Bone, Artery, & Renal Function in CKD

Calcium Supplementation in Patients with Chronic Kidney Disease

Disclosures: none

Objectives: Review previous presentations

1. Assess the impact of Calcium supplementation on Calcium & Phosphate Balance
2. Compare Calcium supplementation to Sevelamer on Calcium & Phosphate Metabolism
3. Compare Calcium supplementation to Sevelamer on Coronary Calcification & Mortality

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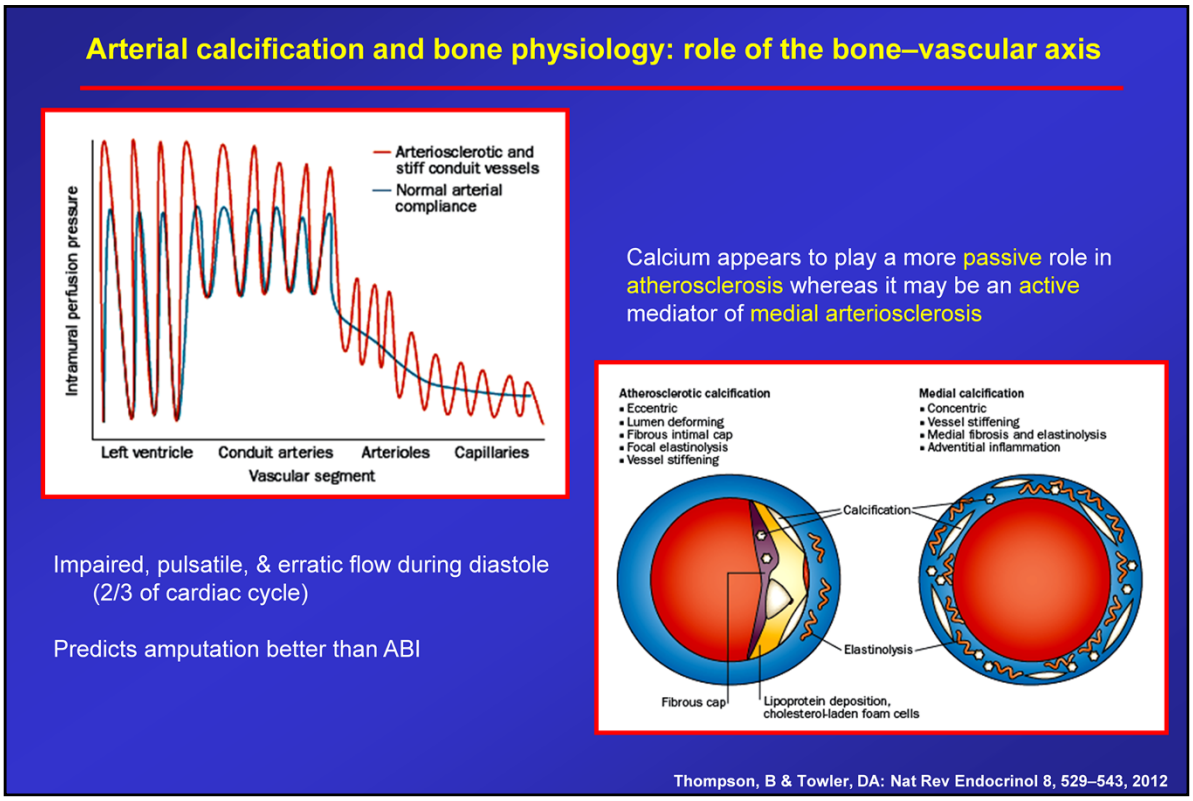


Figure 1 | Consequences of arterial stiffening and impaired Windkessel physiology. During systole, some kinetic energy is stored as potential energy in the elastic conduit arteries. This stored energy permits not only coronary perfusion but also smooth distal capillary perfusion during diastole (blue tracing). With arteriosclerotic stiffening (red tracing), less potential energy is stored during systole, giving rise to impaired, pulsatile and erratic flow during diastole (two-thirds of the cardiac cycle). Systolic blood pressure is also increased.

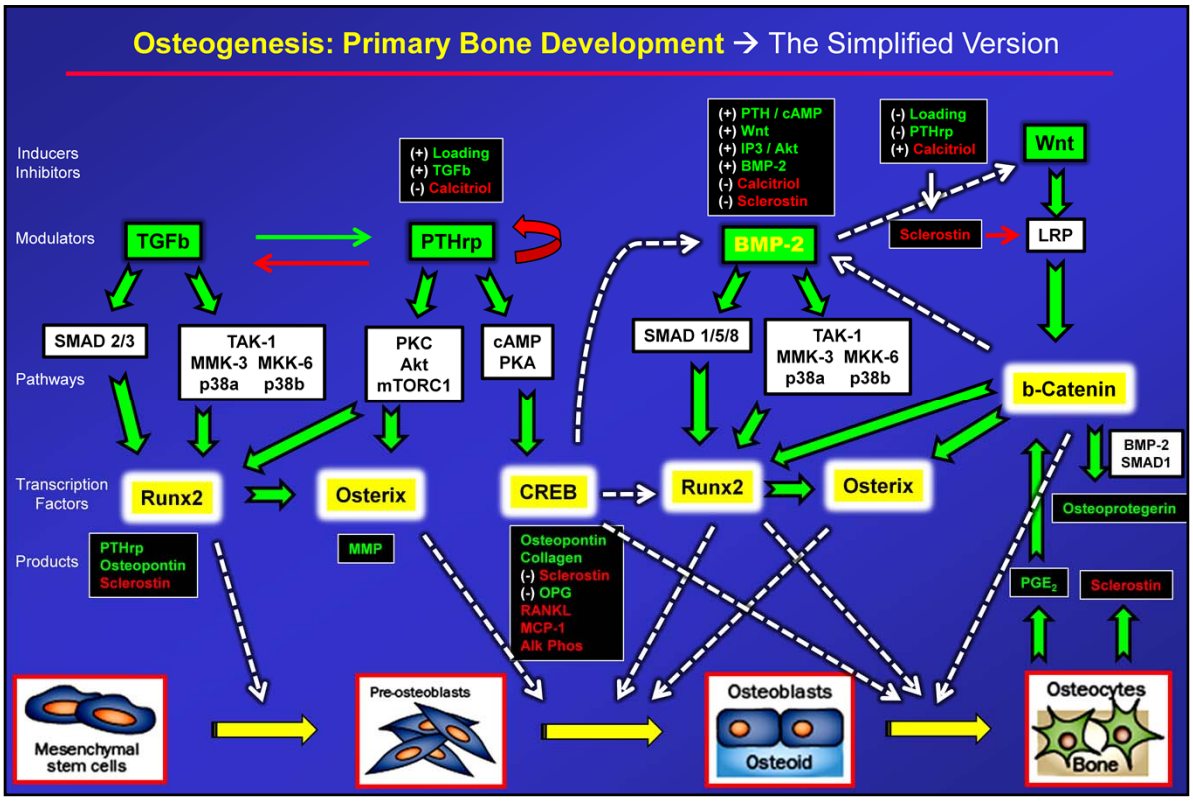
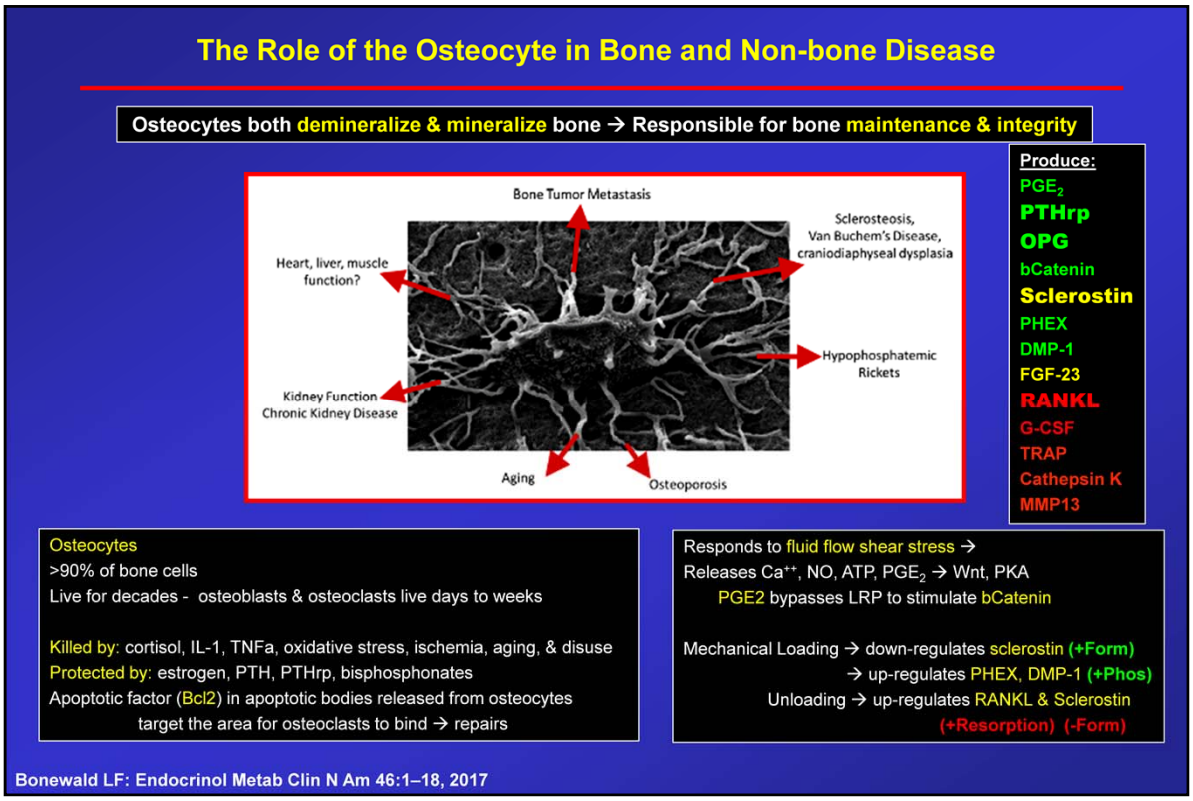


Figure 2 | The osteoblast differentiation program. **a** | *In vivo*: bone surface shows organization of indicated osteoblast lineage cells (black, mineralized tissue). Mesenchymal stem cells and osteoprogenitor cells cannot be seen. **b** | *In vitro*: stages of differentiation of committed preosteoblast cells isolated from newborn rodent calvarium or bone marrow stromal cells. Peak expression of genes that are markers for the three major stages are shown. At mineralization, a feedback signal from sclerostin secreted by osteocytes inhibits BMP and Wnt osteogenic-mediated bone formation by regulating the number of cells entering the osteoblast lineage. **c** | Examples of transcription factors regulating osteoblast differentiation and *in vivo* bone formation are shown. Within the triangle are those that increase during differentiation, whereas those above the triangle are functional on gene promoters at the indicated stages of maturation. Permission obtained from American Society for Bone and Mineral Research © Favus, M. J. (Ed.) *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 6th edn (2006).



Fluid flow shear stress activates the Wnt/b-catenin signaling pathway through the rapid release of prostaglandin, which acts through EP receptors to bypass low density lipoprotein receptor activation. Components of the b-catenin pathway are essential for osteocyte viability, mechano-sensation, transduction, and release of important factors essential for bone homeostasis. The central molecule through which all molecules must go is b-catenin. b-Catenin regulates expression of both the positive activators of this pathway, the wnts, and the negative regulators of this pathway, sclerostin and Dkk1 (for a review see 16). Global deletion of b-catenin is embryonically lethal, but deletion in osteocytes using the Dmp1-Cre results in dramatic bone loss characterized by perforated cortises. Interestingly, deletion of only 1 allele in osteocytes results in mice with a normal skeleton but a completely abrogated response to anabolic loading. b-Catenin plays an important role in bone integrity, osteocyte communication, and osteocyte viability, but also in bone response to loading. This role extends to other components of this signaling pathway.

Before osteocytes were recognized as active essential bone cells necessary for bone health, it was assumed that all the action took place on the bone surface and not within the bone. Osteoblasts and osteoclasts were the major players, osteoblasts making bone and osteoclasts resorbing bone to maintain bone homeostasis. It was

assumed that osteoblasts and osteoclasts were regulated by external factors such as parathyroid hormone (PTH) or 1,25 dihydroxyvitamin D3, and other external regulatory factors. It has also been proposed that osteoblasts make factors that regulate osteoclast activity and, conversely, that osteoclasts make factors that could regulate osteoblast activity. Therapeutics were generated that would target either osteoclasts or osteoblasts. Osteocytes were left out of the picture.

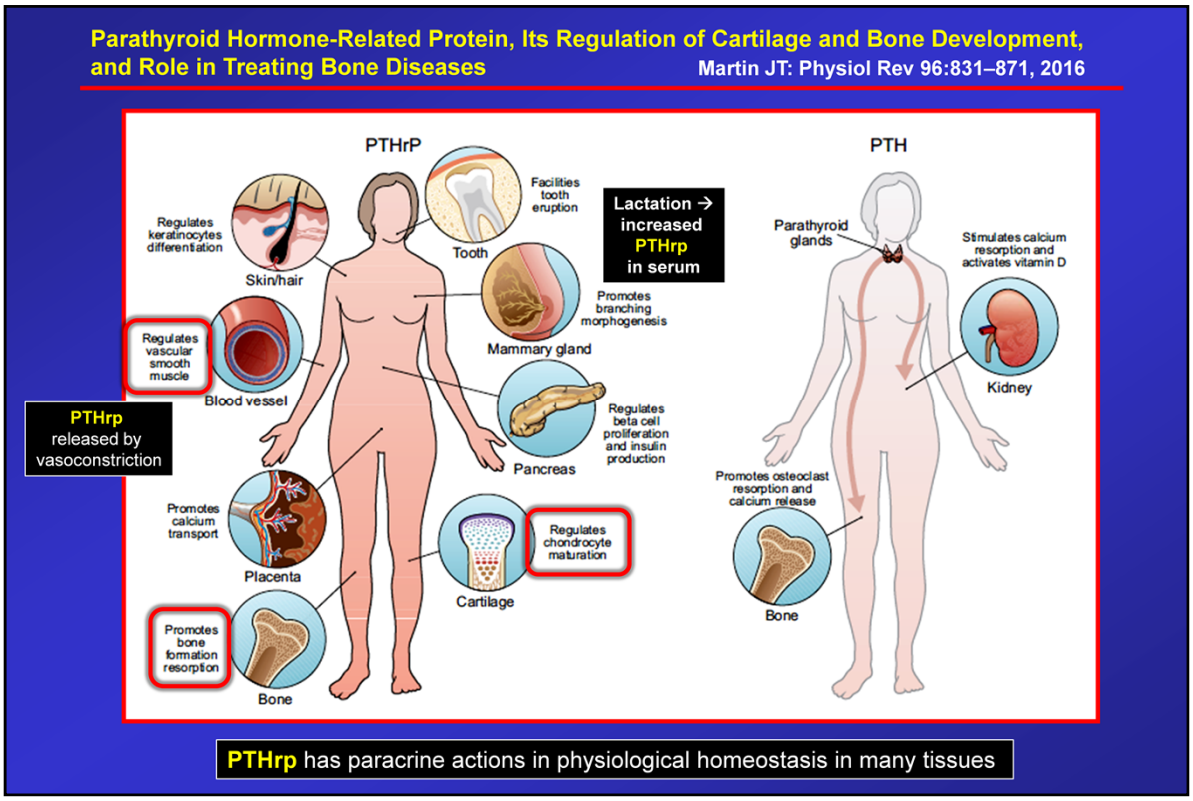
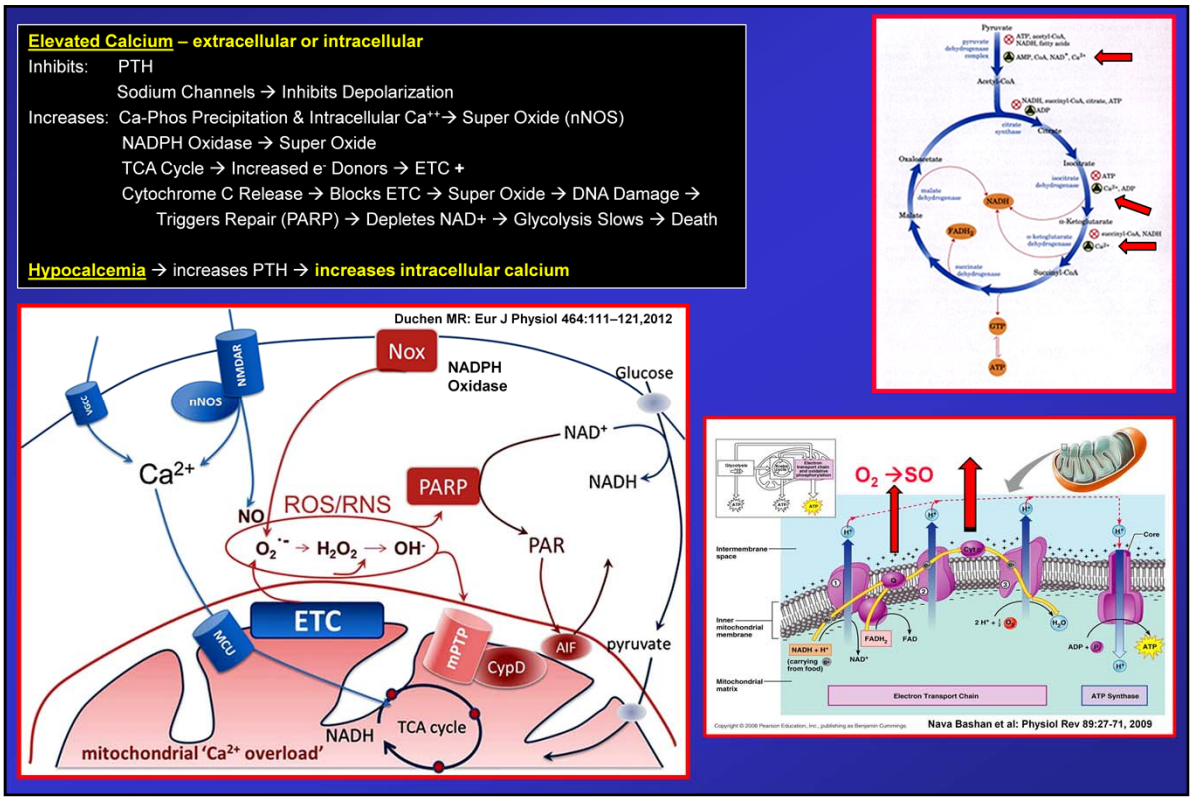


FIGURE 8. Paracrine actions of PTHrP and endocrine actions of PTH. PTHrP has paracrine actions in physiological homeostasis in many tissues, including keratinocytes/hair follicles, cartilage, vascular smooth muscle, bone, mammary gland development, tooth eruption, and pancreas, whereas PTH has relatively fewer physiological actions through its role as a circulating hormone. The summary diagram omits important details such as the role of PTHrP in lactation



Mitochondria, calcium-dependent neuronal death and neurodegenerative disease. Eur J Physiol 464:111–121, 2012. Michael R. Duchen

Fig. 3 Scheme of pathways involved in glutamate-induced excitotoxicity. Calcium influx through voltage-gated or NMDAR-gated channels is followed by mitochondrial Ca2+ influx through the mitochondrial calcium uniporter (MCU). While the physiological consequence of raised intra-mitochondrial [Ca2+] is an increased activity of the three rate limiting enzymes of the TCA cycle, pathological and prolonged Ca2+ influx leads to mitochondrial Ca2+overload. NMDAR mediated Ca2+ influx is closely coupled to the generation of NO by nNOS; raised Ca2+ may activate the NADPH oxidase (Nox), while mitochondrial Ca2+ overload may also increase generation of superoxide by the electron transport chain (ETC). Nitrosative or oxidative stress arising either from the ETC or from Nox activation may cause over activation of PARP. PARP consumes NAD+ to form PAR polymers, causing depletion of NAD+, failure of glycolysis and so failure of mitochondrial substrate supply. This culminates in the loss of $\Delta\psi m$, ATP depletion, and cell death. The PAR polymers generated by PARP may also cause release of AIF which amplifies cell death following its translocation to the nucleus.

Abstract Understanding the mechanisms of neuronal dysfunction and death represents a major frontier in contemporary medicine, involving the acute cell death

in stroke, and the attrition of the major neurodegenerative diseases, including Parkinson's, Alzheimer's, Huntington's and Motor neuron diseases. A growing body of evidence implicates mitochondrial dysfunction as a key step in the pathogenesis of all these diseases, with the promise that mitochondrial processes represent valuable potential therapeutic targets. Each disease is characterized by the loss of a specific vulnerable population of cells--dopaminergic neurons in Parkinson's disease, spinal motor neurons in Motor neuron disease, for example. We discuss the possible roles of cell type-specific calcium signaling mechanisms in defining the pathological phenotype of each of these major diseases and review central mechanisms of calcium-dependent mitochondrial-mediated cell death.

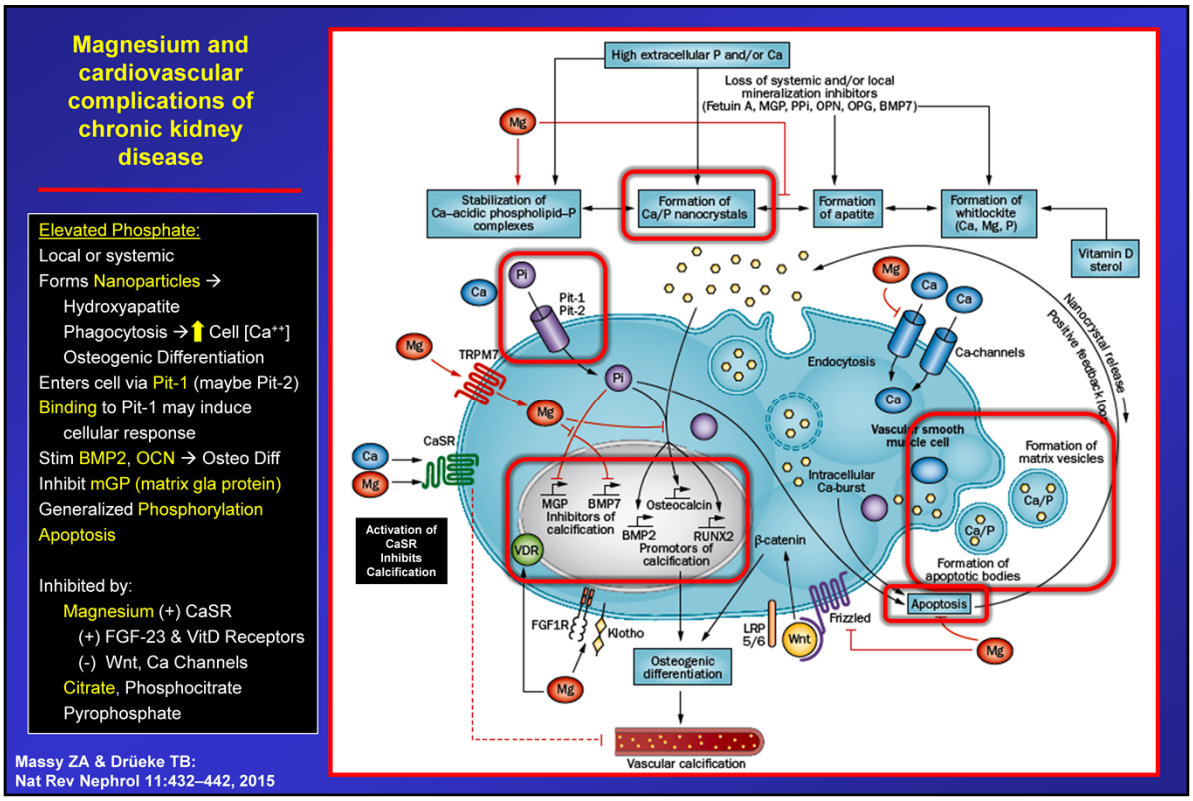


Figure 1 | The putative inhibitory effects of magnesium on the process of vascular calcification. Abnormalities in mineral metabolism, particularly hyperphosphataemia, and loss of inhibitors of mineralization leads to the formation and deposition of Ca/P nanocrystals, which are taken up by VSMCs. Lysosomal degradation of the endocytosed crystals results in intracellular release of Ca and Pi. In addition, Pi accumulates in the cell via uptake through Pit-1 and probably also Pit-2. To compensate for excess Ca/P, VSMCs form matrix vesicles loaded with Ca/P products and the mineralization inhibitors. The intracellular Ca-burst induced by endocytosed nanocrystals and Pi uptake triggers apoptosis, resulting in the formation of Ca/P-containing apoptotic bodies. Matrix vesicles and apoptotic bodies cause a positive feedback loop through nanocrystal release into the surrounding milieu, thus amplifying the calcification process. Furthermore, Ca/P nanocrystals and Pi induce the expression of genes that promote the calcification–mineralization process and repress the expression of factors that inhibit calcification, resulting in transdifferentiation of VSMCs to osteoblast-like cells and, ultimately, vessel calcification. Mg interferes with the process of vascular calcification by inhibiting transformation of amorphous Ca/P to apatite and by forming Mg-substituted whitlockite crystals, which result in smaller, more soluble deposits. Secondly, Mg functions as a Ca-channel antagonist and thus inhibits the entry of Ca into the cells. Thirdly, Mg enters the cell via TRPM7 and restores the balance between expression of calcification promoters and inhibitors by neutralizing phosphate-induced inhibition of MGP and BMP7 and enhanced expression of RUNX2 and BMP2. These effects prevent osteoblastic conversion and calcification

of VSMCs. In addition, Mg acts on the CaSR; activation of this receptor by calcimimetics has been shown to inhibit VSMC calcification but the molecular mechanisms have not yet been identified.

Abbreviations: BMP, bone morphogenetic protein; Ca, calcium; CaSR, calcium-sensing receptor; FGF1R, fibroblast growth factor receptor-1; LRP 5/6, LDL receptor-related protein 5/6; Mg, magnesium; MGP, matrix gla protein; OPG, osteoprotegerin; OPN, osteopontin; Pi, inorganic phosphate; Pit, sodium-dependent phosphate transporter; PPi, pyrophosphate; RUNX2, runt-related transcription factor 2; TRPM7, transient receptor potential cation channel subfamily M member 7; VDR, vitamin D receptor; VSMC, vascular smooth muscle cell. Permission obtained from Oxford University Press © Massy, Z. A. & Drüeke, T. B. *Clin. Kidney J*. 5 (Suppl. 1), i52–i61 (2013).

Abstract Cardiovascular complications are the leading cause of death in patients with chronic kidney disease (CKD). Abundant experimental evidence suggests a physiological role of magnesium in cardiovascular function, and clinical evidence suggests a role of the cation in cardiovascular disease in the general population. The role of magnesium in CKD-mineral and bone disorder, and in particular its impact on cardiovascular morbidity and mortality in patients with CKD, is however not well understood. Experimental studies have shown that magnesium inhibits vascular calcification, both by direct effects on the vessel wall and by indirect, systemic effects. Moreover, an increasing number of epidemiologic studies in patients with CKD have shown associations of serum magnesium levels with intermediate and hard outcomes, including vascular calcification, cardiovascular events and mortality. Intervention trials in these patients conducted to date have had small sample sizes and have been limited to the study of surrogate parameters, such as arterial stiffness, vascular calcification and atherosclerosis. Randomized controlled trials are clearly needed to determine the effects of magnesium supplementation on hard outcomes in patients with CKD.

Arterial Calcification, Bone Physiology, & Renal Function

Summary (Part 1): Pathophysiology

We need to consider 3 processes: **Arteriosclerosis, Osteodystrophy, & Nephropathy**

Osteogenesis is a "normal" function of arteries - **BMP-2** & **PTHrp** are required for this function

All of the modulators for osteogenesis are available in arteries (TGFb, PTHrp, BMP-2, Wnt)

Osteogenesis is triggered by many of the same factors that trigger atherosclerosis

Free Radicals, Inflammation, Oxy-sterols (oxLDL), Hypertension, Hyperglycemia

Phosphate appears to be the dominate promotional mineral

Magnesium may be the dominate inhibiting mineral

As bone becomes "non-responsive" it is less able to buffer changes in Calcium & Phosphate

PTH's primary function is to maintain serum [Ca++], **not** maintain bone integrity & strength

PTHrp & Wnt are the primary pathways for maintaining bone integrity

Osteoblasts, BMP, OPN, & excess phosphate are not good things to have in arteries

Bone, Artery, & Renal Function in CKD

Supplementation of Vitamin D, Calcitriol, &/or Vitamin D Analogs

Summary (Part 2):

1. Vitamin D supplementation:
    1. Lowers PTH, intracellular Ca^{++}, Adhesion Molecules, AGE-P, proteinuria
    2. Increases Serum Ca^{++}, 1-25 Vitamin D, FMD, microcirculatory vasodilatation, NOS
    3. Prevents increase in pulse pressure
    4. Tends to increase aKlotho & FGF-23 (data not shown)
    5. Does not change phosphorus or bone markers
2. Calcitriol supplementation
    1. Lowers Alk Phos, PTH, Renin, angiotensinogen, proteinuria
    2. Increases S & U Ca^{++}, bone density, & hepatic growth factor (**reduces renal fibrosis**)
    3. Combination w/ VitD: reduces mineralization rate, woven osteoid, blast & clast activity
    4. Does not change urinary phosphorus
3. Vitamin D analog supplementation
    1. Similar impact on Ca^{++}, Phos, PTH, & Alk Phos; similar incidence HyperCa & HyperPhos
    2. Reduces osteoid, blast & clast activity
    3. Reduces GFR, proteinuria, BP, & hospitalization for CV events
    4. Increases FMD & FGF-23 → correlate w/ Phos; increase in Phos eliminates increase in FMD
    5. Increases Sclerostin by reducing PTH (data not shown)

Recommendations:

1. Patients with diabetes (everyone?) should have “normal” 25-Vitamin D levels (>40)
2. Low dose calcitriol (0.25 → 0.50 mcg daily – if S. Ca^{++} normal) should be initiated early in CKD

Bone, Artery, & Renal Function in CKD

Supplementation of Calcium in Patients with Normal Renal Function

Summary (Part 3): Calcium Supplementation - usually with low-dose Vitamin D

1. Absorption peaks in 4-5 hours; returns to baseline in ~12 hours
2. Calcium citrate absorbs slightly better than carbonate & suppresses PTH better
3. Has a small positive impact on spine & hip bone density, especially in secondary prevention
4. Reduces hip fractures in women on hormone replacement therapy but not if untreated
5. Reduces recurrent colon polyps by 25%
6. Lowers LDL (2.6%, p=0.02) & Insulin Resistance (6.7%, NS)
7. Reduces death from CHF; may reduce CV death & hospitalization in DM & CAD women
8. May increase MI & Stroke - very small impact [worst case: one event per 143 patient years]
   - Does not occur with dietary calcium
   - Evident with lowest dose (~500 mg daily) – more supplement has no additional impact
   - More likely in high-risk populations: men, high LDL, hypertension, & smokers
9. Improves Cardiac Function
10. Reduces Time to Clot Initiation

Recommendations:

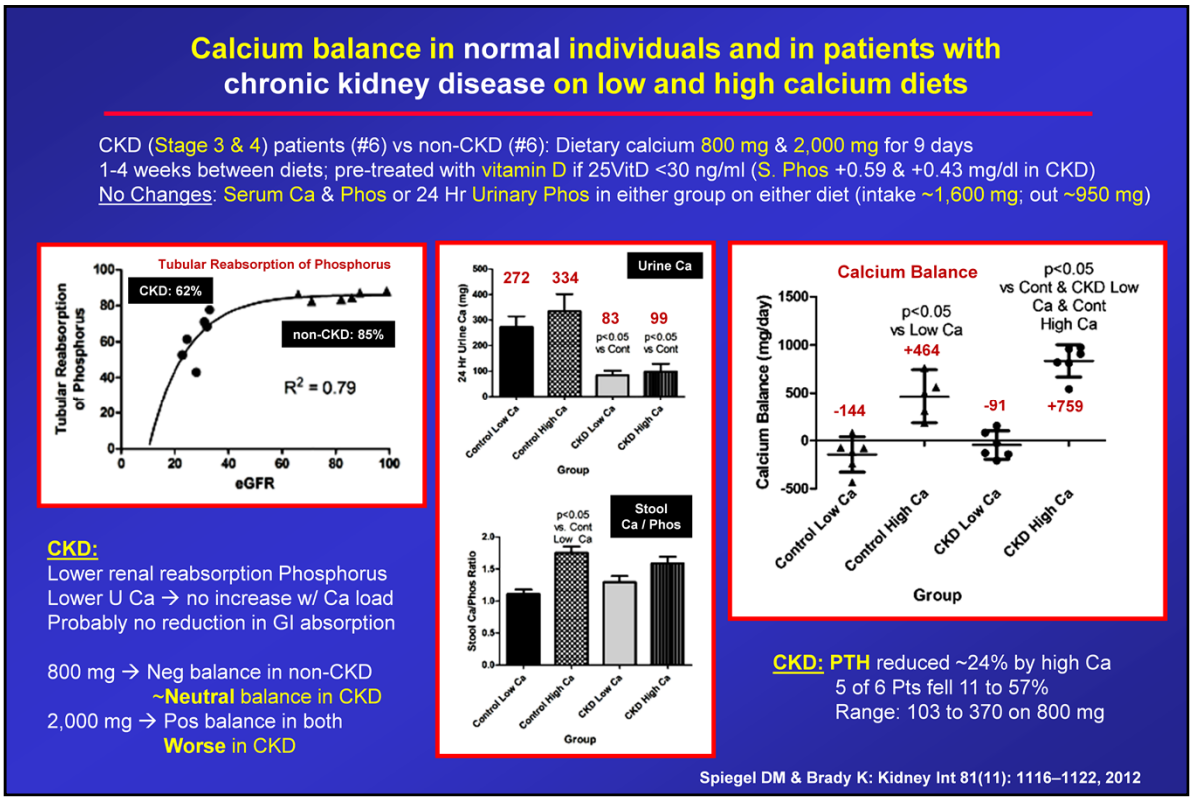
1. Increase Dairy if possible
2. Use small, frequent doses of oral calcium
3. Add aspirin or omega-3 in high-risk patients
4. Monitor PTH to determine adequacy

Bone, Artery, & Renal Function in CKD

Calcium Supplementation in Patients with Chronic Kidney Disease

Objectives: Part 4

1. Assess the impact of Calcium supplementation on Calcium & Phosphate Balance
2. Compare Calcium supplementation to Sevelamer on Calcium & Phosphate Metabolism
3. Compare Calcium supplementation to Sevelamer on Coronary Calcification & Mortality



Calcium balance in chronic kidney disease is poorly understood since its deficiency is a stimulus for secondary hyperparathyroidism and consequent bone loss while calcium excess promotes extra-osseous calcifications. To help resolve this, we evaluated calcium balance in normal individuals and in patients with chronic kidney disease (CKD) on daily diets containing 800 and 2000 mg elemental calcium. Both normal individuals and patients with late stage 3 and stage 4 CKD were in slightly negative to neutral calcium balance on the 800 mg calcium diet. Normal individuals were in modest positive calcium balance on the 2000 mg diet while patients with CKD on the same diet were in marked positive calcium balance at least over the 9 days of study; and significantly greater than the normal individuals. Increased calcium intake significantly decreased 1,25 dihydroxy-vitamin D and intact parathyroid hormone levels but did not alter the serum calcium concentration. Thus, our finding have important implications for both preventing calcium deficiency and loading in individuals with late stage 3 and stage 4 CKD.

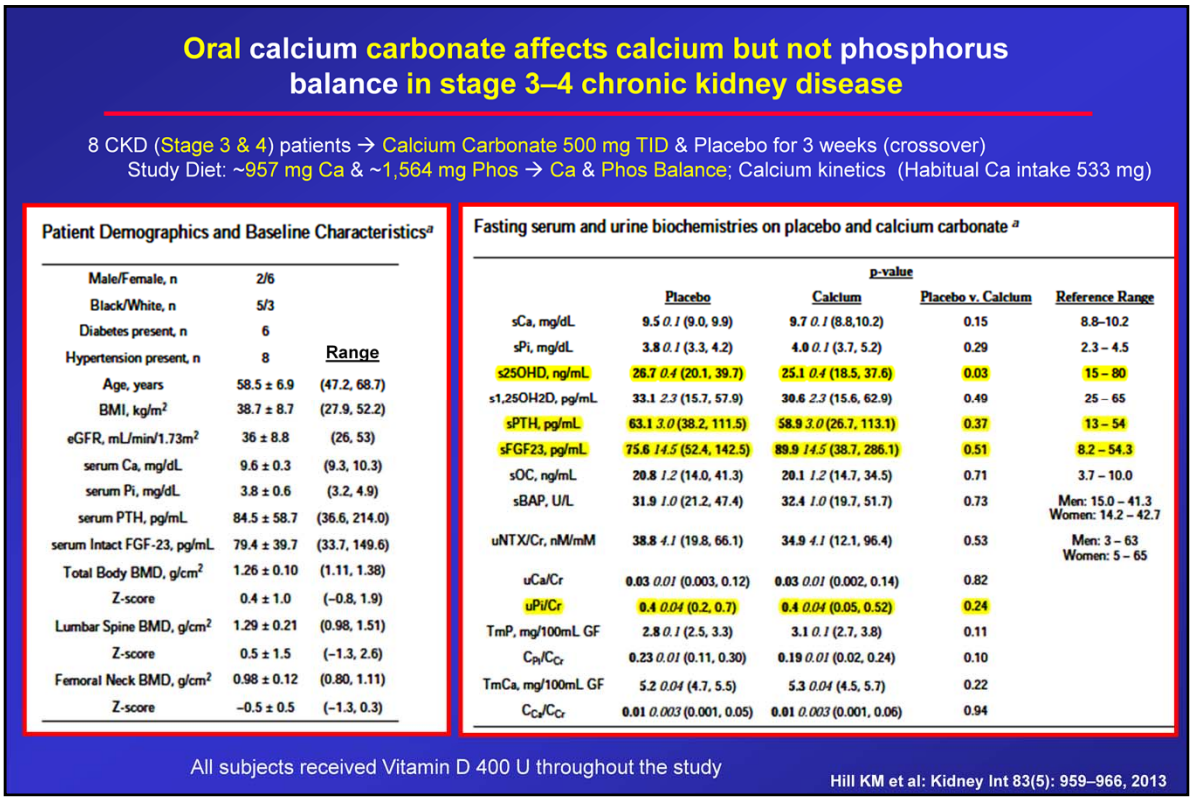


Table 2 Fasting serum calcium and phosphate were within normal reference ranges and did not differ between calcium carbonate and placebo. Fasting serum 25D was within normal range but was slightly lower with calcium carbonate (25.1 vs. 26.7 ng/mL, p=0.03). Fasting serum PTH and FGF-23 were higher than the normal ranges for the assays, while fasting serum 1,25D was within but in the lower end of the normal range for the assay. Serum osteocalcin (OC) was higher than the normal range, and serum bone alkaline phosphatase (BAP) and urine N-telopeptides of type I collage (NTX) were normal. None of these measures differed between calcium carbonate and placebo.

Kidney function measurements (eGFR, serum creatinine, and creatinine clearance) were not different between calcium carbonate and placebo (data not shown). Urine Ca/Cr, tubular maximal reabsorption of calcium (TmCa), and fractional calcium excretion (CCa/CCr) were not different between calcium carbonate and placebo. Urine Pi/Cr and fractional phosphate excretion (CPi/CCr) tended to be lower and tubular maximal reabsorption of phosphate (TmP) tended to be higher with calcium carbonate compared with placebo, but these differences were not statistically significant.

Abstract

Chronic kidney disease (CKD) patients are given calcium carbonate to bind dietary

phosphorus and reduce phosphorus retention, and to prevent negative calcium balance. Data are limited on calcium and phosphorus balance in CKD to support this. The aim of this study was to determine calcium and phosphorus balance and calcium kinetics with and without calcium carbonate in CKD patients. Eight stage 3/4 CKD patients, eGFR 36 mL/min, participated in two 3-week balances in a randomized placebo-controlled cross-over study of calcium carbonate (1500 mg/d calcium).

Calcium and phosphorus balance were determined on a controlled diet. Oral and intravenous ^{45}calcium with blood sampling and urine and fecal collections were used for calcium kinetics. Fasting blood and urine were collected at baseline and end of each week of each balance period for biochemical analyses.

Results showed that patients were in neutral calcium and phosphorus balance while on placebo. Calcium carbonate produced positive calcium balance, did not affect phosphorus balance, and produced only a modest reduction in urine phosphorus excretion compared with placebo. Calcium kinetics demonstrated positive net bone balance but less than overall calcium balance **suggesting tissue deposition**. Fasting biochemistries of calcium and phosphate homeostasis were unaffected by calcium carbonate. If they can be extrapolated to effects of chronic therapy, these data caution against the use of calcium carbonate as a phosphate binder.

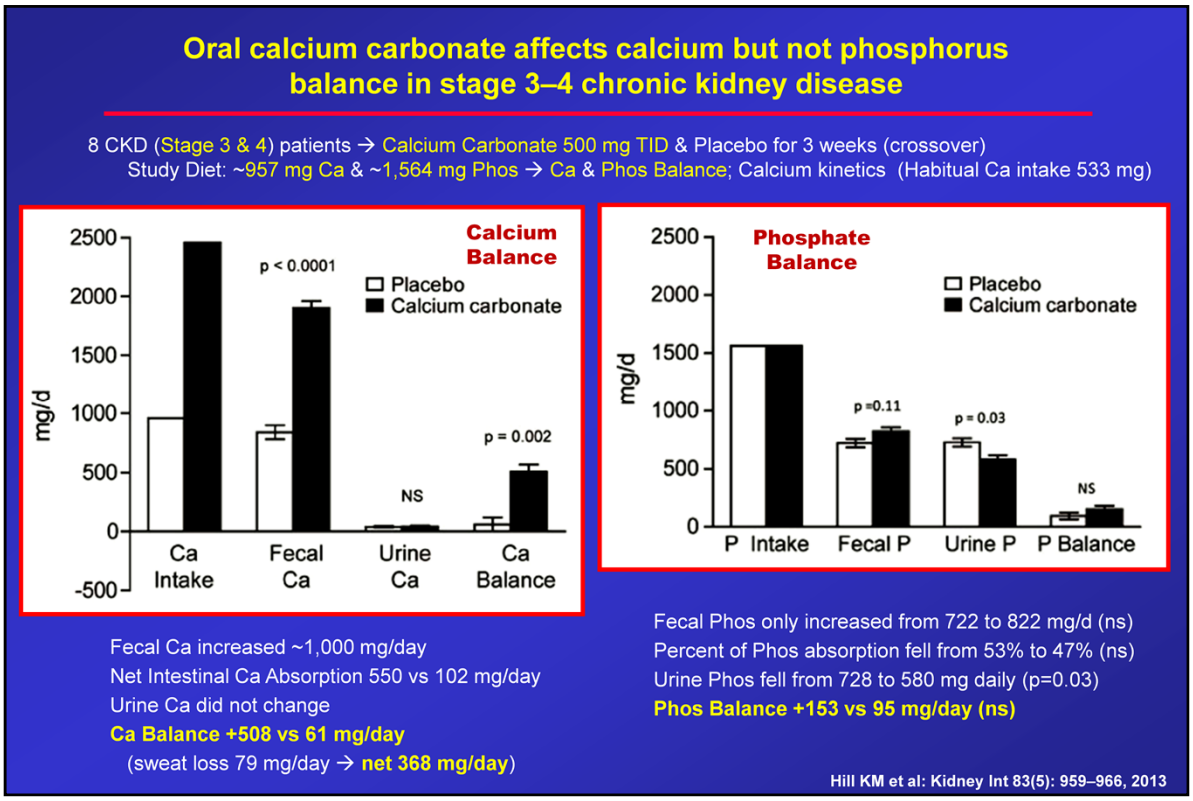


Figure 2. Calcium balance in stage 3/4 CKD patients with and without calcium carbonate. Calcium balance was greater with calcium carbonate compared with placebo. Ca intake was experimentally controlled and statistical analysis does not apply.

White bars = placebo; Black bars = calcium carbonate. Ca = calcium; NS = not significant ($p > 0.05$). Data are presented as least squares mean ± pooled SEM.

Figure 3. Phosphorus balance in stage 3/4 CKD patients with and without calcium carbonate. Phosphorus balance was not different between calcium carbonate and placebo but urine phosphate was lower on calcium carbonate. P intake was experimentally controlled and statistical analysis does not apply.

Abstract

Chronic kidney disease (CKD) patients are given calcium carbonate to bind dietary phosphorus and reduce phosphorus retention, and to prevent negative calcium balance. Data are limited on calcium and phosphorus balance in CKD to support this. The aim of this study was to determine calcium and phosphorus balance and calcium kinetics with and without calcium carbonate in CKD patients. Eight stage 3/4 CKD patients, eGFR 36 mL/min, participated in two 3-week balances in a randomized placebo-controlled cross-over study of calcium carbonate (1500 mg/d calcium).

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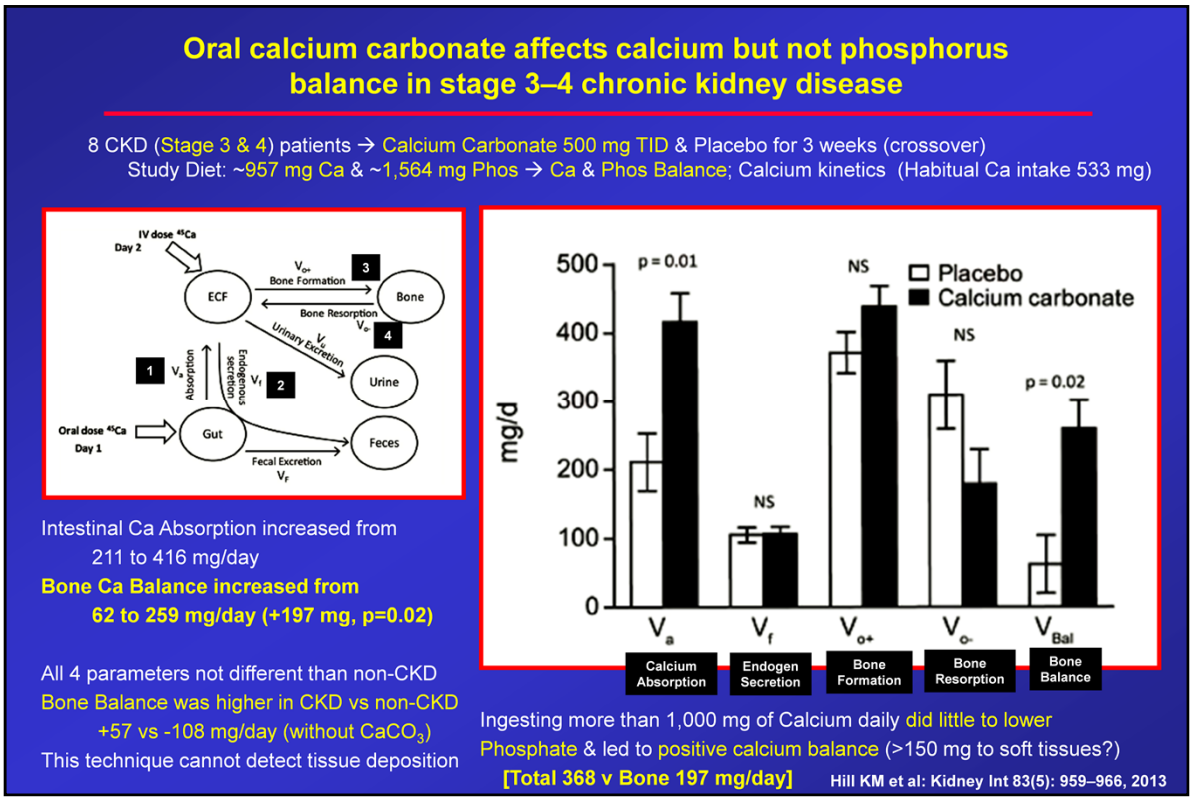

Figure 4. Illustration of calcium kinetics (33). ECF = extracellular compartment. ^{45}Ca = ^{45}Calcium radiotracer; V_a = rate of calcium absorption; V_f = rate of endogenous calcium excretion; V_F = rate of fecal calcium excretion; V_u = rate of urine calcium excretion; V_{o+} = rate of bone formation; V_{o-} = rate of bone resorption. Bone balance is V_{o+} minus V_{o-}, and overall calcium retention is dietary calcium minus urine and fecal calcium.

Figure 5. Calcium kinetics in stage 3/4 CKD patients with and without calcium carbonate. Calcium absorption (V_a, mg/d) and bone balance (V_{Bal}=V_{o+} minus V_{o-}) were higher, and endogenous secretion (V_f) was unchanged with calcium carbonate compared with placebo.

White bars = placebo; Black bars = calcium carbonate. Ca = calcium; NS = not significant ($p > 0.05$). Data are presented as least squares mean ± pooled SEM.

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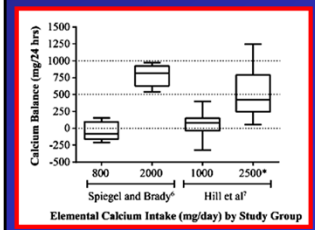
Calcium Balance in Chronic Kidney Disease



Recommendation:
800 to 1,000 mg Ca daily

Dairy contains 300 mg Phos
Replace w/ Ca Supplement?

Hill-Gallant KM & Spiegel DM:
Curr Osteoporos Rep
15:214–221, 2017

Table 1 Comparing sources for absorbable calcium

Source	Serving size[a] (g)	Calcium content[b] (mg/serving)	Estimated absorption efficiency[c] (%)	Absorbable Ca/serving[d] (mg)	Servings needed to = 1 cup milk
Foods					
Milk	240	290	32.1		1.0
Beans, pinto	86	44.7	26.7	11.9	8.1
Beans, red	172	40.5	24.4	9.9	9.7
Beans, white	110	113	21.8	24.7	3.9
Bok choy	85	79	53.8	42.5	2.3
Broccoli	71	35	61.3	21.5	4.5
Cheddar cheese	42	303	32.1	97.2	1.0
Cheese food	42	241	32.1	77.4	1.2
Chinese cabbage flower leaves	85	239	39.6	94.7	1.0
Chinese mustard green	85	212	40.2	85.3	1.1
Chinese spinach	85	347	8.36	29	3.3
Kale	85	61	49.3	30.1	3.2
Spinach	85	115	5.1	5.9	16.3
Sugar cookies	15	3	91.9	2.76	34.9
Sweet potatoes	164	44	22.2	9.8	9.8
Rhubarb	120	174	8.54	10.1	9.5
Whole wheat bread	28	20	82.0	16.6	5.8
Wheat bran cereal	28	20	38.0	7.54	12.8
Yogurt	240	300	32.1	96.3	1.0
Fortified foods					
Tofu, calcium-set	126	258	31.0	80.0	1.2
Orange juice with Ca citrate malate	240	300	36.3	109	0.88
Soy milk with tricalcium phosphate	240	300	24	72	1.3
Bread with calcium sulfate	16.8	300	43.0	129	0.74

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[a] Based on a one-half cup serving size (~85 g for green leafy vegetables) except for milk and fruit punch (1 cup or 240 mL) and cheese (1.5 oz)

[b] Taken from Refs. [34] and [35] (averaged for beans and broccoli processed in different ways) except for the Chinese vegetables which were analyzed in our laboratory

[c] Adjusted for load using the equation for milk (fractional absorption = 0.889–0.0964 ln load) then adjusting for the ratio of calcium absorption of the test food relative to milk tested at the same load, the absorptive index [36]

[d] Calculated as calcium content × fractional absorption

Purpose of Review The kidneys play a critical role in the balance between the internal milieu and external environment. Kidney failure is known to disrupt a number of homeostatic mechanisms that control serum calcium and normal bone metabolism. However, our understanding of calcium balance throughout the stages of chronic kidney disease is limited and the concept of balance itself, especially with a cation as complex as calcium, is often misunderstood. Both negative and positive calcium balance have important implications in patients with chronic kidney disease, where negative balance may increase risk of osteoporosis and fracture and positive balance may increase risk of vascular calcification and cardiovascular events. Here, we examine the state of current knowledge about calcium balance in adults throughout the stages of chronic kidney disease and discuss recommendations for clinical strategies to maintain balance as well as future research needs in this area.

Recent Findings Recent calcium balance studies in adult patients with chronic kidney disease show that neutral calcium balance is achieved with calcium intake near the recommended daily allowance. Increases in calcium through diet or supplements cause high positive calcium balance, which may put patients at risk for vascular calcification. However, heterogeneity in calcium balance exists among these patients.

Summary Given the available calcium balance data in this population, it appears clinically prudent to aim for recommended calcium intakes around 1000 mg/day to achieve neutral calcium balance and avoid adverse effects of either negative or positive calcium balance. Assessment of patients' dietary calcium intake could further equip clinicians to make individualized recommendations for meeting recommended intakes.

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Early Control of PTH and FGF23 in Normophosphatemic CKD Patients: A New Target in CKD-MBD Therapy?

Table 1. Baseline demographical, clinical, and biochemical parameters of the total study population and the two subgroups: Calcium acetate-treated patients and sevelamer hydrochloride-treated patients[a]

Diabetics Excluded – 25 Hypertensive CKD

Calcium vs Sevelamer:
Total Daily Phosphate Intake ~615 mg
(Usual American diet ~1,600 mg Phos)
4 oz meat or 1 cup milk ~ 300 mg phosphate
Therefore, probably ~8 oz meat & no dairy
Dietary Calcium intake <400 mg

	All	Calcium Acetate	Sevelamer Hydrochloride	Reference Values
	40	19	21	
	8 ± 11.40	51.21 ± 9.98	49.62 ± 12.75	–
	8 ± 4.58	26.95 ± 4.16	25.67 ± 4.95	18 to 25
	21/19	9/10	12/9	–
	5 ± 0.78	2.52 ± 0.76	2.59 ± 0.82	0.8 to 1.2/ 0.6 to 1.0
	5 ± 15.89	32.07 ± 9.92	36.9 ± 20	85 to 125/ 75 to 115
Bic (mmol/L)	21.63 ± 3.79	20.82 ± 2.97	22.37 ± 4.34	23 to 30
Alb (g/dl)	4.35 ± 0.30	4.35 ± 0.21	4.36 ± 0.37	3.5 to 5
Ca (mg/dl) Normal	9.29 ± 0.50	9.34 ± 0.56	9.24 ± 0.45	8.6 to 10.2
P (mg/dl) Normal	3.53 ± 0.60	3.61 ± 0.54	3.45 ± 0.65	2.7 to 4.5
TAP (U/L)	81.20 ± 21.72	84.42 ± 25.32	78.29 ± 18.01	35 to 104
BAP (U/L)	35.10 ± 11.46	36.91 ± 12.62	33.46 ± 10.35	11.6 to 42.7
DPD (nmol/L)	10.32 ± 3.38	9.81 ± 3.25	10.80 ± 3.52	3.25 ± 0.66
25vitD (ng/ml) Low-Normal	34.75 ± 20.65	35.71 ± 18.66	33.88 ± 22.73	> 30
1,25vitD (pg/ml)	31.27 ± 21.18	32.82 ± 16.67	29.79 ± 25.08	15.9 to 55.6
PTH (pg/ml) High	101 (70 to 130)	89 (52 to 141)	107 (76 to 130)	10 to 65
FGF23 (pg/ml)	97 (64 to 142)	97 (62 to 148)	103 (62 to 142)	8.2 to 54.3
uCa (mg/24 h)	24.27 ± 25.61	23.39 ± 24.49	25.11 ± 27.27	100 to 320
uP (mg/24 h) Low-Normal	490.5 ± 150.9	444.5 ± 154.6	534.1 ± 137.3	400 to 1300
FeP (%) High – Intake 739 mg/day	59.7 ± 32.4	58.2 ± 37.2	61.0 ± 28.4	5 to 18
uProt (g/24 h)	0.45 ± 0.75	0.35 ± 0.67	0.55 ± 0.82	<0.1

Oliveira RB et al: Clin J Am Soc Nephrol 5: 286–291, 2010

Background and objectives: Levels of parathyroid hormone (PTH) and the phosphaturic hormone FGF23, a fibroblast growth factor (FGF) family member, increase early in chronic kidney disease (CKD) before the occurrence of hyperphosphatemia. This short-term 6-wk dose titration study evaluated the effect of two phosphate binders on PTH and FGF23 levels in patients with CKD stages 3-4.

Design, setting, participants, and measurements: Patients were randomized to receive over a 6-wk period either calcium acetate (n =19) or sevelamer hydrochloride (n =21).

Results: At baseline, patients presented with elevated fractional excretion of phosphate, serum PTH, and FGF23. During treatment with both phosphate binders there was a progressive decline in serum PTH and urinary phosphate, but no change in serum calcium or serum phosphate. Significant changes were observed for FGF23 only in sevelamer-treated patients.

Conclusions: This study confirms the positive effects of early prescription of phosphate binders on PTH control. Prospective and long-term studies are necessary to confirm the effects of sevelamer on serum FGF23 and the benefits of this decrease on outcomes. *Clin J Am Soc Nephrol* 5: 286–291, 2010.

Early Control of PTH and FGF23 in Normophosphatemic CKD Patients: A New Target in CKD-MBD Therapy?

Table 1. Baseline demographical, clinical, and biochemical parameters of the total study population and the two subgroups: Calcium acetate-treated patients and sevelamer hydrochloride-treated patients[a]

Diabetics Excluded – 25 Hypertensive CKD	All	Calcium Acetate	Sevelamer Hydrochloride	Reference Values
n	40	19	21	
Age (yr)	50.38 ± 11.40	51.21 ± 9.98	49.62 ± 12.75	–
Body mass index (kg/m^2)	26.28 ± 4.58	26.95 ± 4.16	25.67 ± 4.95	18 to 25
Gender (male/female)	21/19	9/10	12/9	–
Cr (mg/dl; male/female)	2.55 ± 0.78	2.52 ± 0.76	2.59 ± 0.82	0.8 to 1.2/ 0.6 to 1.0
CrCl (ml/min/1.73 m^2; male/female)	34.55 ± 15.89	32.07 ± 9.92	36.9 ± 20	85 to 125/ 75 to 115
Bic (mmol/L)	21.63 ± 3.79	20.82 ± 2.97	22.37 ± 4.34	23 to 30
Alb (g/dl)	4.35 ± 0.30	4.35 ± 0.21	4.36 ± 0.37	3.5 to 5
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FeP = fractional excretion of phosphate

Oliveira RB et al: Clin J Am Soc Nephrol 5: 286–291, 2010

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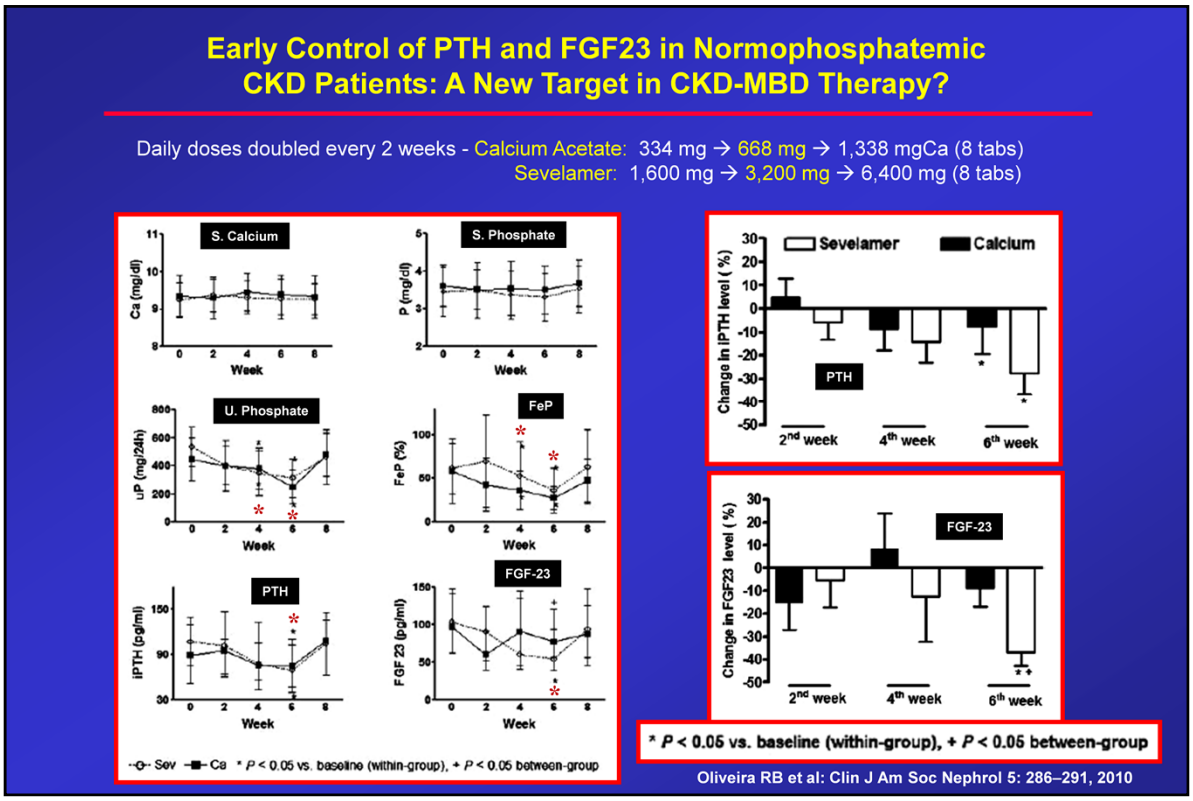

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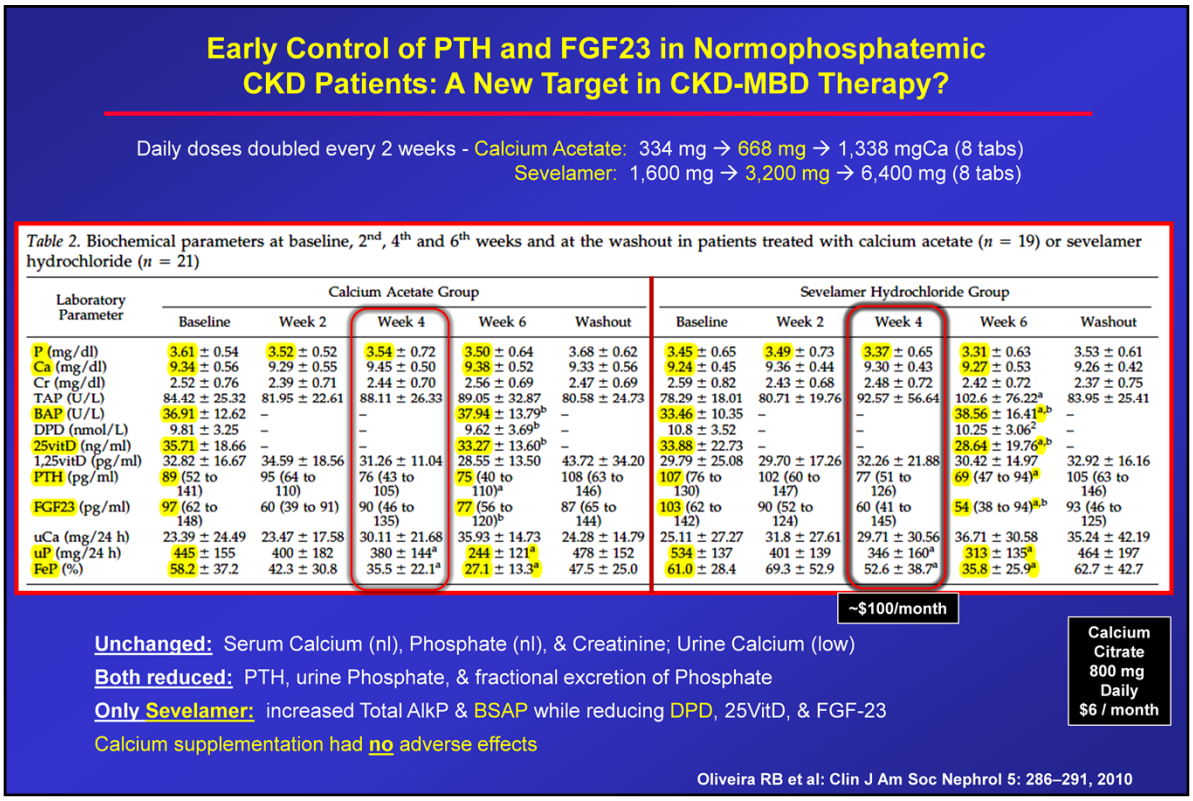

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Bone, Artery, & Renal Function in CKD

Calcium Supplementation in Patients with Chronic Kidney Disease

Objectives: Part 4

1. Assess the impact of Calcium supplementation on Calcium & Phosphate Balance
2. Compare Calcium supplementation to Sevelamer on Calcium & Phosphate Metabolism
3. Compare Calcium supplementation to Sevelamer on Coronary Calcification & Mortality

The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer

84 subjects w/CKD (12 women) age ~55 yrs, BMI ~25, BP ~135/82; Diabetics excluded

Table 2 | Initial and final biochemical variables

$CaCO_3$ 1,000 mg BID | 800 mg BID

2 years

Variables	Controls		Calcium		Sevelamer	
	Initial	Final	Initial	Final	Initial	Final
GFR (ml/min)	33.4 (20.2)	33.6 (25.0)	26.2 (8.3)	25.9 (5.3)	26.3 (15.6)	24.1* (14.7)
PTH (pg/ml)	140.7 (73.2)	146.9 (77.4)	172.1 (73.8)	176.1 (54.8)	136.5 (101.7)	134.9 (72.7)
Serum calcium (mg/dl)	9.2 (0.6)	9.3 (0.5)	9.0 (0.7)	9.1 (0.8)	9.2 (0.2)	9.0* (0.3)
Serum phosphorus (mg/dl)	3.9 (0.7)	3.9 (0.9)	4.6 (1.5)	4.7 (1.5)	4.5 (0.7)	4.8 (0.9)
Calcium × *P* product ($mg^2 \times dl^2$)	35.8 (7.0)	36.0 (7.8)	42.3 (8.0)	40.3 (11.8)	41.7 (6.9)	43.1 (8.4)
Alkaline phosphatase (mg/dl)	113.7 (62.2)	85.1* (25.1)	148.0 (83.2)	143.0 (93.2)	134.2 (67.1)	103.4** (47.6)
Total serum proteins (mg/dl)	7.2 (0.8)	7.5 (0.8)	6.9 (1.0)	7.2 (1.2)	7.2 (0.7)	7.2 (0.7)
Serum albumin (mg/dl)	3.9 (0.52)	4.2 (0.5)	3.8 (0.7)	3.9 (0.8)	3.9 (0.4)	4.2 (0.2)
Carbonate (mEq/l)	23.4 (3.8)	24.3 (3.5)	21.6 (5.3)	23.2 (4.2)	22.3 (3.1)	21.2 (2.3)
Homocysteine (μmol/l)	29.8 (18.7)	27.2 (14.6)	38.0 (14.5)	38.0 (14.5)	31.5 (10.5)	33.5 (19.7)
Fibrinogen (mg/dl)	342.6 (124.5)	385.5 (99.5)	401.3 (96.7)	397.3 (85.7)	424 (222)	332** (57)
Total cholesterol (mg/dl)	189.0 (36.3)	188.6 (38.8)	184.9 (32.5)	184.0 (23.5)	173.0 (50.5)	181.3 (53.1)
Triglycerides (mg/dl)	137.7 (101.8)	131.9 (94.4)	119.2 (50.3)	139.2 (50.3)	141.4 (92.3)	131.6 (109.7)
HDL cholesterol (mg/dl)	59.8 (44.1)	48.9 (13.1)	46.8 (10.2)	46.7 (10.2)	48.8 (10.7)	49.9 (11.8)
LDL cholesterol (mg/dl)	115.9 (32.1)	118.0 (47.5)	121.0 (47.4)	101.0 (33.2)	113.9 (55.1)	107.3 (39.1)
C-reactive protein (mg/dl)	0.98 (2.38)	0.34 (0.08)	1.1 (2.7)	0.33 (0.09)	0.50 (0.27)	0.73 (0.99)
Phosphorus intake (mg/day)	682 (480)	788 (470)	694 (492)	658 (478)	690 (398)	784 (385)
Phosphaturia (mg/24 h)	367 (389)	514* (285)	496 (125)	413* (126)	490 (128)	410** (130)

Serum Ca & Phos normal & unchanged
PTH high & unchanged
Calcium & Sevelamer both reduced phosphaturia

Only Sevelamer reduced Fibrinogen

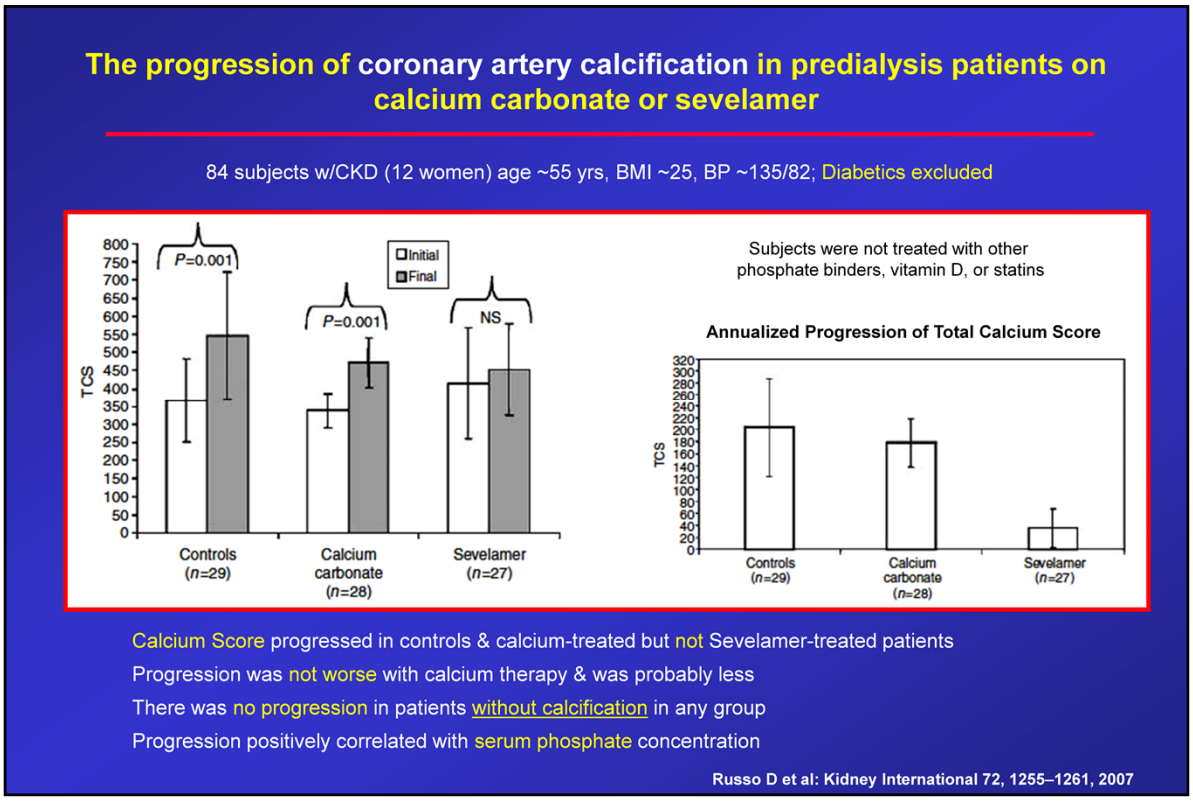
Russo D et al: Kidney International 72, 1255–1261, 2007

Coronary artery calcification is more prevalent in dialysis patients than in patients without kidney disease and this is associated with high serum phosphorus. In this study, we evaluate the effect of calcium carbonate or sevelamer treatments on the progression of calcification in 90 predialysis patients.

Inclusion criteria were stable serum calcium, phosphorus, parathyroid hormone, and a similar baseline total calcium score (TCS). These patients were not treated by phosphate binder, vitamin D, or statin. They were given low-phosphorus diets without or with daily calcium carbonate or sevelamer throughout the study that averaged 2 years.

Baseline demographic or clinical characteristics along with biochemical parameters were not different among the three groups. The TCS significantly increased in patients on the low-phosphorus diet alone, to a lesser extent in calcium carbonate-treated patients, and not at all in sevelamer treated patients. The progression of coronary calcification paralleled that of the calcium score.

Our study shows that sevelamer treatment should not be restricted to dialysis patients; however, a larger study should be undertaken to confirm these results.



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Mortality in Kidney Disease Patients Treated with Phosphate Binders: A Randomized Study

CKD (Stage 3 & 4 → 5) patients (#212): Calcium Carbonate (2,000 mg → 2,950) vs Sevelamer (1,600 mg → 2,184)
Phosphate Goals: Stage 3 & 4: 2.7 - 4.6 Stage 5: 3.5 - 5.5 → Calcium Score q6 months for 2 years
Endpoints: Primary - All Cause Mortality & Secondary - Dialysis Inception (over 3 years)

Diabetes 28%

Sevelamer Group:
Higher inital Ca Score
Lowered PTH, Phos, & LDL
(PTH increased in Ca group)
S. Calcium fell
(Higher in Ca group)

Table 1. Clinical and laboratory characteristics of the whole study population and according to the phosphate binder

	Total Cohort (*N*=212)	Sevelamer (*n*=107)			Calcium Carbonate (*n*=105)			*P* Value
	Baseline	Baseline	Final[a]	Average[b]	Baseline	Final[a]	Average[b]	
Age (yr)	57.9 (12.2)	57.4 (12.0)			58.5 (12.4)			0.09
Male (%)	61	61			61			0.55
Diabetes (%)	28	27			29			0.16
Hypertension (%)	74.5	72.9			76.1			0.31
CAC (%)	55.2	62.6			47.6			0.02
CAC score, median (IQR)	42 (0–200)	122 (0–180)			0 (0–207)			<0.01
CAC score <100 (%)	54.2	46.7			61.9			0.03
CAC score >100	45.8	53.3			38.1			
CCr (ml/min)	32.7 (6.0)	31.7 (5.9)			32.7 (6.0)			0.12
Serum albumin (g/dl)	3.7 (0.45)	3.6 (0.45)	3.8 (0.47)	3.7 (0.42)	3.7 (0.44)	3.6 (0.47)	3.8 (0.45)	0.18
SBP (mmHg)	138 (17)	138 (19)	140 (20)[c]	137 (17)	136 (17)	134 (16)	137 (17)	0.04[c]
DBP (mmHg)	75 (10)	72 (10)[a]	74 (8)[c]	76 (7)[c,d]	77 (9)[c]	79 (8)	81 (9)	<0.01[d]
								<0.01[c]
Phosphorus (mg/dl)	4.84 (1.3)	4.82 (1.2)	4.16 (1.3)[c,e]	4.37 (0.62)	4.87 (1.33)	4.72 (0.98)	4.85 (0.79)	<0.01[e]
								<0.01[c]
								<0.01[d]
Calcium (mg/dl)	8.9 (0.73)	9.0 (0.8)	8.5 (0.7)[e]	8.6 (0.5)[d]	8.8 (0.7)	9.6 (1.0)[e]	9.4 (0.6)[d]	<0.01[e]
								<0.01[d]
PTH (pg/ml), median (IQR)	200 (121–337)	200 (120–320)	180 (76–300)[c,e]	209 (168–257)	188 (122–337)	250 (173–442)[c,e]	317 (244–397)[c,d]	0.02[e]
								<0.01[c]
								0.01[d]
Cholesterol (mg/dl)	167.1 (51.8)	165 (47)	146 (39)[e]	152 (24)[d]	169 (56)	166 (108)	166 (58)	<0.01[e]
								<0.01[d]
Triglycerides (mg/dl)	166 (110)	165 (113)	199 (127)[e]	170 (66)	167 (107)	201 (221)[e]	186 (81)	0.02[e]
LDL cholesterol (mg/dl)	100.4 (31.0)	95 (32)[c]	80 (22)[c,e]	86 (12)[c,d]	106 (29)	112 (60)	109 (33)	0.01[e]
								<0.01[c]
								<0.01[d]
CRP	6.7 (8.8)	9.0 (12)[c]	7.7 (11)[e]	7.6 (6.1)[d]	4.9 (3.7)	7.6 (7.0)[e]	7.8 (7.1)[d]	<0.01[e]
								<0.01[c]
								<0.01[d]

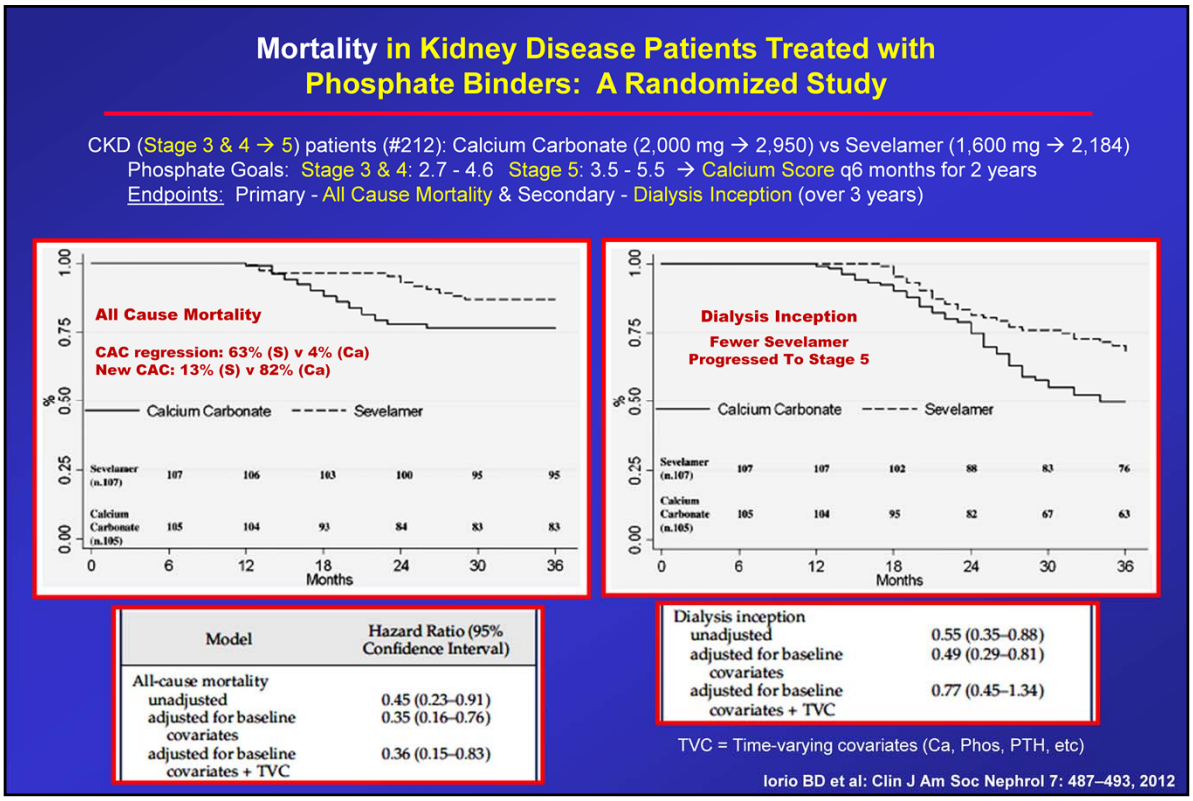
Data are expressed as mean (SD) or median (IQR) for the variables not normally distributed (CAC score and PTH) CAC score, baseline coronary artery calcification score; IQR, interquartile range; CCr, 24-hour measured creatinine clearance; SBP, systolic BP; DBP, diastolic BP; PTH, parathyroid hormone; CRP, C-reactive protein.
[a]Final indicates closer to event or end of study.
[b]Average indicates mean of all available values after assignment to binder up to the event or closing of the study.
[c]*P* value between sevelamer and calcium carbonate–treated patients at the same study point.
[d]*P* value between on-treatment average with its own baseline value.
[e]*P* value between final with its own baseline value.

Iorio BD et al: Clin J Am Soc Nephrol 7: 487–493, 2012

Calcium balance in chronic kidney disease is poorly understood since its deficiency is a stimulus for secondary hyperparathyroidism and consequent bone loss while calcium excess promotes extra-osseous calcifications. To help resolve this, we evaluated calcium balance in normal individuals and in patients with chronic kidney disease (CKD) on daily diets containing 800 and 2000 mg elemental calcium.

Both normal individuals and patients with late stage 3 and stage 4 CKD were in slightly negative to neutral calcium balance on the 800 mg calcium diet. Normal individuals were in modest positive calcium balance on the 2000 mg diet while patients with CKD on the same diet were in marked positive calcium balance at least over the 9 days of study; and significantly greater than the normal individuals. Increased calcium intake significantly decreased 1,25 dihydroxy-vitamin D and intact parathyroid hormone levels but did not alter the serum calcium concentration.

Thus, our finding have important implications for both preventing calcium deficiency and loading in individuals with late stage 3 and stage 4 CKD.



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Bone, Artery, & Renal Function in CKD

Supplementation of Calcium in Patients with Chronic Kidney Disease

Calcium Supplementation - usually combined with low-dose Vitamin D:

1. Does not change serum Calcium or Phosphate; no change **urinary Calcium**
2. Can lower serum PTH
3. Lowers urinary phosphate but minimal increase in fecal phosphate (NS)
4. Does not change overall phosphate balance
5. 1,000 mg daily → neutral Calcium balance
6. >1,000 mg daily → positive Calcium balance, only partially absorbed by bone
7. High dose Calcium does not increase coronary calcium score

Sevelamer Supplementation:

1. Reduced PTH, urine Phosphate, & fractional excretion of Phosphate
2. Increased Total AlkP & BSAP while reducing DPD, 25VitD, FGF-23, & fibrinogen
3. Prevents progression of coronary calcium
4. Reduces mortality & progression to dialysis vs high-dose Calcium (2,000 to 3,000 mg daily)

Recommendations:

1. Supplement Calcium (small doses - citrate or acetate) to total daily intake of ~1,000 mg daily
2. Add Sevelamer (800 mg BID) early in CKD – may increase to 1,600 mg BID
3. Monitor serum Calcium, Phosphate, & PTH to determine adequacy

Arterial Calcification, Bone Physiology, & Renal Function

Recommended Therapies

Prevent or reverse: **Arteriosclerosis, Osteodystrophy, & Nephropathy**

Established therapies that reduce inflammation, oxidative stress, fibrosis, and arterial calcification:

- Control Lipids – Statins (atorvastatin reduces proteinuria), niacin, fibrates, omega-3, sequestrants
- Control BP – RAAS (ACE-I/ARB & spironolactone), Verapamil (prot), anti-Adrenergic (b-blocker, clonidine)
- Control Glucose – Pioglitazone & Metformin (inhibit mTORC1 & NF-kB)

Prevent **Calcification**

Monitor: Renal Panel (Ca^{++}, Phos, Album), Mg^{++}, 25VitD, PTH, BSAP, & mAlb; DEXA, Calcium Score

- Maintain Serum Phosphate between 3 & 4; Maintain corrected Ca^{++} within normal range
- Prevent Crystallization → Mg^{++} & Citrate [Klotho & mGP (matrix gamma-carboxyglutamic acid protein)]
- Maintain or reduce **PTH** to <50 if possible without causing hypercalcemia; works best early in disease process

Supplements:

- Calcium Citrate or Acetate → total intake ~1,000 mg daily (multiple small doses, for example: 200 mg QID)
- Replace Vitamin D → high normal (~60 to 90), Calcitriol (0.25 to 0.50 mcg), & MagCitrate (serum >2.0)
- Add Sevelamer (800 mg → 1,600 mg BID) early in CKD

Osteodystrophy prevention: estradiol, testosterone, DHEA, bisphosphonates, teriparatide, denosumab, & calcitonin

- Prevent bone ischemia

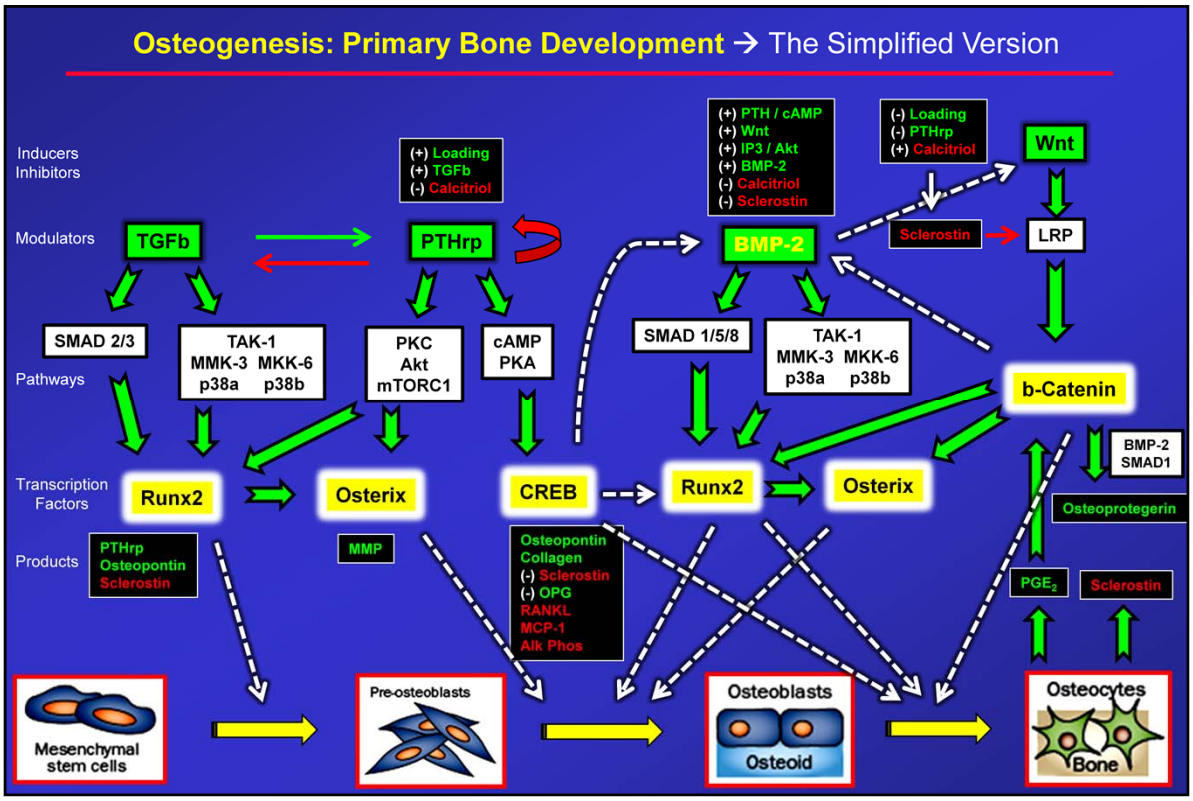

Figure 2 | The osteoblast differentiation program. **a** | *In vivo*: bone surface shows organization of indicated osteoblast lineage cells (black, mineralized tissue). Mesenchymal stem cells and osteoprogenitor cells cannot be seen. **b** | *In vitro*: stages of differentiation of committed preosteoblast cells isolated from newborn rodent calvarium or bone marrow stromal cells. Peak expression of genes that are markers for the three major stages are shown. At mineralization, a feedback signal from sclerostin secreted by osteocytes inhibits BMP and Wnt osteogenic-mediated bone formation by regulating the number of cells entering the osteoblast lineage. **c** | Examples of transcription factors regulating osteoblast differentiation and *in vivo* bone formation are shown. Within the triangle are those that increase during differentiation, whereas those above the triangle are functional on gene promoters at the indicated stages of maturation. Permission obtained from American Society for Bone and Mineral Research © Favus, M. J. (Ed.) *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 6th edn (2006).