ administration, $NaHCO_3$ administration was not accompanied by a sustained reduction in daily urinary Ca excretion, also as observed previously [6]. The administration of KCl and of $KHCO_3$ as well as of $NaHCO_3$ were accompanied by reduced daily rates of PO_4 excretion. Urinary PO_4 excretion did not change detectably during KCl deprivation but fell when KCl was restored to the diets during recovery. Daily urinary PO_4 excretion rates rose during dietary $KHCO_3$ deprivation and decreased to rates below control during recovery when $KHCO_3$ was restored to the diets. Also as observed previously [6], the administration of either $KHCO_3$ or $NaHCO_3$ was accompanied by reduced daily urinary Mg excretion rates. Dietary $KHCO_3$ deprivation but not KCl deprivation was, conversely, accompanied by increased rates of Mg excretion that declined to control during recovery (except for the final day).

As shown in Figure 3, most of the same directional changes in

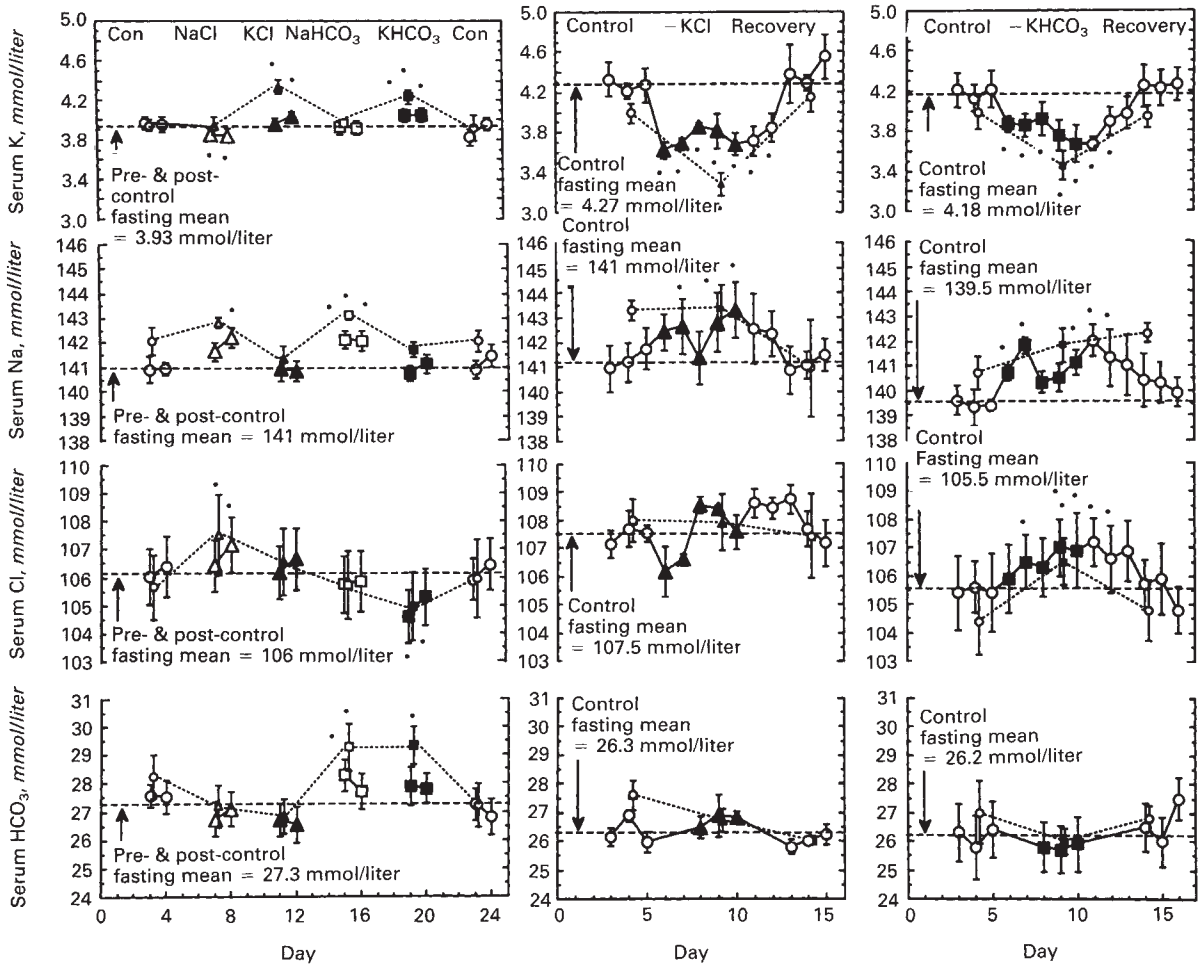

Fig. 4. *Mean serum K, Na, Cl and HCO_3 concentrations during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).* Symbols as in Fig. 1.

daily urinary excretion rates of Ca, Mg and PO_4 were also seen when fasting and post-breakfast urine composition was measured. $U_{Ca}V/GFR$ fell during $KHCO_3$ administration, rose during dietary K deprivation and decreased to control during recovery. Fasting $U_{Ca}V/GFR$ also rose during NaCl administration. Fasting $U_{PO_4}V/GFR$ rose during $KHCO_3$ deprivation. Fasting and post-breakfast $U_{Mg}V/GFR$ rose slightly at the end of recovery from $KHCO_3$ deprivation but was otherwise unaffected by the increases or decreases in the intake of the salts.

Effects of NaCl, KCl, $NaHCO_3$ and $KHCO_3$ administration and of KCl and $KHCO_3$ deprivation on serum K, Na, Cl and HCO_3 and urine K, Na, Cl and net acid

As summarized in Figures 4 and 5, the expected directional and quantitative changes in serum K, Na, Cl and HCO_3 concentrations, if any, and in both daily urinary excretion of K, Na, Cl and net acid were observed during the administration of the salts and during K deprivation. Notably, as shown in Figure 5, a Na and Cl diuresis occurred on the first day of $KHCO_3$ administration, and there was an insignificant trend for Na excretion to rise during the first three days of KCl administration, consistent with the long known natriuretic effects of K salts [24–26]. Conversely, both dietary KCl and $KHCO_3$ deprivation were accompanied by reduced rates of urinary Na and Cl excretion and a subsequent Na diuresis during recovery when the K salts were restored to the diets. The decrease in urinary Cl excretion during KCl deprivation exceeded the reduction in dietary Cl intake (cumulative Δ intake −321 ± 12 mmol and cumulative $\Delta U_{Cl}V$ −394 ± 24 mmol). A Cl diuresis occurred when KCl was restored to the diets. Similar directional changes in K, Na, Cl and net acid excretion were observed in fasting and post-breakfast urines (data not shown).

Body weight and blood pressure

As shown in Figure 6, absolute and relative body weights tended to fall as urinary Na and Cl excretion rates increased during the administration of the K salts and increase as Na and Cl were retained during dietary K deprivation. Weight increased during the administration of NaCl and of $NaHCO_3$. Blood pressure during control periods for all subjects averaged 116 ± 2 mm Hg systolic and 75 ± 2 mm Hg diastolic. No significant blood pressure changes were detected during administration of the salts or during dietary K deprivation.

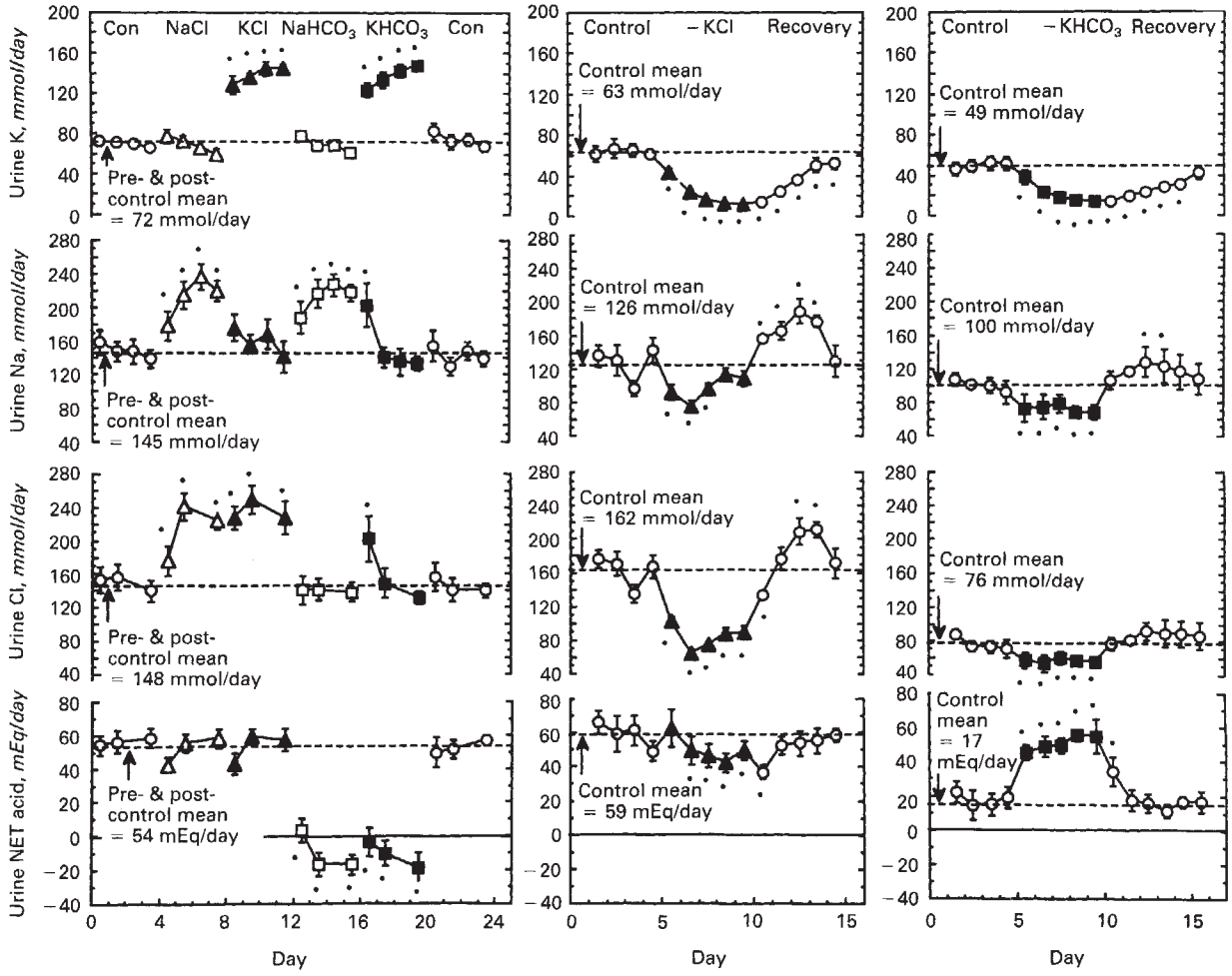

Fig. 5. *Mean daily urinary excretion of K, Na, Cl and net acid during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).* Symbols as in Fig. 1. Urine Cl and net acid were not measured on the 3rd day of each phase because the urine collections were preserved with HCl (**Methods**).

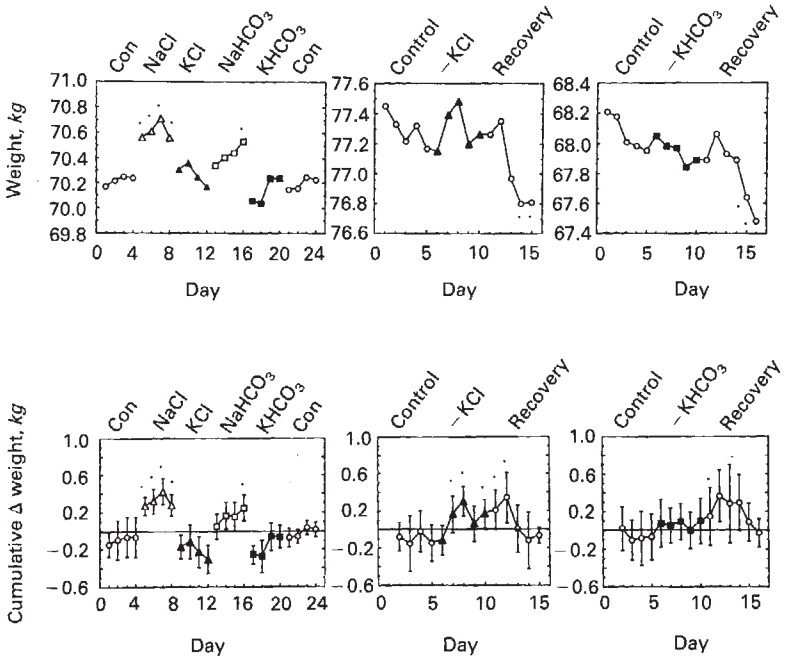

Fig. 6. *Mean body weight and mean cumulative change in body weight, corrected for individual changes during study attributed to caloric balance, during salt administration (**left**), KCl-deprivation (**middle**) and $KHCO_3$ deprivation (**right**).* Symbols as in Fig. 1.

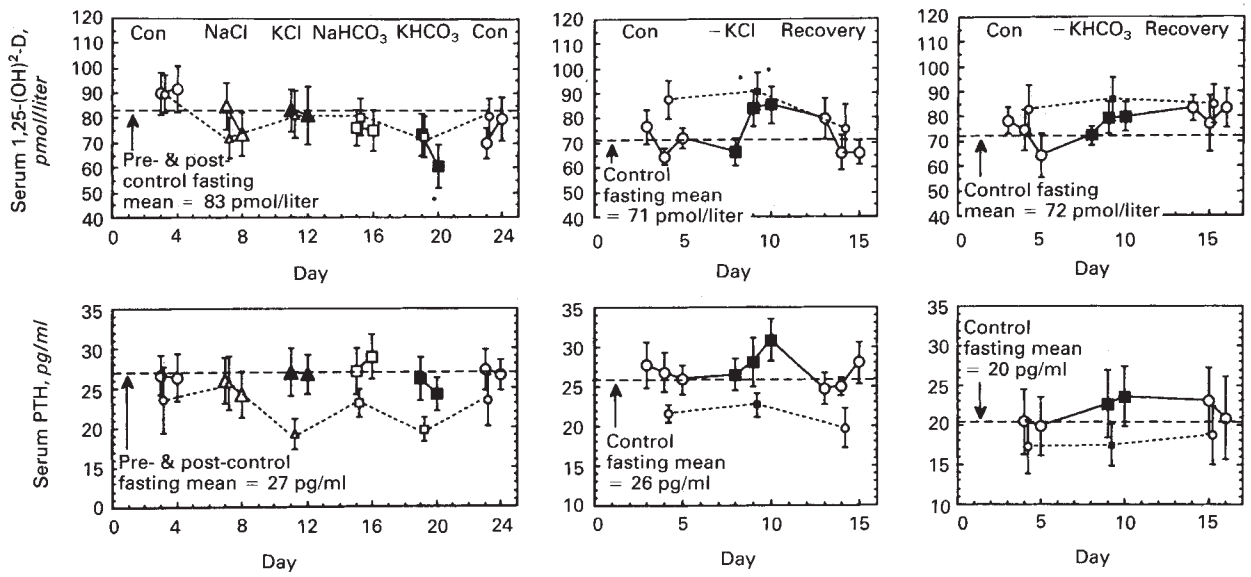

Fig. 7. *Serum 1,25-$(OH)_2$-D (**top**) and PTH (**bottom**) concentrations during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).* Symbols as in Fig. 1.

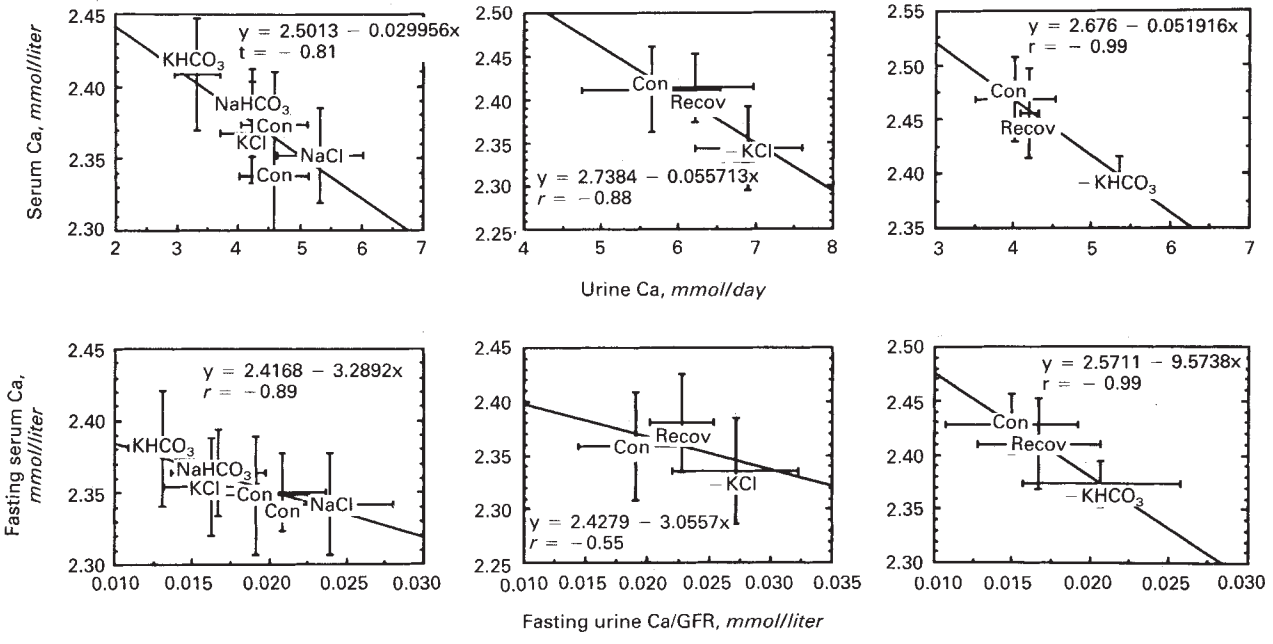

Fig. 8. *Relationships between the group means of two fasting and a single post-breakfast serum total Ca concentrations, as an estimate of serum total Ca prevailing throughout the day, and daily urine Ca excretion (**top**) and the relationships between group mean fasting serum total Ca concentrations and fasting $U_{Ca}V/GFR$ (**bottom**) during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).*

Serum 1,25-$(OH)_2$-vitamin D, PTH, osteocalcin concentrations and fasting urinary hydroxyproline/creatinine excretion

Figure 7 summarizes serum 1,25-$(OH)_2$-D and PTH concentrations during the studies. Serum 1,25-$(OH)_2$-D levels fell slightly but significantly during $KHCO_3$ administration and rose slightly during dietary KCl deprivation. Changes in serum 1,25-$(OH)_2$-D levels were not detectable during $KHCO_3$ deprivation. Fasting serum PTH levels did not change in response to any of the salts administered nor in response to dietary K deprivation. Post-breakfast PTH levels were always lower than fasting concentrations.

Among four subjects deprived of K (two deprived of KCl and two deprived of $KHCO_3$) serum osteocalcin concentrations did not change, averaging 4.9 ± 0.6 ng/ml during control, 4.6 ± 0.3 ng/ml at end K deprivation and 4.8 ± 0.4 ng/ml at end recovery.

Fasting urinary hydroxyproline excretion on the final control day for all 18 studies averaged 15.9 ± 0.5 μmol/mmol creatinine

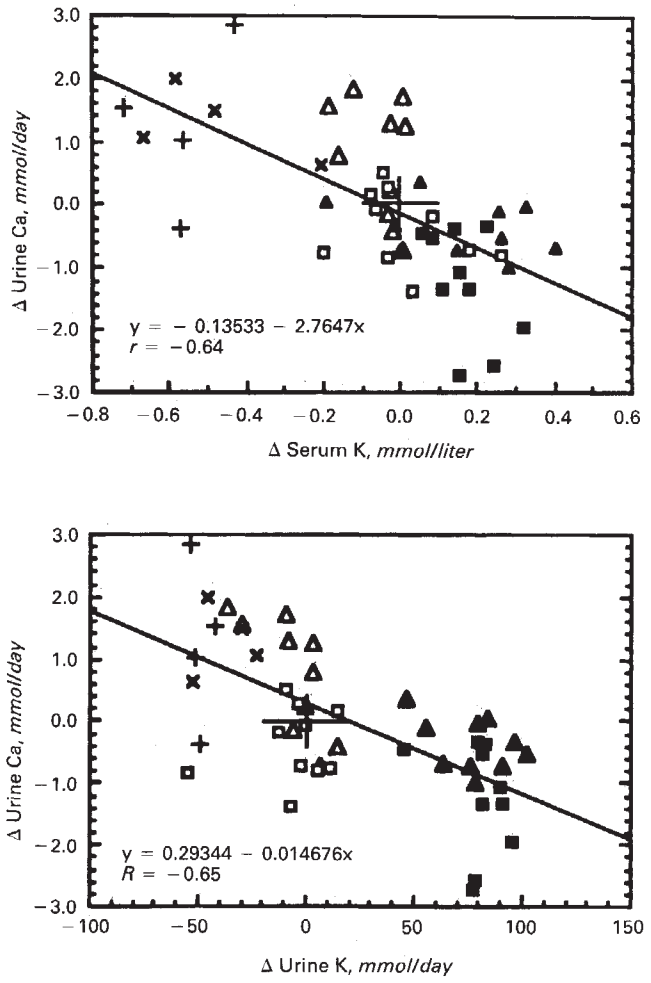

Fig. 9. *Relationships between the individual changes from control of daily urine Ca excretion on the final day of each study phase and the changes from control of serum K concentrations (**top**) or the changes from control of urine K excretion (**bottom**).* Symbols are: administration of NaCl (△), of KCl (▲), of $NaHCO_3$ (□), of $KHCO_3$ (■); KCl deprivation (+) and $KHCO_3$ deprivation (×).

and did not change detectably during the administration of the salts or during dietary K deprivation (data not shown).

Discussion

The data demonstrate that the administration of K is accompanied by a relative or absolute decrease in urinary Ca excretion and that dietary K deprivation, regardless of whether the accompanying anion is Cl^- or HCO_3^-, results in increased urinary Ca excretion. Furthermore, urinary Ca excretion decreased toward or to control rates when KCl or $KHCO_3$ were restored to the diets. As observed previously [6], $KHCO_3$ administration reduced urinary Ca excretion while the administration of $NaHCO_3$ had no sustained effect.

Further correlative evaluation of the results was undertaken in an effort to clarify the possible mechanisms for these effects of K on urinary Ca excretion.

As shown in Figure 8, when group mean data were considered, the mean of two fasting and the post-breakfast measurement of serum total Ca concentrations, an estimate of serum total Ca concentrations prevailing throughout the day, fell as daily urinary Ca excretion rates rose during K deprivation and increased as daily urinary Ca excretion fell during $KHCO_3$ administration. In addition, similar inverse relationships were observed between fasting serum total Ca concentrations and fasting urine Ca/GFR. Since serum Ca concentrations are regulated by renal tubular Ca reabsorption, these relationships imply that the observed changes in urinary Ca excretion were the result of changes in renal tubular Ca reabsorption, although direct measurements of serum ultrafilterable Ca concentrations and of GFR during both K deprivation and $KHCO_3$ administration are needed to verify that net tubular Ca reabsorption decreased, as urinary Ca rose during K-deprivation, and that net tubular Ca reabsorption increased, as urinary Ca excretion fell during $KHCO_3$ administration. Bicarbonate has been shown to increase Ca reabsorption in the proximal tubule [27]. However, it is unlikely that changes in proximal tubular Ca reabsorption accounted for the changes in urinary Ca excretion since Ca excretion increased during both KCl and $KHCO_3$ deprivation and urinary Ca excretion fell during $KHCO_3$ administration but not during $NaHCO_3$ administration. Changes in tubular Ca transport are unlikely to have occurred in the thick ascending loop where Ca and Mg are both reabsorbed [28, 29] since no changes in urinary Mg excretion occurred in relation to K loading or deprivation. Similarly, changes in Ca reabsorption in the distal convolution that are augmented by HCO_3 [30] are unlikely since Ca excretion rose during K deprivation regardless of whether net acid excretion fell slightly during KCl deprivation or rose during $KHCO_3$ deprivation (Figs. 2 and 5). Similarly, $NaHCO_3$ had no sustained effect to reduce Ca excretion despite even greater reductions in net acid excretion and bicarbonaturia (Figs. 2 and 5). Nevertheless, bicarbonate, in addition to K, appears to have a further effect to reduce urinary Ca excretion [30], since $NaHCO_3$ prevented the increase in urinary Ca excretion observed during NaCl and urinary Ca excretion was lower during $KHCO_3$ than during KCl. Since serum PTH concentrations were unchanged, alterations in PTH-stimulated distal renal tubular Ca reabsorption [31, 32] are also unlikely, unless the responsiveness of that transport process to PTH was stimulated by K loading and inhibited by K deprivation.

As shown in Figure 9, the individual changes from control of daily and fasting urinary Ca excretion rates on the last day of each study phase were inversely correlated to both the changes from control of serum K concentrations and the changes from control of urinary K excretion rates. The mechanism for these relationships is not apparent. Moreover, the effects of K loading to decrease and of K deprivation to increase urine Ca excretion are unlikely to be direct, since there was a temporal delay of several days after changing dietary K intake before changes in Ca excretion were apparent (Figs. 2 and 3).

Despite the well known effect of enhanced urinary Na excretion to be associated with enhanced rates of Ca excretion, as exemplified by the increased excretion of Ca during NaCl administration, this cannot be a direct effect since urinary Ca excretion was reduced during $KHCO_3$ administration when urinary Na excretion was unchanged from control rates and urinary Ca excretion increased during K deprivation when urinary Na excretion was reduced (Fig. 5). The possibility that the changes in urinary Ca excretion were related to changes in

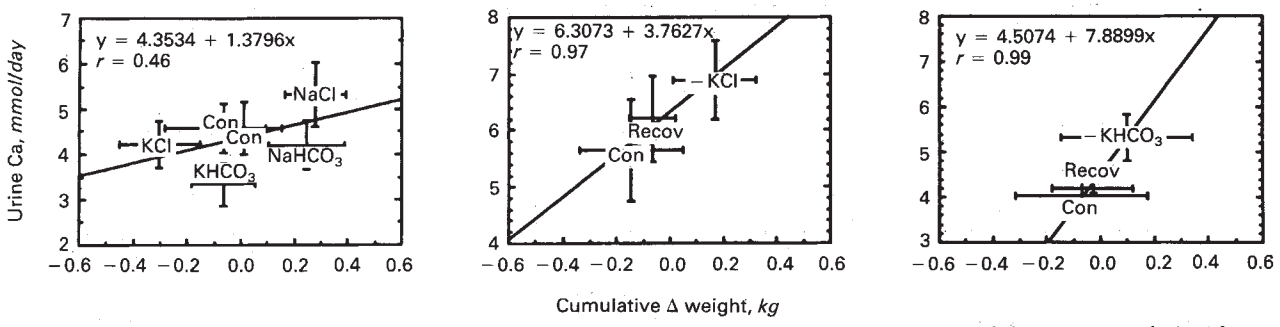

Fig. 10. *Relationships between group mean daily urine Ca excretion on the last day of each study phase and the mean cumulative change from control of body weight at the end of that day during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).*

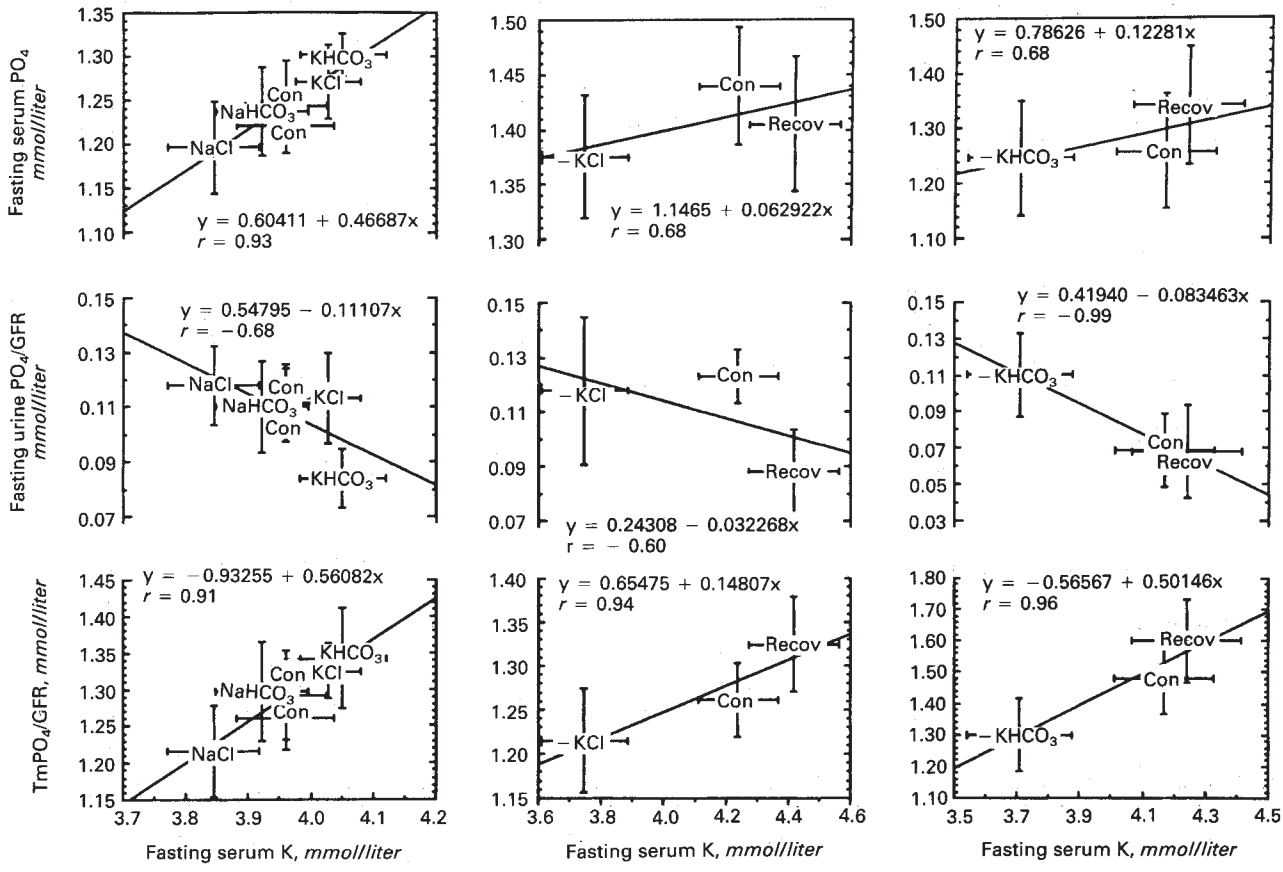

Fig. 11. *Relationships between group mean fasting serum PO_4 concentrations (**top**), fasting $U_{PO_4}V/GFR$ (**middle**) or $TmPO_4/GFR$ (**bottom**) and mean serum K concentrations during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).*

ECF volume were evaluated, as shown in Figure 10, by examining the relationships between urinary Ca excretion on the last day of each study phase and the cumulative changes in body weight. Urinary Ca excretion rose in association with increases in body weight and fell as body weight declined when group mean data for the salt-loading studies, KCl deprivation and $KHCO_3$ deprivation were separately evaluated. Similar increases in urinary Ca excretion in association with weight gain have been observed when Na was substituted for dietary K [14]. The mechanism for these relationships are not further clarified. However, they would not appear to be related to the presumed suppression of aldosterone secretion that occurred during NaCl loading or K deprivation [14], since similar increments in urinary Ca excretion appearing with a similar time delay were observed when ECF volume expansion (and hypokalemia) were produced experimentally by the administration of mineralocorticoid [33].

Because of the temporal delay in the appearance of the changes in Ca excretion in response to alterations in K intake, we have considered the possibility that they may be hormonally

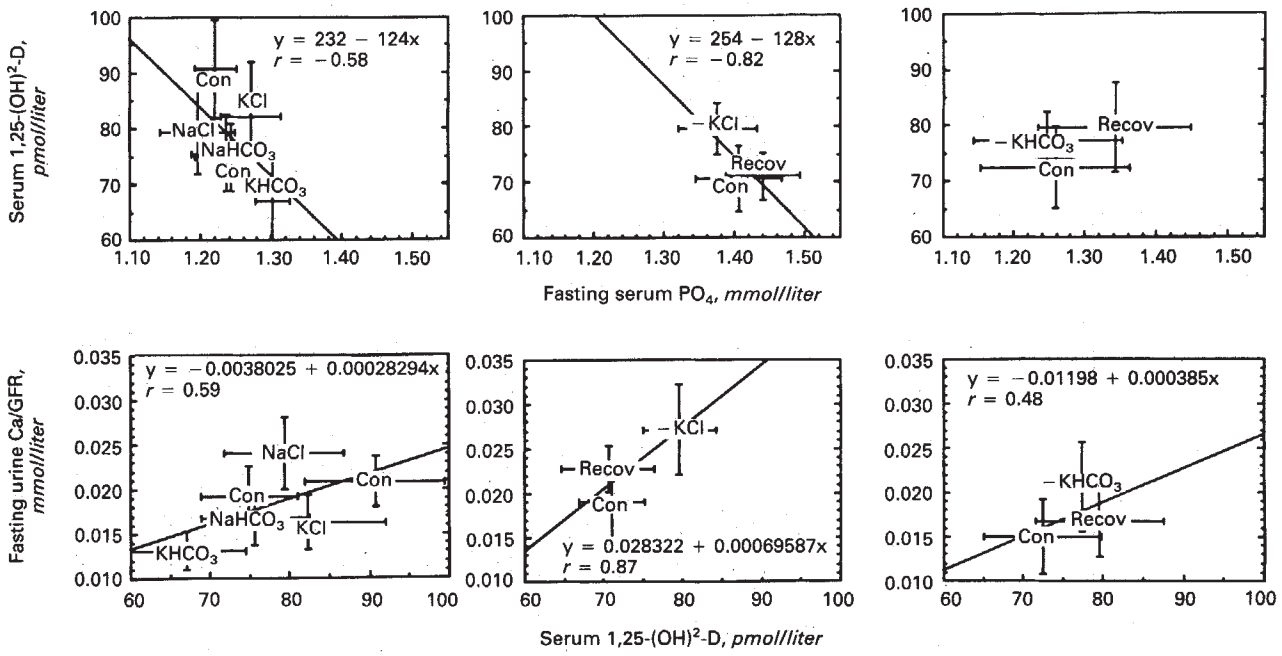

Fig. 12. *Relationships between group mean serum 1,25-$(OH)_2$-D concentrations and serum PO_4 concentrations (**top**) and between mean fasting $U_{Ca}V/GFR$ and serum 1,25-$(OH)_2$-D concentrations (**bottom**) during salt administration (**left**), KCl deprivation (**middle**) and $KHCO_3$ deprivation (**right**).*

mediated. Daily urinary Ca excretion rates are importantly determined by serum 1,25-$(OH)_2$-D concentrations as a consequence of enhanced intestinal Ca absorption [34]. Fasting urinary Ca excretion rates are also importantly determined by 1,25-$(OH)_2$-D concentrations, independent of dietary Ca intake, presumably as a result of the effects of 1,25-$(OH)_2$-D to stimulate bone resorption [34, 35]. Serum PO_4 concentrations or rates of renal tubular PO_4 transport are important determinants of the renal synthesis of 1,25-$(OH)_2$-D and serum levels of the hormone [36–38]. In addition, K is known to acutely enhance renal tubular PO_4 reabsorption [8]. Moreover, a recent study has shown that the administration of KCl or $KHCO_3$ to healthy men was accompanied by reduced urinary PO_4 excretion rates, increased serum PO_4 concentrations and reduced serum 1,25-$(OH)_2$-D excretion rates [9]. In view of these relationships, we have evaluated the interrelationships between serum K, serum and urinary PO_4, serum 1,25-$(OH)_2$-D and urinary Ca excretion for the present studies. As shown in Figure 11, in relation to serum K concentrations, fasting serum PO_4 concentrations tended to rise, fasting urinary PO_4/GFR fall and $TmPO_4$/GFR rise during the administration of K salts, while directionally opposite changes occurred during K deprivation. Moreover, as shown in Figure 12, during salt-loading and during KCl deprivation, although not during $KHCO_3$ deprivation, serum 1,25-$(OH)_2$-D concentrations were inversely correlated to serum PO_4 concentrations, as observed during KCl and $KHCO_3$ loading [9], and as we have also observed previously [39, 40]. In addition, as also shown in Figure 12, fasting urinary Ca/GFR tended to be directly related to the prevailing serum 1,25-$(OH)_2$-D concentrations, also as observed previously [34, 35].

The quantitative effect of K to reduce urinary Ca excretion, 0.015 mmol urine Ca/day/mmol urine K/day or about 0.6 mg urine Ca/day/mmol K/day (Fig. 9) is relatively small. Nevertheless, increases in urinary K excretion of 20 mmol/day would be expected to reduce urinary Ca excretion by about 0.35 mmol/day or 12 mg/day, a significant quantity when cumulated over time. Whether the diet or bone are the ultimate sources of the increased quantities of Ca appearing in the urine during dietary K deprivation are not clarified by the present studies. Our previous balance studies [6] demonstrated that prolonged $KHCO_3$ administration was associated with more positive Ca balances, suggesting that the skeleton may provide the source of the Ca loss during dietary K deprivation. However, further studies of other markers of bone turnover will be needed to clarify the possible role of the skeleton since neither changes in urinary hydroxyproline excretion nor serum osteocalcin concentrations were demonstrable during K deprivation.

If the effect of K to reduce Ca excretion is sustained, as supported by our previous study of more prolonged $KHCO_3$ administration [6], the present data provide further support for the view that diets containing relatively more K and actual or potential HCO_3 in fruits, vegetables and cereals and less potential acid in protein, serve to protect skeletal mass. Moreover, the data suggest that when HCO_3 therapy is required for the treatment of metabolic acidosis, most of the HCO_3 would best be provided as $KHCO_3$ rather than $NaHCO_3$, in the interest of protecting skeletal stores of Ca and PO_4, unless impaired renal K secretion precludes the use of K supplements.

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