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Hypothesis

Hypercalcaemia and metabolic alkalosis with betel nut chewing: emphasis on its integrative pathophysiology

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Abstract

Background. Events in the gastrointestinal tract that might contribute to a high absorption of calcium were simulated *in vitro* to evaluate why only a small proportion of individuals who ingest alkaline calcium salts develop hypercalcaemia, hypokalaemia and metabolic alkalosis.

Methods. A patient who chewed and swallowed around 40 betel nuts daily developed hypercalcaemia, metabolic alkalosis, hypokalaemia with renal potassium wasting, and renal insufficiency. The quantities of calcium and alkali per betel nut preparation were measured. Factors that might increase intestinal absorption of calcium were evaluated.

Results. Hypercalcaemia in the index case was accompanied by a high daily calcium excretion (248 mg, 6.2 mmol). Circulating levels of 1,25-dihydroxyvitamin D_3 and parathyroid hormone were low. Hypokalaemia with a high transtubular K^+ concentration gradient, metabolic alkalosis, a low excretion of phosphate and a very low glomerular filtration rate were prominent features.

Conclusions. Possible explanations for the pathophysiology of metabolic alkalosis and hypokalaemia are provided. We speculate that a relatively greater availability of ionized calcium than inorganic phosphate in the lumen of the intestinal tract could have enhanced dietary calcium absorption.

Keywords: bicarbonate; calcium; hypokalaemia; milk-alkali syndrome; phosphate

Introduction

The triad of hypercalcaemia, metabolic alkalosis, and renal insufficiency characterizes the milk-alkali syndrome [1]. In the past, its most common presentation was in patients with peptic ulcer disease who took large amounts of milk and calcium carbonate ($CaCO_3$). With the advent of better antacid therapy such as H_2 blockers and gastric H^+ pump inhibitors, the incidence of this syndrome has decreased. Recently, features of the milk-alkali syndrome have been described in patients who take alkaline calcium salts and vitamin D supplements to treat osteoporosis [2]. Another predisposing cause, betel nut chewing, is an under-estimated source of oral alkaline calcium salts [3]. Betel nuts are the main ingredient of a masticatory drug used in the Far East, Asia, and the South Pacific by an estimated 600 million people [4]. To overcome their bitter taste, alkaline calcium salts are included in the oral preparation.

To understand why only a few of the many individuals who ingest alkaline calcium salts develop hypercalcaemia, hypokalaemia and metabolic alkalosis, we simulated events in the gastrointestinal tract that could contribute to excessive intestinal absorption of calcium. This involves an interplay between the products of bacterial fermentation and the relative proportions of alkaline calcium salts and inorganic phosphate in segments of the intestinal tract where passive, paracellular, non-regulated absorption of ionized calcium occurs [5].

Subjects and methods

Case

A 60-year-old male patient who developed hypercalcaemia, metabolic alkalosis, hypokalaemia with renal potassium (K^+) wasting, and renal insufficiency associated with a heavy consumption of betel nuts was examined.

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Analysis of betel nut paste

Samples of betel nut paste were obtained from vendors in Toronto, Canada, and in Taipei, Taiwan, to determine the amounts and nature of its calcium compounds. Single preparations were weighed and added to 10 ml of distilled water ($n=6$) or 0.9% saline ($n=5$). Prior to centrifugation, the mixture was vortexed vigorously at room temperature until the pH of the supernatant became constant (~ 12.4). The clear aqueous phase was assayed for ionized calcium. To obtain an estimate of its total calcium content, the entire preparation was dissolved in 1 N HCl prior to assay for calcium. A portion of the aqueous HCl extract was titrated back to the original pH with 0.1 N NaOH to determine whether some of the alkali in that solution was $CaCO_3$ rather than calcium hydroxide ($Ca(OH)_2$) or calcium oxide. If fewer H^+ ions were to remain in solution after HCl addition, this would indicate that some of the anions accompanying calcium were bicarbonate and/or carbonate (CO_3^{2-}) (a total CO_2 analysis by titration [6]). The quantity of chloride (Cl^-) and sodium (Na^+) added was verified by direct assay.

A solution containing 1 mmol of $CaCO_3$ and 2.5 mmol of phosphate buffer (pH 7.4) was incubated for up to 12 h at room temperature. The 2.5-fold excess of phosphate over calcium was selected to represent a typical dietary composition [7]. The aqueous phase was assayed for calcium and phosphate, and the quantity of precipitate was also determined.

$CaCO_3$ (1 mmol) was exposed to increasing amounts of HCl (total volume adjusted to 10 ml with distilled water, $n=24$). Control solutions ($n=6$) consisted of 1 mmol $CaCO_3$ in a total volume of 10 ml H_2O. The clear aqueous phase was aspirated and assayed for ionized calcium. The quantity of HCl added was verified by direct measurement of Cl^-.

Analytical techniques

Calcium was measured by an ion-selective electrode (Model 97–20, Orion Research Inc., Beverley, MA, USA), and pH was measured by an Orion pH meter (perpHect Log R meter, Model 370, Orion Research Inc.). The concentration of Cl^- was measured by a Cl^- titrator (Radiometer, Model CMT-10) and Na^+ and K^+ were measured by flame photometry as previously described [8].

Results

Case synopsis

The 60-year-old male sought medical attention because of anorexia and constipation that were more marked over the past several weeks. He had lost 7 kg of weight in this period. There was no other pertinent past medical history. He denied any consumption of vitamin D supplements. By habit, he chewed approximately 40 betel nuts from *Areca catechu* on a daily basis, and had done so for more than 40 years. These nuts were wrapped in the leaves of *Piper betle* along with a calcium-containing paste. He had developed a psychological and physical dependence on this stimulant. Typically, he swallowed the saliva and the remainder of the betel nut preparation. The calcium content of samples that were estimated to represent the amount of paste used in one preparation (0.1 g dry weight) was 1.4 ± 0.06 mmol. Therefore, he consumed approximately 50 mmol of calcium per day in the 40 betel nuts. Back-titration with NaOH confirmed that the alkali was $Ca(OH)_2$ rather than $CaCO_3$. The solubility of the $Ca(OH)_2$ paste at room temperature was 11.3 ± 0.64 mmol/l in water ($n=6$) and 12.5 ± 0.57 mmol/l in 0.9% saline ($n=5$); the pH of the latter solution was 12.4. In contrast, $CaCO_3$ was very sparingly soluble in water so its calcium and alkali load would have depended almost exclusively on swallowing if it had been the oral alkaline salt.

On physical examination, the patient was conscious and alert with a supine blood pressure of 114/70 mmHg, heart rate of 80 beats/min, respiratory rate of 14 breaths/min, and his body temperature was 36.6°C. In the upright position, his blood pressure fell to 102/64 mmHg and his pulse rate rose to 94 beats/min. The jugular veins were flat and there was no peripheral oedema. Cardiopulmonary and abdominal examinations were unremarkable. There were no focal neurological deficits except for bilateral hyporeflexia. His tongue, oral mucosa and the angles of his mouth were stained brick-red by the betel nut juice.

The most striking features revealed by the laboratory examination were hypercalcaemia (12.8 mg/dl, 3.2 mmol/l), metabolic alkalosis (plasma pH 7.47, bicarbonate 36 mmol/l), and a very high plasma creatinine and BUN level (calculated creatinine clearance was 8.1 ml/min) (Table 1). Serum intact parathyroid hormone (PTH) (2.7 pg/ml) and 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$) levels (8.2 pg/ml) were below the normal range (PTH, 10–65 pg/ml; 1,25-$(OH)_2D_3$, 16.4–42.4 pg/ml). Hypokalaemia (3.2 mmol/l) was present and accompanied by a urine K^+ concentration of 21 mmol/l, a urine K^+/creatinine ratio of 2.3 and a transtubular K^+ concentration gradient (TTKG) of 7. The urinary excretion of calcium was high (248 mg/day, 6.2 mmol/day, calcium/creatinine 0.64 *vs*

Table 1. Values on admission in the index case

	Plasma	Urine
pH	7.47	7.5
Bicarbonate (mmol/l)	36	–
PCO_2 (mmHg)	50	–
Na^+ (mmol/l)	137	64
K^+ (mmol/l)	3.2	21
Cl^- (mmol/l)	91	42
Anion gap (mEq/l)	10	43
BUN (urea) (mg/dl (mmol/l))	47 (17)	–
Creatinine (mg/dl (μmol/l))	9.7 (844)	108 (9400)
Glucose (mg/dl (mmol/l))	88 (5.0)	0
Calcium (mg/dl (mmol/l))	12.8 (3.2)	23.4 (5.9)
Phosphate (mg/dl (mmol/l))	5.7 (1.84)	5.9 (2.1)
Volume (l/day)	–	1.1
Albumin (g/dl)	3.9	–
Calculated values		
FE_K (%)	6.5	
TTKG	7.0	
Ca/creatinine (mmol/mmol)	–	0.64

our upper limit of normal being 0.4 in mmol terms), and the urinary excretion of inorganic phosphate was very low (65 mg/day, 2.1 mmol/day).

The patient's haemoglobin level was 9.2 g/dl, white cell count was 7200/mm^3 and platelet count was 239 000/mm^3. Trace proteinuria was present on urinalysis and there were granular casts seen on microscopic examination of the urine sediment.

Soft tissue calcification was not seen on a chest X-ray, abdominal X-rays or a 99mTC-diphosphonate whole body bone scan. Abdominal sonography revealed normal-sized kidneys, and nephrocalcinosis was not detected. There was no evidence of parathyroid gland enlargement on sonography. Band keratopathy was not seen on slit lamp examination. Panendoscopy did not reveal any malignancy.

Initial therapy included intravenous isotonic saline to re-expand his extracellular fluid (ECF) volume. His plasma calcium concentration fell between days 1 and 3 to 7.0 mg/dl (1.8 mmol/l); his plasma PTH level was 10-fold higher when he became hypocalcaemic. These data suggest that the fall in calcium input and the expanded ECF volume may have led to hypocalcaemia. At this point, his PTH level rose to 32 pg/ml. The degree of rise in PTH was less than reported by previous workers [9] and may represent the degree of PTH reserve or down-regulation that may occur with chronic hypercalcaemia. Nevertheless, either this degree of rise in PTH and/or a decreased rate of calcium excretion led to the subsequent rise in his plasma calcium concentration to the normal range (Table 2). Hypercalcaemia and metabolic alkalosis resolved completely within 1 week (Table 2). Although the patient's renal function improved considerably in this time interval, his GFR remained significantly depressed on discharge; serum creatinine declined initially from 9.7 to 3.0 mg/dl (844 to 251 μmol/l) (Table 2). The progress of his recovery in GFR could not be documented because he was lost to medical follow-up. The patient was advised to stop chewing betel nuts and, while in our care, he decreased his consumption to fewer than five nuts per day.

Additional studies

Exposure of a calcium carbonate precipitate to an inorganic phosphate buffer. This experiment was designed to simulate events in the intestinal tract downstream from the duodenum. When 1 mmol of $CaCO_3$ was added to 2.5 mmol of inorganic phosphate at pH 7.4 for 12-h, much of the flaky $CaCO_3$ precipitate was converted to a hard, white precipitate of insoluble calcium phosphate ($Ca_3(PO_4)_2$) over 12 h despite the absence of added H^+. There was no detectable ionized calcium remaining in the solution. The content of inorganic phosphate fell progressively to 2.1 mmol as more precipitate formed, implying that 60% of the $CaCO_3$ was converted to $Ca_3(PO_4)_2$ at this time point.

Calcium carbonate exposure to HCl. When increasing amounts of HCl were added to a solution containing 1 mmol $CaCO_3$, ionized calcium was released in a linear and equivalent fashion by the added H^+ (Figure 1). Hence, 100 mEq H^+ would need to be produced by bacterial fermentation in the lower intestinal tract to convert the total amount (50 mmol) of ingested $CaCO_3$ to ionized calcium. Much smaller amounts of H^+ would be needed to dissolve only a portion of the $CaCO_3$; the patient only excreted 6 mmol of calcium in 24 h.

Table 2. Serial serum biochemical values in the index case

Day	0	1	3	7	14
BUN (mg/dl)	47	50	45	41	37
Creatinine (mg/dl)	9.7	9.3	6.3	5.6	3.0
Total calcium (mg/dl)	12.8	12.1	7.0	9.8	10.1
Phosphate (mg/dl)	5.7	3.6	3.3	–	–
Bicarbonate (mmol/l)	36	33	24	23	–
PCO_2 (mmHg)	50	47	39	–	–
Intact PTH (pg/ml)	2.7	–	32	44	–
1,25-$(OH)_2D_3$ (pg/ml)	8.2	–	–	–	–

Discussion

Our aim was to identify the risk factors leading to the development of the major electrolyte abnormalities, including hypercalcaemia, metabolic alkalosis, and hypokalaemia, in association with excessive calcium and alkali intake. Considerable emphasis was placed on the case synopsis because it illustrates an underemphasized cause being a high intake of alkaline

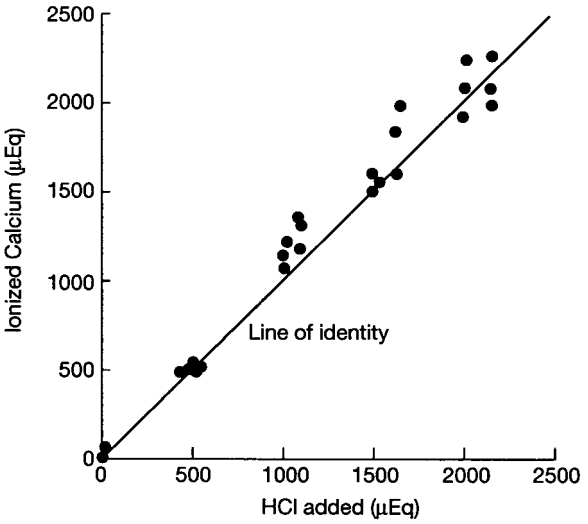

Fig. 1. Formation of ionized calcium by adding HCl to $CaCO_3$. Increasing amounts of H^+, when added to a solution containing 1 mmol of $CaCO_3$, leads to the release of ionized calcium in a linear and equivalent amount. The source of these H^+ *in vivo* are gastric secretion of HCl and H^+ production during fermentation of carbohydrates downstream in the intestinal tract.

calcium salts in conjunction with a low absorption of inorganic phosphate.

Hypercalcaemia

Calcium is absorbed in the duodenum by a highly regulated transcellular route, and downstream in the intestinal tract both by a regulated and by a passive non-regulated paracellular route, provided that calcium is in its ionized form [5]. The major regulator of intestinal ionized calcium absorption is $1,25\text{-}(OH)_2D_3$; ionized calcium is formed when $Ca(OH)_2$ or $CaCO_3$ reacts with HCl secreted in the stomach (Figure 2). Calcium remains ionized until sufficient sodium bicarbonate is secreted into the duodenum to form a luminal $CaCO_3$ precipitate.

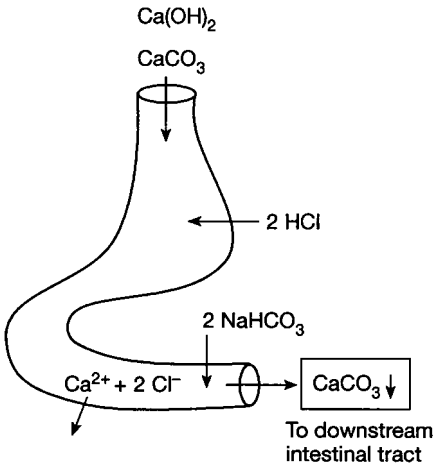

Fig. 2. Generation and absorption of ionized calcium in the upper intestinal tract. Alkaline calcium salts ($Ca(OH)_2$ and $CaCO_3$) are poorly soluble in water. They are converted to ionized calcium by gastric HCl. There are three possible fates for ionized calcium leaving the stomach. Firstly, it can be removed by precipitation with inorganic phosphate (but not with organic phosphate). Secondly, while in its ionic form, calcium can be absorbed in the duodenum. Thirdly, when sufficient $NaHCO_3$ is secreted into the duodenum, ionized calcium will be precipitated as $CaCO_3$. This $CaCO_3$ will not react readily with inorganic phosphate produced by digestion of organic phosphates. Hence $CaCO_3$ and inorganic phosphate are delivered downstream in the intestinal tract (see Figure 3).

The aim of the first *in vitro* experiments was to determine the maximum concentration of ionized calcium in water or isotonic saline solutions that represent the possible extremes of salivary Na^+ concentration [10]. With a typical salivary flow of 0.5 ml/min for 12 h per day [10] and an ionized calcium concentration of approximately 12 mmol/l, a maximum of about 4–5 mmol of calcium could be dissolved in saliva and swallowed daily. In contrast, if the entire betel nut paste and saliva were swallowed, the intake of calcium would be close to 52 mmol/day (1.4 mmol/sample × 40 samples). These values for calcium ingestion should be compared with a typical intake of 20 mmol of calcium per day and with the normal net absorption of up to 5 mmol/day [7]. Higher absorption rates cause hypercalciuria [11].

If the $CaCO_3$ precipitate formed in the duodenum were to remain intact downstream in the intestinal tract, there might be little further absorption of calcium. However, $CaCO_3$ can be converted to ionized calcium in the lumen of the lower intestinal tract if there is a local source of H^+ (Figure 3) [5]. Bacterial fermentation of undigested carbohydrates can provide 300 mmol of H^+ per day [12]. Only a few mmol of H^+ would be needed to dissolve enough $CaCO_3$ to yield a luminal ionized calcium concentration exceeding that of plasma. This would permit passive calcium absorption if anions, such as inorganic phosphate, that could remove ionized calcium by precipitation were not

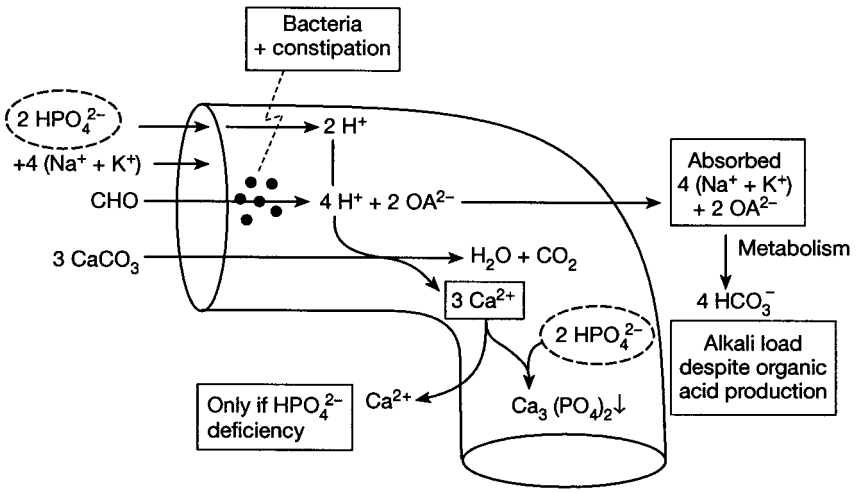

Fig. 3. Absorption of calcium downstream in the intestinal tract. The central structure represents downstream segments of the intestinal tract where calcium can be reabsorbed if it exists in an ionized form. Delivery of calcium is via a precipitate of calcium carbonate; ionized calcium (Ca^{2+}) is formed when H^+ is produced by bacterial fermentation and by conversion of inorganic phosphate (HPO_4^{2-}) to PO_4^{3-}. Should the delivery of HPO_4^{2-} be less than required to precipitate Ca^{2+} as $Ca_3(PO_4)_2$, some Ca^{2+} could remain in the lumen and be absorbed. A potential bicarbonate load (organic anions (OA^{2-})) is also absorbed representing the conversion of some of the alkali in $CaCO_3$ to bicarbonate in the body when OA^{2-} are metabolized to neutral end-products [19].

present in the lumen of the intestinal tract, as shown by Equation 1:

$$3CaCO_3 + 2(HPO_4^{2-} + 2(K^+ \text{ or } Na^+)) \rightarrow Ca_3(PO_4)_2 + 4(K^+ \text{ or } Na^+) + 2CO_3^{2-} + H_2O + CO_2 \quad (1)$$

The interplay between inorganic phosphate and ionized calcium is complex. Firstly, the bulk of inorganic phosphate is formed after the digestion of organic phosphates later in the upper intestinal tract. In quantitative terms, a typical diet supplies more than twice as much phosphate as calcium [7]. Nevertheless, as shown by our results, mixing insoluble $CaCO_3$ with the expected 2.5-fold excess of inorganic phosphate at pH 7.4 removed 60% of the calcium from $CaCO_3$ over a 12 h period, without ionized calcium being measurable in solution. Once $Ca_3(PO_4)_2$ is formed, it should remain intact in the rest of the intestinal tract because the luminal pH distal to the stomach is not low enough to re-dissolve this precipitate. Secondly, to have a large enough quantity of ionized calcium in the lumen of downstream intestinal sites, $CaCO_3$ would need to be present in quantities in excess of inorganic phosphate. This could occur if the source of dietary calcium was an intake of alkaline calcium salts, rather than sources of animal or vegetable origin (which need a low phosphate content). Moreover, once initiated, hypercalcaemia can cause a vicious cycle by leading to anorexia such that the intake of alkaline calcium salts in betel nut preparation, or as $CaCO_3$, might further exceed the dietary intake of phosphate. The net result would be increased calcium, but low phosphate absorption due to the precipitation of $Ca_3(PO_4)_2$ in the lumen of the intestinal tract, as was suggested by the low excretion of phosphate (2 mmol/day *vs* the normal 20–30 mmol/day) in our case (Table 1). The soluble products of this precipitation reaction are CO_3^{2-} anions, yielding an absorbable alkali load (Figure 3, Equation 1).

One should also consider the properties of the anions produced by bacterial fermentation when there is less phosphate than calcium in the distal intestinal lumen. If some of these anions had properties similar to oxalate, ionized calcium would be removed by precipitation in the lumen of the intestinal tract. Hence, less ionized calcium would be available for absorption by the paracellular route. A low intake of milk could contribute to the development of the features in our patient [13]. Because milk is rich in phosphate, a low phosphate intake could diminish the precipitation of $Ca_3(PO_4)_2$ downstream in the intestinal tract, allowing higher local ionized calcium levels (Figure 3). On the other hand, milk provides lactose that is said to augment the intestinal absorption of calcium [14]. Several mechanisms have been proposed to explain why a high oral lactose intake might increase intestinal calcium absorption. Firstly, the number of osmoles in the lumen could rise when lactose is hydrolysed into its component monosaccharides (glucose plus galactose) or into volatile fatty acid products by bacterial fermentation (lactic, butyric and propionic acid). As a result of this osmole load, water might enter the lumen and cause it to distend. This distention could increase the permeability of the junctions between enterocytes and allow more ionized calcium to be absorbed by solvent drag [15,16]. In lactase-deficient subjects, there is an additional mechanism to consider. The very large H^+ load from bacterial fermentation would increase the concentration of ionized calcium (Figure 3), thereby increasing its potential absorption [17,18].

Metabolic alkalosis

The ingestion of $CaCO_3$ could provide an absorbable form of alkali if organic acids were produced in the lumen of the intestinal tract, provided that their conjugate bases (acetate, proprionate and butyrate) were absorbed and metabolized to yield neutral metabolic end-products plus bicarbonate ions [19] (Figure 3). In fact, hypercalcaemia might augment the formation of organic acids and enhance the absorption of ionized calcium by slowing GI motility. One can obtain a crude estimate of how much alkali was absorbed along with calcium in our index case by examining the rate of excretion of calcium, at least in one 24 h urine collection period [7]. For the alkali accompanying calcium to remain as a bicarbonate in the body, calcium must remain in an ionic form or be excreted with an anion other than bicarbonate (e.g. Cl^- from NaCl). Therefore the alkali load attributed to the net absorption of $Ca(OH)_2$ is equal to the daily renal excretion of ionized calcium (12 mEq/day). Because our patient was excreting more than 12 mEq of bicarbonate per day in his urine (pH 7.5, volume 1.1 l/day), another source of alkali would be needed to be in positive alkaline balance. Given his urine pH and GFR, the alkaline source was likely to have been a non-renal one because low excretion of ammonium means little addition of new bicarbonate to the body [20]. As shown in Figure 3 and Equation 1, the patient could, in theory, convert two-thirds of the alkali (carbonate) from the poorly absorbable $CaCO_3$ into absorbable alkali by precipitation reactions in the intestinal tract.

Nevertheless, ingesting alkaline substances, even in large amounts, is not sufficient to cause the development of chronic metabolic alkalosis in normal subjects [21]. In subjects with marked renal insufficiency, the intake of $NaHCO_3$ could lead to the development of metabolic alkalosis. If this were the sole cause, the ECF volume should be expanded. In contrast, if vomiting provided the bicarbonate load, the ECF volume would remain near its normal value. Given our patient's very low GFR, the metabolic alkalosis could be due in part to the input of bicarbonate, and due to a low rate of bicarbonate excretion because of the low filtered load for this ion. Therefore, the presence of calcium in the alkali load or the absence of a large intake of Na^+ (in $NaHCO_3$) might play a critical role in the metabolic alkalosis in our index case. Hence renal mechanisms were sought to explain why chronic metabolic alkalosis was present in this patient.

Hypercalcaemia and suppressed levels of PTH enhance the renal reabsorption of bicarbonate (left portion of Figure 4) [22] by stimulating the Na^+/H^+ exchanger [23]. If enhanced proximal reabsorption of bicarbonate were the sole mechanism involved in this process, one would anticipate an expanded rather than a contracted ECF volume, as was seen in our case. Therefore we looked for a link between hypercalcaemia, metabolic alkalosis and a low ECF volume.

There were two important stimulators of proximal bicarbonate reabsorption in our case: angiotensin II (A_{II}) [24] and hypokalaemia [25]. Hypercalcaemia might lead to high levels of A_{II} and hypokalaemia by producing a Bartter's-like effect because of occupancy of the calcium receptor on the basolateral aspect of cells of the medullary thick ascending limb of the loop of Henle (LOH) [26]. When occupied by calcium, the ROM-K ion channel in its luminal membrane becomes inhibited, and the lumen lacks K^+ and its usual positive voltage. As a result, there is less reabsorption of Na^+ and Cl^- as well as ionized calcium in the LOH. The consequences of this reabsorptive defect could lead to findings akin to the ROM-K defect subtype of Bartter's syndrome, with wasting of Na^+, Cl^-, K^+ and calcium in the urine and the subsequent development of metabolic alkalosis [27]. A deficit of Na^+ and Cl^- lowers the ECF volume, and leads to the release of renin and the formation of A_{II} [28]. Both hypokalaemia and high levels of A_{II} augment the reabsorption of bicarbonate in the proximal convoluted tubule (right side of Figure 4) [24]. Hence, there could be direct and indirect roles for calcium in causing an augmented proximal reabsorption of bicarbonate. This form of metabolic alkalosis can be distinguished from that of vomiting because there is an abundant excretion of Cl^- in the urine in the absence of a diuretic (Tables 1 and 2).

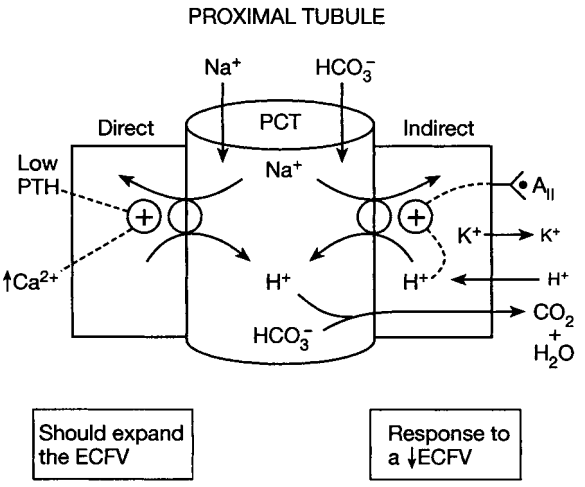

Fig. 4. Possible mechanisms to explain metabolic alkalosis and a contracted ECF volume. There are two possible and not mutually exclusive ways that metabolic alkalosis could occur as a result of hypercalcaemia. As shown on the left side of the figure, both hypercalcaemia and a suppressed PTH level can augment the reabsorption of HCO_3^- in the PCT. If these were the only actions, one might expect to find an expanded ECF volume. A second effect of hypercalcaemia is due to its loop diuretic-like effect that produces $Na^+ + Cl^-$ and K^+ wasting. The resultant high A_{II} levels and hypokalaemia could both act in concert to stimulate the reabsorption of bicarbonate in the PCT (right side of the left-hand portion of the figure). This mechanism of action is associated with a contracted ECF volume.

Renal failure

Hypercalcaemia can cause arteriolar vasoconstriction within the kidney, a reduction in the ultrafiltration coefficient, a reduction in tubular Na^+ reabsorption, acute tubular necrosis, nephrocalcinosis, and tubulointerstitial fibrosis, all of which can result in renal dysfunction via decreased GFR or direct tubular damage [29–31]. The coexistence of hyperphosphataemia, hypercalcaemia, ECF volume reduction and metabolic alkalosis could promote renal parenchymal calcification, an important pathological aspect of the syndrome that contributes to the development of renal dysfunction.

Perspectives

Patients who may be at risk of developing hypercalcaemia and secondary metabolic alkalosis include those individuals given $CaCO_3$ and vitamin D supplements to delay the development of osteoporosis. Risk factors, such as low phosphate intake and factors that might affect the process of bacterial fermentation, should also be considered. These patients may be recognized initially by finding hypercalciuria, subtle symptoms attributable to hypercalcaemia, an unexplained fall in GFR, or by the presence of electrolyte abnormalities such as hypercalcaemia, hypokalaemia and metabolic alkalosis. A high urine calcium : creatinine ratio in a random urine sample might be a reasonable screening test for the detection of a population at risk of these complications.

Patients with renal failure are often treated with $CaCO_3$ to ensure that some of their dietary phosphate is converted to a non-absorbable form. This therapy should not lead to harmful effects related to excessive calcium absorption as long as their intestinal lumen contains more inorganic phosphate plus oxalate than ionized calcium. Notwithstanding, should a rare patient take too much $CaCO_3$, ingest too little dietary phosphate, and/or have an altered bacterial flora that decreases the availability of luminal oxalate, excessive absorption of calcium could occur. In this situation, hypercalcaemia and/or metastatic calcification might develop.

Concluding remarks

Our interpretation of the pathophysiology of hypercalcaemia, hypokalaemia and metabolic alkalosis in the case presented includes roles for the conversion of oral alkaline calcium salts to an absorbable form of ionized calcium due to bacterial production of H^+ in the GI tract. Key to this being a potential clinical problem is the presence of a low phosphate intake

and/or the presence of phosphate binders in the lumen. Another risk factor is the consumption of the precursors of $1,25\text{-}(OH)_2D_3$ that could stimulate calcium absorption in the intestinal tract. At the renal level, hypercalcaemia could cause a Bartter's-like syndrome due to a loop diuretic-like effect contributing to the development of hypokalaemia, a K^+ deficit, a contracted ECF volume and an enhanced reabsorption of bicarbonate in the proximal convoluted tubule.

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