Calcium (Ca) balance is the net of Ca intake and output from the body over a period of time. Although the concept of Ca balance is instructive, it does not consider the redistribution of Ca that often occurs in patients with chronic kidney disease (CKD), especially those who are on dialysis. This redistribution of Ca, often in the form of soft tissue and/or vascular calcification, suggests that consideration of overall balance is insufficient for our patients with CKD. Patients with extrasosseous calcification may be in positive, neutral, or negative total Ca balance. In dialysis patients, total body Ca is often maldistributed. Thus, in this article, we consider movement of Ca related to the extracellular fluid (ECF).

The ECF, especially the plasma water, provides a conduit to connect the gastrointestinal (GI) tract, kidney, and bone. The daily fluxes of Ca between these organs are often far greater than the total Ca content of the ECF. Although there is continual input of Ca into and out of the ECF, net Ca movement relative to the ECF in adults should ideally be 0. If there is net Ca input into the ECF from intestinal Ca absorption or bone resorption or, in the case of patients who are on dialysis, an influx of Ca from the dialysis procedure, then the Ca input into the ECF must be deposited “somewhere,” because the ECF Ca concentration must be held relatively constant to maintain optimal cellular function. In patients with CKD, that “somewhere” is often at extrasosseous sites such as soft tissue or vessels (1–3). The blood Ca concentration is not informative as to whether Ca is moving into or out of the ECF. The level of blood Ca, specifically the concentration of the biologically active ionized Ca, is set by a variety of hormones and other factors, such as the amount of unmineralized collagen, to provide optimal cellular function and is not a “gauge” of how much Ca is in the body or moving into or out of the ECF. Continual movement of Ca into the ECF from the intestine and/or bone will increase blood Ca concentration only when it exceeds the rate of Ca deposition at other ECF sites (e.g., soft tissue).

**Determinants of Extracellular Ca Content**

At a constant ECF volume, a change in the ECF Ca content reflects a change in the difference between the continual input and output of Ca from the ECF (equation 1),

\[
\Delta ECFCa = ECF\ input_{Ca} - ECF\ output_{Ca}
\]

where \( \Delta ECFCa \) is change in the ECF Ca content (mass/unit time), \( ECF\ input_{Ca} \) is gain of Ca into the ECF (mass/unit time), and \( ECF\ output_{Ca} \) is loss of Ca from the ECF (mass/unit time) (4). \( \Delta ECFCa \) will normally be 0, because the input and output of Ca over a short period of time (seconds to minutes) are identical. \( \Delta ECFCa \) will become positive when the input of Ca to the...
ECF exceeds the output of Ca from the ECF and negative when output exceeds the input. A change in $\Delta ECFCa$ will alter the Ca content in the ECF according to the following relationship:

$$\text{(ECFCa)}_{\text{new}} = \text{(ECFCa)}_{\text{old}} \times \text{time} + \text{(ECFCa)}_{\text{old}}$$  \hspace{1cm} (2)

where $(\text{ECFCa})_{\text{new}}$ is new ECF volume Ca content (mass) at the end of the time period (time), and $(\text{ECFCa})_{\text{old}}$ is ECF Ca content at the beginning of the time period.

In this analysis, we are most concerned with ECF Ca content. It is understood that the ECF consists not only of the plasma water but also of the interstitial, transcellular, bone, and connective tissue fluid. The equilibrium of Ca between the many ECF compartments, especially the bone fluid, is not well understood. Although the bone mineral, strictly speaking, is part of the ECF, for the purposes of this analysis, it is treated as a separate compartment because only approximately 1% of the Ca contained within the bone mineral is readily accessible to the ECF (5). In addition, Ca deposition in bone has far different consequences than Ca deposition in soft tissues such as the vasculature.

### Calcium Input to the ECF

In people with normal renal function, net input of Ca into the ECF can come only from bone mineral resorption and intestinal Ca absorption (equation 3; Figure 1) because the kidney can reabsorb only filtered Ca.

$$\text{ECF input}_{\text{Ca}} = \text{Br}_{\text{Ca}} + D_{\text{Ca}} \times \alpha_{\text{Ca}}$$  \hspace{1cm} (3)

where $\text{Br}_{\text{Ca}}$ is Ca released during bone resorption (mass/unit time), $D_{\text{Ca}}$ is dietary Ca supply (mass/unit time), and $\alpha_{\text{Ca}}$ is fraction of intestinal Ca absorbed (4). $\alpha_{\text{Ca}}$ is defined as follows:

$$\alpha_{\text{Ca}} = \frac{\text{dietary Ca intake} - \text{fecal Ca excretion}}{\text{dietary Ca intake}}$$  \hspace{1cm} (4)

Ca may be absorbed in all segments of the small intestine through paracellular diffusion and active transport (6–8). The active transport is regulated by 1,25-dihydroxycholecalciferol [1,25(OH)$_2$D$_3$] and occurs in three distinct steps. There is first movement of Ca across the luminal membrane into the intestinal cell. The cellular Ca concentration is small, so this step occurs down a steep concentration gradient. The mechanism of this transport involves opening of a Ca channel, TRPV6 (7). Ca is then transported through the cytosol by binding to a 1,25(OH)$_2$D$_3$-dependent Ca-binding protein, calbindin D$_{9K}$. Last, Ca is transported across the basolateral cell membrane against a steep concentration gradient, a step that requires either Ca ATPase or sodium/Ca exchange. Both absorption and secretion of Ca have been demonstrated in the duodenum, jejunum, and ileum, and 1,25(OH)$_2$D$_3$ seems to stimulate Ca active transport in all segments of small intestine. Although absolute net Ca transport in the colon is limited, at least in rats the feces is capable of Ca transport (9).

For this analysis, it is not necessary to subdivide the reabsorption of secreted Ca from the absorption of dietary Ca. Note that $\alpha_{\text{Ca}}$ reflects overall net Ca absorption, which takes into account reabsorption of any Ca secreted into the intestine. Thus, $\alpha_{\text{Ca}}$ may be negative, for example, during consumption of an extremely low-Ca diet, when there is little intake of Ca and some of the secreted intestinal Ca is lost in the feces.

In patients who are on dialysis, Ca can enter the ECF through the dialysis procedure when the dialysis bath Ca concentration exceeds that of the blood ionized Ca (equation 5):

$$\text{ECF input}_{\text{Ca}} = \text{Br}_{\text{Ca}} + D_{\text{Ca}} \times \alpha_{\text{Ca}} + \text{Dial}_{\text{Ca}} \text{In}$$  \hspace{1cm} (5)

where Dial$_{\text{Ca}}$In is Ca input to the ECF from the dialysis procedure.

### Calcium Output from the ECF

In patients with normal renal function, output of Ca from the ECF can occur through any combination of bone formation, renal Ca excretion, or sweat (equation 6):

$$\text{ECF output}_{\text{Ca}} = \text{Bf}_{\text{Ca}} + \text{GFR} \times \text{UF}_{\text{Ca}} \times (1 - f_{\text{Ca}}) + \text{Sweat}_{\text{Ca}}$$  \hspace{1cm} (6)

where $\text{Bf}_{\text{Ca}}$ is Ca being deposited on the bone (mass/unit time); $\text{UF}_{\text{Ca}}$ is ultrafilterable Ca; $f_{\text{Ca}}$ is overall renal tubule fractional reabsorption of Ca; and $\text{Sweat}_{\text{Ca}}$ is the calcium lost in sweat, which includes other minor losses such as hair, desquamated skin, finger nails, etc. (4). We have excluded from this equation the large Ca loss in the milk of lactating women, although this analysis could be extended to lactating women by simply adding a term for this loss. Pregnant women are included because there is no distinction between bone formation in the mother or the fetus.

Patients who are on dialysis can also lose Ca from the ECF into the dialysate. Patients who are on dialysis may have residual renal function with the loss of some urinary Ca:

$$\text{ECF output}_{\text{Ca}} = \text{Bf}_{\text{Ca}} + \text{GFR} \times \text{UF}_{\text{Ca}}$$

$$\times (1 - f_{\text{Ca}}) + \text{Sweat}_{\text{Ca}} + \text{Dial}_{\text{CaOut}}$$  \hspace{1cm} (7)

where Dial$_{\text{CaOut}}$ is Ca lost from the ECF during the dialysis procedure.
Thus,
\[
\Delta \operatorname{ECF}_{Ca} = (B_{Ca} + D_{Ca} \times \alpha_{Ca} + \text{Dial}_{Ca,In}) - (B_{fCa} + GFR \times UF_{Ca} \\
\times [1 - fr_{Ca}] + Sweat_{Ca} + \text{Dial}_{Ca,Out})
\] (8)

\[J_{B_{Ca}}\] is defined as the net efflux of Ca from the bone mineral:
\[
J_{B_{Ca}} = B_{Ca} - B_{fCa}
\] (9)

and \(J_{B_{Ca}}\) consists of the combination of a net cellular Ca flux and a net physicochemical Ca flux, both in units of mass/unit time. A positive \(J_{B_{Ca}}\) indicates an efflux of Ca from bone into the ECF, whereas a negative \(J_{B_{Ca}}\) indicates an influx of Ca from the ECF into bone. The vast majority of body Ca is contained within bone mineral (10,11).

\(J_{\text{Dialysis}_{Ca}}\) is defined as the net flux of Ca from the dialysis procedure:
\[
J_{\text{Dialysis}_{Ca}} = \text{Dial}_{Ca,In} - \text{Dial}_{Ca,Out}
\] (10)

A positive \(J_{\text{Dialysis}_{Ca}}\) indicates an efflux of Ca from dialysate into the ECF, and a negative \(J_{\text{Dialysis}_{Ca}}\) reflects an influx of Ca from the ECF into the dialysate.

Finally, over a period of time,
\[
\Delta \operatorname{ECF}_{Ca} = J_{B_{Ca}} + J_{\text{Dialysis}_{Ca}} + (D_{Ca} \times \alpha_{Ca}) \\
- (GFR \times UF_{Ca} \times [1 - fr_{Ca}]) - Sweat_{Ca}
\] (11)

**Sites of Regulation of Calcium Concentration**

\(\operatorname{ECF}_{Ca}\) is the total ECF Ca concentration (\(\operatorname{ECF}[\text{Ca}_{\text{total}}]\)) multiplied by the ECF volume (\(\operatorname{ECF}_{\text{volume}}\)) plus any Ca deposited in the ECF (\(\text{Deposited}_{Ca}\)):
\[
\operatorname{ECF}_{Ca} = \operatorname{ECF}[\text{Ca}_{\text{total}}] \times \operatorname{ECF}_{\text{volume}} + \text{Deposited}_{Ca}
\] (12)

\(\operatorname{ECF}[\text{Ca}_{\text{total}}]\) equals the blood ionized Ca concentration (\(\operatorname{ECF}[\text{Ca}_{\text{ion}}]\)) plus the concentration of protein-bound Ca (\(\operatorname{ECF}[\text{Ca}_{\text{bound}}]\)) plus the concentration of complexed Ca (\(\operatorname{ECF}[\text{Ca}_{\text{complexed}}]\)), which are the three components of the blood Ca:
\[
\operatorname{ECF}[\text{Ca}_{\text{total}}] = \operatorname{ECF}[\text{Ca}_{\text{ion}}] \\
+ \operatorname{ECF}[\text{Ca}_{\text{bound}}] + \operatorname{ECF}[\text{Ca}_{\text{complexed}}]
\] (13)

Large quantities of Ca are transported through the ECF between the GI tract, kidney, and bone, yet the \(\text{Ca}_{ion}\), especially in plasma water, must be tightly regulated to maintain cellular metabolic processes (12). The maintenance of a stable \(\text{Ca}_{ion}\) must depend on (1) GI Ca absorption; (2) renal Ca reabsorption; (3) bone Ca deposition or release through either cell-mediated or physiochemical mechanisms (13); (4) movement of Ca into and from nonosseous sites; and (5) in patients who are on dialysis, the influx and efflux of Ca during the dialysis procedure.

Although in patients who are not on dialysis the GI tract provides the only route for net Ca influx into the body, the intestine is a poor site for the control of \(\text{Ca}_{ion}\). The ability of the intestine to absorb Ca is diet dependent, yet, even then, much of the absorption is unregulated (14). The regulated component of Ca absorption occurs through changes in the level of 1,25(OH)\(_2\)D\(_3\), a hormone that is not stored for release and must be synthesized de novo in response to parathyroid hormone (PTH) or decreases in phosphorus, fibroblast growth factor 23 (FGF-23), or ionized Ca. There is little evidence to suggest that the intestine can respond to the short-term requirements for the regulation of \(\text{Ca}_{ion}\).

One reasonable hypothesis is that regulation of \(\text{Ca}_{ion}\) occurs by alterations in renal tubular reabsorption of Ca. Approximately 97% of filtered Ca is reabsorbed, and the normal daily reabsorption of approximately 270 mmol is large relative to the normal \(\text{ECF}_{Ca}\) of approximately 35 mmol (see Normal Individuales below), indicating that small changes in tubular reabsorption will have large effects on \(\text{Ca}_{ion}\) (15). A small increase in \(fr_{Ca}\) would increase \(\text{Ca}_{ion}\). Although alterations in the tubular reabsorption of Ca must have an effect on \(\text{Ca}_{ion}\), control cannot occur solely at the level of the kidney as evidenced by two clinical examples: CKD (16,17) and pseudohypoparathyroidism (18,19). During the later stages of CKD, when there is less glomerular filtration of Ca, the \(\text{Ca}_{ion}\) is reasonably well regulated, even during dialysis, when the ECF may be exposed to large Ca gradients. If renal excretion of Ca were the sole regulator of \(\text{Ca}_{ion}\), then an acute loss of GFR would lead to the entire excreted load of Ca remaining in the ECF. Given an average urinary excretion of approximately 1.25 to 7.50 mmol/d, the ECF \(\text{Ca}_{total}\) would steadily increase by approximately 0.1 to 0.5 mmol each day, which clearly does not happen. Similarly, during the hypocalcemia of pseudohypoparathyroidism, renal reabsorption of Ca seems to be normal or only slightly impaired, yet the level of ECF \(\text{Ca}_{total}\) is maintained below normal (19).

Regulation of \(\text{Ca}_{ion}\) at the level of the bone is also an attractive hypothesis. Bone formation and resorption are regulated by alterations in the physicochemical driving forces for mineralization and demineralization and by alterations in osteoclastic and osteoblastic activity (13). The ECF is markedly supersaturated with respect to apatite, which is the most abundant phase of the bone mineral (20,21). There seems to be a barrier to the free diffusion of Ca from the ECF into the mineral, which would prevent circulating Ca from being readily incorporated into apatite (22). The nature of this barrier is not clear but seems to be an early phase of the mineral, perhaps Ca phosphate (CaHPO\(_4\)) or Ca carbonate (CaCO\(_3\)) or a cellular-organic layer. Cultured bone seems to be in passive physicochemical equilibrium with CaCO\(_3\) in the bone mineral (21). Lowering the driving force of the medium for crystallization with respect to CaCO\(_3\) induces loss of bone mineral, whereas increasing the driving forces results in an increase in the mineral. If experimental results with cultured bone can be applied to humans, then this would suggest that a lowered \(\text{Ca}_{ion}\) would decrease the driving force for mineralization with respect to an early, relatively unstable phase of the mineral and result in an efflux of Ca from bone to increase \(\Delta \operatorname{ECF}_{Ca}\). Similarly, an increase in \(\text{Ca}_{ion}\) would result in movement of Ca from the ECF onto an early phase of the resident mineral. Thus, changes in the \(\text{Ca}_{ion}\) are lessened or “buffered” by the bone mineral. Regulation of \(\text{Ca}_{ion}\) can also occur through hormonal
alterations in cell-mediated bone resorption and formation, as described already, although these processes would probably not be operative during very short periods of time (minutes).

There is a time dependence of the responses of the different organs to a change in [Ca_in]_t. The physicochemical response of the bone mineral to alterations in [Ca_in]_t almost certainly occurs most rapidly. Changes in [Ca_in]_t alter the filtered load of Ca and provoke changes in PTH, which subsequently affect renal tubular reabsorption and cell-mediated bone resorption. Finally, changes in [Ca_in]_t affect 1,25(OH)2D3 levels to alter GI Ca absorption and cell-mediated bone formation and resorption.

Specific Examples

Ideally, in healthy, nonpregnant adults without osteoporosis, ΔECFCa will remain at 0 for long periods of time. If it increases, then the additional Ca will migrate out of the ECF and into bone, soft tissues and/or vessels. Although in patients with CKD phosphate seems to be a prime regulator driving the transition of vascular smooth muscle cells to become collagen-secreting osteoblasts (23,24), soft tissue and vascular calcification cannot occur unless Ca is deposited with phosphate on the collagen matrix. If ΔECFCa becomes negative for any period of time, then Ca must leave the bone mineral, which is the only substantial repository of Ca in the body (10,11). Let us examine each of these parameters in normal individuals, then in patients with excess PTH and those with acidosis, two principal metabolic disorders that occur in patients with CKD. We also address the addition of 1,25(OH)2D3 and, finally, discuss patients who have complete renal failure and receive dialysis.

Normal Individuals

A 70-kg man has an ECF volume of approximately 14 L with an ECF[Ca_in]_t of approximately 2.5 mM, leading to a total ECFCa (excluding the bone mineral) of approximately 35 mmol, which is approximately 0.1% of total body Ca (11,25–27). The vast majority of total body Ca is contained within the mineral phases of bone (10,11). Although there clearly are differences in total skeletal Ca content on the basis of genetic background and gender (28), through cadaveric chemical analysis and neutron activation analysis, it is estimated that bone contains approximately 31,350 mmol of the total body Ca content of approximately 31,500 mmol. Thus, >99.5% of total body Ca resides within the bone (11,25–27). Bone mass peaks at approximately age 25, and loss of trabecular mineral begins at approximately age 35 in women (29). Much of the Ca contained within the bone mineral is inaccessible to the ECF, at least in the short term, but approximately 1% of total body Ca resides within a freely exchangeable pool between the bone and the ECF (5).

The normal American diet contains approximately 20 mmol of Ca, approximately 16 mmol of which is excreted in the feces, indicating that the fraction of Ca absorbed, α_Ca, equals approximately 0.20 (14,25,30). Intestinal absorption of Ca is increased during periods of rapid growth and during pregnancy and lactation.

Excretion of Ca by the kidney represents the difference between the renal filtered load of Ca and the tubular reabsorption of Ca. To date, there is no evidence of net renal secretion of Ca (14). The filtered load of Ca is equal to the GFR (approximately 180 L/d in normal individuals) multiplied by the ultrafilterable Ca concentration (approximately 1.5 mM).

The average urinary Ca excretion (U_Ca), with a typical American diet is approximately 4 mmol/d, indicating that normally >98% of the filtered load of Ca is reabsorbed; thus, (1 – fr_Ca) is approximately 0.015 (15,30–32). U_Ca varies directly but not linearly with Ca intake, as well as with the intake of sodium and protein and inversely with phosphorus intake (15). The mass of elemental Ca filtered by the normal kidney each day is far greater than the total mass of Ca circulating in the ECF. Loss of Ca from sweat has been estimated at 1.6 mmol/d but may increase substantially during exercise (33).

During the course of a day in the normal adult who ingests a diet adequate in Ca, there is no appreciable net bone formation or resorption (i.e., J_B_Ca = 0). For the normal adult, the input of Ca from the GI tract is approximately balanced by the U_Ca and the Sweat_Ca. Thus, there is no appreciable net change in ΔECFCa during this period and [ECFCa]_new will not differ from [ECFCa]_old.

Excess PTH

Chronic excess PTH, as occurs in primary hyperparathyroidism (34–37), leads to predictable physiologic responses. The excess PTH results in increased renal tubule fractional reabsorption of Ca, fr_Ca, leading to an increase in [Ca_in]_t. The increase in [Ca_in]_t tends to increase bone formation (i.e., positive Bf_Ca) by physicochemical mechanisms; however, the marked PTH-induced increase in bone turnover favors osteoclastic bone resorption (i.e., Br_Ca > Bf_Ca) as indicated by radiographic evidence of bone mineral resorption, leading to a positive J_B_Ca. With a continued large excess of PTH, there is a positive ΔECFCa [ECFCa]_new and [Ca_in]_t. UFCa will increase to such an extent that the elevated U_Ca exceeds the increase in fr_Ca, leading to an absolute increase in U_Ca (38,39). In many patients, the excess PTH stimulates an increase in 1,25(OH)2D3 (40), resulting in an increase in α_Ca and the product D_Ca × α_Ca (41,42). This further increases ΔECFCa [ECFCa]_new, [Ca_in]_t, and UFCa, resulting in greater U_Ca (38). 1,25(OH)2D3 does not increase in all patients, perhaps because of the rise in [Ca_in]_t that has been shown to suppress directly the level of serum 1,25(OH)2D3 (43–47).

The chronic excess PTH that occurs in CKD (16,17) also leads to predictable responses. The excess PTH increases fr_Ca and, as the GFR falls, the loss of filtration makes the term [GFR × UFCa] × (1 – fr_Ca)] approach 0 (17). Indeed, in stage 2 CKD, U_Ca is already significantly lower compared with stage 1 CKD, and in stages 3, 4, and 5 CKD, U_Ca is <2.5 mmol/24 h (17). The PTH-induced increase in bone turnover favors osteoclastic bone resorption (i.e., Br_Ca > Bf_Ca), leading to a positive J_B_Ca. Because of the loss of renal mass and the increase in phosphorus and FGF-23, there is a marked reduction in production of 1,25(OH)2D3 (48,49), and α_Ca therefore falls. D_Ca × α_Ca will decrease unless patients are given activated vitamin D that will increase α_Ca or Ca-containing phosphate binders that will increase D_Ca. With either activated vitamin D administration or...
use of Ca-containing phosphate binders or even more with the combination, \((D_{Ca} \times \alpha_{Ca})\) will increase. The actual amount of this increase cannot be determined without the proper studies, which have yet to be performed.

**Excess 1,25(OH)\(_2\)D\(_3\)**

The administration of excess 1,25(OH)\(_2\)D\(_3\) will have the primary effect of increasing \(\alpha_{Ca}\), leading to an increase in the product \(D_{Ca} \times \alpha_{Ca}\) (50). \(\Delta ECF_{Ca}\) will be positive, resulting in an increase in \([ECF_{Ca}]_{new}\) and \(U_{Ca}\) and thus, in the product \(GFR \times U_{Ca} \times [Ca_{ion}]\) will also increase, causing a fall in PTH (37) and thus \(fr_{Ca}\) and a rise in \((1 - fr_{Ca})\) and in \(GFR \times U_{Ca} \times (1 - fr_{Ca})\). There is no consistent evidence that 1,25(OH)\(_2\)D\(_3\) itself will alter \(fr_{Ca}\) independent of PTH. \(U_{Ca}\) will increase markedly under the influence of an increased \(U_{Ca}\) and decreased \(fr_{Ca}\) (39). In *vitro* 1,25(OH)\(_2\)D\(_3\) causes marked cell-mediated resorption of the bone mineral (51), whereas an increase in Ca in the medium causes physicochemical-induced Ca deposition in bone (21). In *vitro* the net effect of 1,25(OH)\(_2\)D\(_3\) on bone is critically dependent on \(D_{Ca}\) (52–54). When normal rats are injected with 1,25(OH)\(_2\)D\(_3\), a high-Ca diet will protect their bone mineral stores (52); however, when normal adult humans were fed a low-Ca diet (2 mmol/d) and injected with 1,25(OH)\(_2\)D\(_3\), net intestinal Ca absorption (\(D_{Ca} \times \alpha_{Ca}\)) was also approximately 2 mmol/d, yet \(U_{Ca}[GFR \times U_{Ca} \times (1 - fr_{Ca})]\) rose to 6 to 10 mmol/d, indicating negative Ca balance (55). The source of this additional \(U_{Ca}\) could only have been bone mineral, indicating that \(Br_{Ca}\) was greater than \(Bf_{Ca}\). Because \(\Delta ECF_{Ca}\) was positive and \([Ca_{ion}]\) rose, physicochemical forces would actually favor bone formation. This indicates that 1,25(OH)\(_2\)D\(_3\)-induced cell-mediated bone resorption must account for the enhanced \(U_{Ca}\) on a low-Ca diet.

**Metabolic Acidosis**

A lowered systemic pH will increase the displacement of albumin-bound Ca, increasing \([Ca_{ion}]\) and \(U_{Ca}\) (27,56). \(\Delta ECF_{Ca}\) is not altered, because acidosis displaces only Ca bound to albumin (27,56) but does not increase the \([Ca_{total}]\) (57). Acidosis will also decrease \(fr_{Ca}\) through a direct effect of lowered bicarbonate on renal tubular Ca reabsorption (58,59). Decreased pH independent of decreased HCO\(_3\) will not decrease \(fr_{Ca}\) (60). The net result of an increased \(U_{Ca}\) and decreased \(fr_{Ca}\), despite some fall in GFR (58), is a marked increase in \(U_{Ca}\) (15,61).

The effect of acidosis on serum levels of PTH and 1,25(OH)\(_2\)D\(_3\) have been studied in some detail in humans (62,63) and animals (43,57). In the rat, there is impaired conversion of \(^3\)H-25(OH)D\(_3\) to \(^3\)H-1,25(OH)\(_2\)D\(_3\) during metabolic acidosis (64) and impaired production of 1,25(OH)\(_2\)D\(_3\) in the isolated perfused kidney obtained from rats with metabolic acidosis (65). Basal serum levels of PTH and 1,25(OH)\(_2\)D\(_3\) are not directly increased by acidosis (62,63) despite the calciria and negative Ca balance; however, during acidosis, the infusion of PTH will increase serum 1,25(OH)\(_2\)D\(_3\) (67). \(\alpha_{Ca}\) does not seem to change appreciably in humans during acidosis (58,62,68).

During metabolic acidosis, the increase in \(U_{Ca}\) seems to come from bone (58,69,70). Indeed, bone mineral, especially carbonate, has been reported to decrease during metabolic acidosis (66,71,72), and provision of bicarbonate increases bone mineral (73,74). In *vitro* metabolic acidosis increases Ca efflux from bone both by promoting physicochemical mineral dissolution within hours (13), especially of CaCO\(_3\) (21), and by enhancing osteoclastic bone resorption over longer periods (13).

**CKD in Patients Who Are not on Dialysis**

Elevated levels of PTH are consistently found in patients with renal failure, and the greater the impairment of renal function, the higher the level of PTH (16,17,75–77). Secretion of PTH is increased principally as a result of the decline in \([Ca_{ion}]\) (78); however, the reduction in 1,25(OH)\(_2\)D\(_3\) and the increase in phosphate itself (as a result of the reduction in phosphate excretion coupled with continued intestinal absorption) both will increase PTH secretion (79,80). The factors that are responsible for the low \([Ca_{ion}]\) are multiple, and the importance of each remains controversial. Phosphate retention, decreased serum 1,25(OH)\(_2\)D\(_3\) production with the consequent reduction of \(\alpha_{Ca}\), alteration in the set point for PTH secretion, skeletal resistance to PTH, and impaired degradation of PTH all may contribute to the increase in serum levels of PTH. The excess PTH and the acidemia produced by failure to excrete endogenous acids will promote bone mineral resorption *in vitro* (81) and potentially in patients with CKD (82).

Phosphate retention will increase PTH levels in humans (83) and experimental animals (84) with no impairment in renal function. In animals with renal failure and in patients with CKD, elevated PTH levels are a function of the degree of hyperphosphatemia (85–88). Hyperphosphatemia itself will lead to an increase in PTH secretion in intact cultured parathyroid glands (89). \([Ca_{ion}]\) may fall because increased phosphate will decrease the physicochemical driving forces for bone mineral dissolution (21) and favor ectopic precipitation of Ca phosphate complexes (90). In addition, phosphate retention will directly decrease serum 1,25(OH)\(_2\)D\(_3\), leading to a fall in \(\alpha_{Ca}\), a negative \(\Delta ECF_{Ca}\), and a decrease in \([Ca^{2+}]\) (91).

The enzyme responsible for the conversion of 25(OH)D\(_3\) to 1,25(OH)\(_2\)D\(_3\), 25-hydroxycholecalciferol-1α-hydroxylase, is located in the renal proximal tubule (50). Decreases in functional renal mass and increases in FGF-23 decrease the conversion and thus the serum levels of 1,25(OH)\(_2\)D\(_3\) (48–50,77). The decrease in 1,25(OH)\(_2\)D\(_3\) leads to an increase in PTH through at least two distinct mechanisms: (1) The fall in intestinal Ca absorption and subsequent negative \(\Delta ECF_{Ca}\) leading to a fall in \([ECF_{Ca}]_{new}\) and \([Ca_{ion}]\), and (2) the direct effect of 1,25(OH)\(_2\)D\(_3\) to suppress PTH synthesis and secretion.

During CKD, serum levels of 1,25(OH)\(_2\)D\(_3\) seem to be relatively normal until the GFR falls below approximately 50 ml/min (16,17,77). With a further decline in GFR, levels of 1,25(OH)\(_2\)D\(_3\) continue to fall and are extremely low in patients.
who are on hemodialysis despite the usual elevations in PTH (16, 17, 77, 92–94). This lack of 1,25(OH)2D3 results in depressed αCa, and Ca balance has actually been shown to be negative with fecal excretion exceeding dietary intake (95–98). The lack of 1,25(OH)2D3 also directly leads to increased PTH secretion.

Parathyroid cells have specific receptors for 1,25(OH)2D3 (37, 99–101), and 1,25(OH)2D3 suppresses PTH gene expression and the secretion of PTH (99, 102–105). In addition, during renal failure, there is decreased binding of 1,25(OH)2D3 to the parathyroid cells (106). Thus, during renal failure, the combination of lower levels of 1,25(OH)2D3 and decreased binding of the available 1,25(OH)2D3 to the parathyroid cells results in a marked increase in secretion of PTH at all levels of [Caion]. This so-called “altered set point” for PTH secretion can be reversed by the administration of intravenous 1,25(OH)2D3 (107, 108) or vitamin D analogues (109). PTH is degraded principally in the liver and kidney into carboxy-terminal fragments, which are catabolized by the kidney (110–112). With renal failure, there is accumulation of PTH fragments in the serum, some of which are biologically active (113, 114). Despite evidence for the skeletal action of the actions of PTH on bone during renal failure, excess PTH promotes resorption of bone mineral in uremia, leading to increased BrCa and JBCa (88, 115–117).

Thus, in renal failure, ΔECFΔCa is negative as a result of a decrease in the product DΔCa × αCa, despite a decrease in the UCa as a result of a lowered GFR and a PTH-induced increase in BrCa. When 1,25(OH)2D3 is administered, especially with additional Ca from Ca-based phosphate binders, there is an increase in αCa, often leading to a positive ΔECFΔCa and frank hypercalcemia (107–109).

CKD in Patients Who Are on Dialysis

The dialysis procedure itself can lead to a net influx of Ca to the ECF, DialΔCa, or a net efflux of Ca from the ECF, DialΔCa. Ca flux is a function of diffusion and convection. With respect to diffusion, a higher dialysate Ca will lead to Ca influx from Ca-based phosphate binders, there is an increase in αCa, often leading to a positive ΔECFΔCa and frank hypercalcemia (107–109).

A Model of ΔECFΔCa during a 1-Wk Period

To model ΔECFΔCa for a patient who is on dialysis, we must make a number of assumptions because experimental data are not yet available. Each assumption is backed by available data in the literature; however, there is a paucity of data on intestinal Ca absorption and secretion in dialysis patients. There are almost no data on movement of Ca between the intestine, bone, and kidney in patients who are on dialysis. These data are critical because movement of a small amount of Ca from bone to the soft tissue—with no change in overall Ca balance—can result in substantial vascular and soft tissue calcification. The assumptions are as follows:

1. Hemodialysis three times per week
2. Dialysis bath Ca = 1.25 mM (2.5 mEq/L)
3. No net Ca flux during dialysis when there is no ultrafiltration
4. Three liters of ultrafiltration during each dialysis treatment
5. GI Ca absorption = 19% of DΔCa without activated vitamin D and 25% with activated vitamin D, regardless of the dosage
6. Ca secretion into the stool = 3.6 mmol/d
7. All activated vitamin D preparations increase αCa equally
8. All Ca from food and binders will be absorbed equally
9. Ca loss from sweat = 1.6 mmol/d
10. UCa [GFR × UFCa × (1 – frCa)] = 0
11. JBCa = 0

Thus, equation 11 simplifies to

\[
\Delta ECF_{Ca} = JDialysis_{Ca} + (D_{Ca} \times \alpha_{Ca})
\]

with a constant correction for secretion of Ca into the GI tract and sweat. Changing any of these assumptions will obviously have important effects on the outcome. For example, any appreciable UCa will lessen ΔECFΔCa, and any appreciable BrCa from excess PTH or administered activated vitamin D will increase ΔECFΔCa.

In Figure 2, ΔECFΔCa, the change in the ECF Ca content (mmol/wk), is plotted as a function of Ca intake (mmol/d), calculated on the basis of the aforementioned assumptions. With no activated vitamin D, an intake of 25 mmol (1 g) of elemental Ca results in a negative ΔECFΔCa during the week, whereas an intake of 50 mmol results in a positive ΔECFΔCa. Addition of activated vitamin D increases ΔECFΔCa.
of Ca intake. These results are consistent with those of Hsu et al. (127), except that they did not consider Ca secretion into the stool and sweat; with those of Malberti and Ravani (123), who used a slightly higher dialysate Ca; and with those of Sigrist and McIntyre (121), who also did not take into account losses from sweat and secretion of Ca into the stool. The ΔECF_Ca, both with and without the addition of activated vitamin D, at levels of 50 mmol (2 g) Ca intake is not insubstantial.

Conclusions

This analysis, with the assumptions made, suggests that dialysis patients who consume >37.5 mmol (1.5 g) of elemental Ca have a positive ΔECF_Ca that becomes numerically more positive when patients are given activated vitamin D. This Ca cannot stay in the ECF but must be deposited in either osseous or extraosseous sites or [Ca_total] would increase substantially. The extensive soft tissue calcification that is seen in many dialysis patients suggests that extraosseous sites may be the repository for this Ca (2,128–135). The quantity of Ca retained is not insignificant; 25 mmol/wk is approximately 1300 mmol/yr, or approximately 4% of normal skeletal Ca (10,11).

Far more research needs to be done, however, to support or refute these conclusions. We clearly need an overall Ca balance study of dialysis patients using isotopic labeled Ca to measure fluxes between organs. We are administering Ca to bind intestinal phosphate yet do not even know how much is absorbed. Net Ca absorption should be measured at various levels of CKD, with and without activated vitamin D. We need to determine whether there are differences in human intestinal Ca absorption with the different activated vitamin D preparations. How does the anion administered with the Ca influence net Ca absorption? Can we influence where Ca is deposited—bone is not simply due to Ca overload into the ECF_Ca, there can be no vascular calcification without Ca to complex with phosphate. An increased ΔECF_Ca will increase the driving force for mineralization of the unmineralized matrix in both bone and the collagen secreted by vascular smooth muscle cells that have been transformed into osteoblasts (23,24). It is incumbent on nephrologists who administer additional dietary Ca to patients in the form of phosphate binders to know how much of this Ca is absorbed, especially when patients receive concurrent activated vitamin D, and, after absorption, whether this Ca is deposited in osseous or extraosseous sites. Although on a daily basis nephrologists administer grams of elemental Ca to dialysis patients, the fate of this additional Ca is not known. It would be tragic if we were doing more harm than good.

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References

8. Brown EM: Ca^{2+}-sensing receptor. In: Primer on the Meta...


