Cardiovascular Calcification and Bone: A Comparison of The Effects of Dietary and Serum Calcium, Phosphorous, Magnesium and Vitamin D

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Abstract

This comparison of the effects of calcium, phosphorus, magnesium and vitamin D on cardiovascular (CV) calcification and bone has shown that in general the micronutrients that promote bone health also protect the arteries. We have shown that adequate amounts of all three minerals should be ingested, paying particular attention to supplementing calcium to bind high phosphorus and to ensure the maximum benefit from supplementing vitamin D. It appears that the optimum intake for bone is >800 mg/d calcium, with postmenopausal women possibly requiring a total intake of >1100mg/d. Both CV and bone studies suggest achieving a serum 25(OH)D level of >75nmol/l. These relationships are valid for a Caucasian population, however, and may not hold in African Americans and Asians. The recent concerns that calcium supplementation may increase CV disease risk has largely proved groundless, with higher calcium intake improving dyslipidaemia, hypertension and mortality. With respect to higher serum phosphate, there is an association with CV calcification and CVD risk even within the normal range, suggesting that the reference ranges may need to be redefined for ‘at risk’ patients. CV calcification was reduced in CKD patients with magnesium intake in the range 384-669mg/d. When considering the complex interplay of the action of the minerals together with their regulators vitamin D, PTH and FGF23, it is clear that this is a very sophisticated system which attempts to maintain calcium homeostasis to the possible detriment of bone and arteries. This reinforces the need to ensure adequate calcium intake before supplementing vitamin D.

Introduction

Osteoporosis and atherosclerosis are leading causes of morbidity and mortality in the Western world. Although these conditions commonly co-occur in older adults, growing evidence suggests an association between vascular calcification and skeletal fragility that is independent of age and other shared risk factors. Older adults with the greatest bone loss have the greatest progression of vascular calcification1,2 and the incidence of cardiovascular (CV) events is greater in women with lower bone mass3 and in men with higher levels of bone resorption4,5. The association between both pathologies also depends on the mechanisms involved in the regulation of bone and CV metabolism6. We have previously shown that the nutrients and micronutrients that benefit the CV system generally also benefit bone7,8. In this article we discuss the effect and interactions of the principal dietary bone minerals (calcium, phosphorus, magnesium) and vitamin D on CV calcification and bone health in principally older adults. Where these studies also investigated other aspects of CV health, we report these as well. Although other minerals, such as potassium, sodium, selenium and zinc are known to be involved in bone health, there are no human or animal studies investigating their association with CV calcification, so we have not included them. We have taken an effect on bone to mean an effect on at least one skeletal site but not necessarily all sites.

Calcium

Calcium fulfils vital roles in the body, particularly with respect to cell signalling functions; for this reason it is critical that serum calcium be maintained in a very narrow range. There are two modes of intestinal calcium absorption: active transcellular absorption, mediated by 1,25(OH)2D binding to the intestinal vitamin D receptor (VDR), and passive paracellular absorption, dependent on the calcium gradient, with high intake stimulating increased absorption independent of 1,25(OH)2D9,10. Active calcium absorption decreases when serum 25(OH)D concentration is <20nmol/L and consequently low calcium intake aggravates the consequences of vitamin D deficiency9. 1,25(OH)2D also increases renal reabsorption of calcium and upregulates bone resorption by facilitating osteoclast maturation, thereby increasing serum calcium11. Animal studies demonstrate that maintaining normocalcaemia takes priority over skeletal integrity because of calcium’s multiple intracellular and extracellular roles12. Dietary sources of calcium are mainly dairy products, fish, legumes, grains and vegetables13,14.

CV calcification

Observational studies generally show little association of calcium intake, dietary or supplemental, with coronary artery calcification (CAC) or abdominal aortic calcification (AAC) incidence or extent in older adults15,16, although a large study showed that calcium intake was significantly higher in postmenopausal men and women without AAC at baseline and in women only after five years17. Koreans with the highest calcium intake (>840mg/d) also had improved serum lipid profiles18. Many studies of serum calcium show no association with calcification19,20, although some show a positive correlation with presence, extent and progression of AAC in older adults.
Kidney supplementation on the risk of coronary artery disease

studies found no evidence of any significant effect of calcium intake is not generally associated with calcification in adults, with mixed results for presence of CAC, although there may be an association with extent or progression. Serum calcium was an independent predictor of calcified plaque and higher concentrations were associated with lower in-hospital mortality among MI patients. Nevertheless, serum calcium levels often bear little relationship to intake, as evidenced by the study by Wang et al., where higher serum calcium was associated with increased AUC but a higher calcium intake was found in those with no AAC. Nunes has suggested that it is the deranged metabolism of calcium and phosphorus, rather than the intake, which may be promoting CV calcification, particularly in CKD. Animal studies have shown that low calcium intake induces higher nephrocalcinosis and aortic calcium content, while high calcium intake is not generally associated with calcification in health but in rats with chronic kidney disease (CKD) and secondary hyperparathyroidism calcium supplementation increased arterial calcification.

In view of the recent concern by Bolland et al. that elevated calcium intake in white but not Hispanic, black or Mexican-American women, there was a positive association between BMD and calcium intake in white but not Hispanic, black or Mexican-American women, whereas among older men there was a correlation between BMD and calcium intake in blacks but not whites. Where calcium intake has been found predictive of BMD, the necessary intake for bone health appears to be >800 mg/day.

Phosphorus

Phosphate is critical for bone mineralisation but also for cell signalling and energy storage in the form of ATP, requiring strict control over blood concentrations, as with calcium. The main dietary sources of organic phosphorus are animal and plant proteins, while inorganic phosphorus is mostly seen in food preservatives or as phosphoric acid in colas; phosphoric acid may also bind with calcium in the intestine, so preventing calcium absorption. Although up to 100% of inorganic phosphorus may be absorbed, only 40-60% of organic phosphorus is absorbed. Furthermore, much of plant phosphorus is in the form of phytate (myo-inositol hexakisphosphate), found principally in unrefined cereals and legumes, which can inhibit absorption of several minerals by forming non-digestible mineral complexes. As with calcium, there are two mechanisms of phosphorus absorption: an active 1,25(OH)2D-dependent process, utilising sodium phosphate co-transporters, and a passive diffusional process dependent on the phosphorus gradient. Phosphorus restriction can also increase synthesis of 1,25(OH)2D. There are growing concerns that excess phosphorus intake from food additives and colas, with concomitant decrease in calcium intake from vegetables, in the general population may be a risk factor for CV disease, osteoporosis and mortality, possibly through induction of secondary hyperparathyroidism, even when serum phosphate remains within the normal range.

Bone

Although osteoporosis appears to have little association with serum calcium, a review of observational studies found an association of low calcium intake and osteoporosis risk, with an intake threshold of <400mg/d. This may only be a short-term association, possibly suggesting adaptation to a low calcium intake. As with CV calcification, several recent meta-analyses and systematic reviews of studies of healthy adults have concluded that the evidence for an association between calcium intake and BMD or fracture risk was insufficiently clear, although a Cochrane Review and recent studies have shown an effect of calcium supplementation on BMD but not fracture incidence in postmenopausal women, with an effective mean intake being >800mg/d, although much higher intakes have reduced fracture risk in other studies.

CV calcification

In the few studies of the effect of dietary phosphorus on human CV calcification there is no association in older Koreans, although animal studies show a positive association between phosphorus intake and aortic and renal calcification and atheroma incidence. Two large studies by Linefsky et al.
found a significant association between baseline mean serum phosphate levels (>1.292mmol/l vs ≤0.969mmol/l) and baseline aortic valve calcification (AVC), mitral annulus calcification (MAC) and AAC presence but not with extent, progression or new development after a mean of 2.4 years; the association with AAC lost significance after adjustment\textsuperscript{25,73}. These studies demonstrate that even a serum phosphate value within the reference range (0.8-1.4mmol/l) is associated with CV calcification, as well as increased CV risk \textsuperscript{66}. Studies of older adults and CKD patients also found a significant association between higher serum phosphate and presence and extent of calcification\textsuperscript{18,21,22,26,28,29}, with each 0.0323mmol/l rise in serum phosphorus being associated with 6.1% higher odds of having CAC\textsuperscript{21}. Wang et al found a gender difference: in postmenopausal women, serum phosphate was significantly higher (1.15 vs 1.17mmol/l) in subjects with AAC, while in older men there was no association\textsuperscript{15}. Elevated serum phosphate was also associated with coronary obstructive lesions and CV events, although results for mortality were mixed\textsuperscript{27,74-75}. A similar association with arterial and valvular calcification and increased carotid intima/media thickness (cIMT) is generally seen in CKD, although the serum phosphate levels tend to be considerably higher\textsuperscript{20,76-79} and are due to failure to excrete excess phosphate, which may be the driver for ectopic calcification\textsuperscript{80}. In CKD, arterial calcification can be suppressed by reducing serum phosphate levels, even in the presence of high serum calcium and 1,25-dihydroxyvitamin D levels\textsuperscript{61}. CKD rats showed phosphorus intake-dependent increases in markers of inflammation and oxidative stress as well as CV calcification and mortality\textsuperscript{72}, while VSMCs cultured in normal levels of phosphorus do not calcify\textsuperscript{73} but high inorganic phosphorus can induce calcification, endothelial dysfunction and increased markers of inflammation\textsuperscript{71,79,82,83}.

**Bone**

Results of adult human studies show mixed results for associations between total phosphorus intake and osteoporosis or fractures\textsuperscript{64-66}, although inorganic phosphorus intake from colas induced a higher incidence of osteopenia and lower BMD among women only; since this was not seen with other soft drinks it is likely to be attributable to phosphoric acid\textsuperscript{64}. Among healthy women, dietary and serum phosphorus were generally not associated with BMD or markers of bone formation or resorption\textsuperscript{45,85,87}. Phosphorus supplementation in young women resulted in decreased markers of bone formation and increased markers of resorption\textsuperscript{46} but had no adverse effect on young men\textsuperscript{86}. A further intervention study found that the adverse effects of high phosphorus supplementation could be negated by high calcium supplementation\textsuperscript{87}. Animal studies show that diets creating either a phosphorus excess or deficiency lower BMD and bone mineralisation\textsuperscript{17,97}.

**Magnesium**

Magnesium is an essential mineral, acting as cofactor in more than 300 enzymatic reactions. It is a natural calcium channel blocker and plays an important role in CV, neurological and metabolic functions, although approximately 60% of body magnesium is found in bone\textsuperscript{90}. Dietary sources include legumes, vegetables, nuts, seeds, fruits, grains, fish and dairy foods\textsuperscript{93}. As with calcium and phosphorus, there is a vitamin D-dependent intestinal absorption and gradient-driven absorption\textsuperscript{94}.

**Ectopic calcification**

The principal intake study found that CV calcification was lowest in the quartile with intake ranging from 384-669mg/d\textsuperscript{65}, while higher intake was inversely associated with stroke risk\textsuperscript{69}, diabetes incidence and hypertension\textsuperscript{65}. The only studies of blood concentrations involve dialysis patients and show a clear association between lower serum magnesium (1.106mmol/l vs 1.241mmol/l) and peripheral artery calcification\textsuperscript{97-98} and MAC\textsuperscript{99}, the protective amount being above the reference range (upper limit 1.2mmol/l), although this should not be extrapolated to non-renal patients. Serum magnesium was also inversely correlated with cIMT and aortic pulse wave velocity in renal and non-renal patients\textsuperscript{100}. In animals, a low magnesium diet increased cardiac magnesium and calcium deposition\textsuperscript{72,100-102} but the CV and renal calcification was worse when low magnesium intake was combined with high phosphorus\textsuperscript{100-103}. Experimental magnesium deficiency also induced arterial damage, hypertriglyceridaemia and a decrease in HDL cholesterol transport\textsuperscript{104}. A high magnesium intake, however, was associated with a reduction in plasma cholesterol and triglycerides in rats\textsuperscript{105}. There are no trials of magnesium supplementation on CV calcification in humans but in renal patients supplementation resulted in significantly lower cIMT\textsuperscript{106}, while in animals supplementation dose-dependently lowered myocardial, carotid and arterial calcium content\textsuperscript{107,108}. Similarly, in vitro studies showed that increasing magnesium concentration reduced calcification in VSMC\textsuperscript{93,109}.

**Bone**

Dietary and serum, but not red cell, magnesium were generally lower among the elderly with osteoporosis\textsuperscript{15,86,109} and among healthy older adults, magnesium intake was positively associated with BMD, BMC and bone mass\textsuperscript{86,110-111}, with an intake of >422.5mg/d vs <206.5 mg/d improving BMD\textsuperscript{110}. A large multiethnic study found that this association may apply to older whites but not blacks\textsuperscript{112}. Some studies also found an association with BMD in younger women\textsuperscript{113-114}. Study results are mixed with respect to intake and fracture risk\textsuperscript{14,110,115} and among Japanese subjects low serum magnesium was associated with increased fracture incidence\textsuperscript{116}. Short term intervention studies...
show that 1830mg/d magnesium citrate significantly decreased levels of urinary deoxypyridinoline (a marker of bone resorption) in postmenopausal osteoporotic women with normal baseline serum magnesium and calcium, while concentrations of serum osteocalcin (a marker of bone turnover) were increased\textsuperscript{117}, but there was no effect in young women\textsuperscript{118}. Longer studies of postmenopausal women with low BMD showed that magnesium supplementation increased BMD\textsuperscript{119-120}.

**Vitamin D**

Vitamin D is a steroid hormone which has multiple roles in the body, in particular an autocrine function, which acts to promote skeletal health, and an endocrine function, which includes maintenance of serum calcium within a narrow range\textsuperscript{121}. Since serum calcium homeostasis is of vital importance, the endocrine function can often operate to the detriment of the autocrine function\textsuperscript{122}, which may account for the lack of clear results in vitamin D studies. Low serum calcium or phosphate triggers the synthesis of the vitamin D metabolite 1,25(OH)\textsubscript{2}D in kidney and bone, which in turn binds to the intestinal vitamin D receptor (VDR) and increases intestinal calcium\textsuperscript{10,123} and magnesium\textsuperscript{94} absorption and renal reabsorption but also inhibits bone mineralisation\textsuperscript{94} and upregulates bone resorption by facilitating osteoclast maturation to release calcium and phosphate, thereby increasing serum concentrations\textsuperscript{117}.

Active calcium absorption decreases when serum 25(OH)\textsubscript{D} concentration is <20nmol/L and consequently low calcium intake aggravates the consequences of vitamin D deficiency\textsuperscript{23}. There is a decreasing ability with age to synthesise either 25(OH)\textsubscript{D} or 1,25(OH)\textsubscript{2}D as well as intestinal resistance to its action\textsuperscript{124-125}; it appears that the optimal level of serum 25(OH)\textsubscript{D} for calcium absorption is >80nmol/L in postmenopausal women\textsuperscript{126}. Vitamin D also has key roles in CV health, as vitamin D deficiency is associated with reduced bone loss\textsuperscript{150-152} but with respect to fracture incidence, there appears to be little association with vitamin D intake\textsuperscript{115}. Animal studies measuring serum 25(OH)\textsubscript{D} demonstrate an absence of association with presence or extent of CAC, MAC, cIMT, degree of carotid stenosis or mean arterial pressure\textsuperscript{122,133-135}, although patients with calcific aortic stenosis\textsuperscript{136} and poor coronary collateral circulation\textsuperscript{137} had significantly lower serum 25(OH)\textsubscript{D}. After three years serum 25(OH)\textsubscript{D} was associated with new CAC development, but not CAC progression, with those with serum 25(OH)\textsubscript{D} of <37.55nmol/L having increased risk\textsuperscript{138}. The association is usually clearer in those with previously diagnosed disease. In CKD patients, arterial calcification was significantly inversely associated with serum 25(OH)\textsubscript{D}\textsuperscript{139} and a high peripheral arterial calcification score was significantly associated with lower 25(OH)\textsubscript{D} concentrations\textsuperscript{138}. Similarly in type 1 diabetics, serum 25(OH)\textsubscript{D} <49.9nmol/L was associated with the presence and development of CAC after 3 years\textsuperscript{139} with valvular calcification in dilated cardiomyopathy patients (serum 25(OH)\textsubscript{D} <75nmol/L)\textsuperscript{140} and with the calcification score in peripheral arterial disease\textsuperscript{27}. Likewise with respect to serum 1,25(OH)\textsubscript{2}D, some studies show no association with CAC extent or progression\textsuperscript{133,141}, although in subjects at risk for CHD, serum 1,25(OH)\textsubscript{2}D was inversely correlated with the extent of calcification\textsuperscript{142}.

There have been few intervention studies of vitamin D alone but in CKD patients the incidence of aortic calcification was significantly lower in treated patients\textsuperscript{142}, while in heart failure, 4000IU/d for six months significantly improved the left ventricular ejection fraction\textsuperscript{144}. Trials of vitamin D supplementation combined with calcium showed that up to 1000g/d calcium plus 400 IU/d vitamin D3 did not affect CAC scores or incidence of myocardial infarction (MI), CHD mortality or stroke in postmenopausal women\textsuperscript{145-146}, although there was an improvement in dyslipidaemia\textsuperscript{147}; this lack of result may be because the vitamin D dose was low. Nevertheless, although a 2011 systematic review found that serum 25(OH)\textsubscript{D} was not significantly associated with mortality, MI or stroke\textsuperscript{148}, a meta-analysis of RCTs found that vitamin D supplementation for at least three years significantly decreased all-cause mortality\textsuperscript{149}.

**Bone**

A 2006 systematic review and more recent studies of older adults showed that a vitamin D intake of ≥400 IU/d was associated with reduced bone loss\textsuperscript{150-152} but with respect to fracture incidence, there appears to be little association with vitamin D intake\textsuperscript{115}. Two large reviews found that in older adults, serum 25(OH)\textsubscript{D} was positively associated with BMD but there was inconsistent evidence for an association with fractures\textsuperscript{153}. In elderly postmenopausal women, those with serum 25(OH)\textsubscript{D} levels <50 nmol/L had increased fracture risk, bone loss and mortality, leading to recommendations that 50nmol/L should be the minimum level to ensure optimum bone health, below which supplementation is recommended at 800-1000IU/d but above

**Ectopic calcification**

There are no human intake studies with respect to CV calcification, probably because dietary vitamin D provides only a relatively small contribution to serum 25(OH)\textsubscript{D}. Animal studies, however, show that high vitamin D intake can induce CV calcification and impair endothelial function\textsuperscript{138,139} but they also show that a vitamin D deficient diet can induce an increase in calcified lesions\textsuperscript{136,139}, indicating that both excess and deficiency are detrimental. Several epidemiological studies measuring serum 25(OH)\textsubscript{D} demonstrate an absence of association with presence or extent of CAC, MAC, cIMT, left ventricular ejection fraction\textsuperscript{144}.
this threshold there was no clear evidence for additional benefit except in fragile elderly subjects, for whom serum 25(OH)D should be ≥75nmol/l\(^{154}\). Recent Korean studies confirm the positive association, which may not be linear\(^{155}\) and indicate that BMD increases until 25(OH)D ≥70nmol/l in men and 50 nmol/l in women\(^{156}\). Ethnicity may have a bearing on the effect of vitamin D. A prospective study showed that higher 25(OH)D levels were associated with a lower risk of fracture in white women but a higher risk in black and Asian women and no association in Hispanic or Native American women\(^{151}\); the NHANES study showed that mean 25(OH)D levels were highest in whites and lowest in blacks yet blacks had the highest BMD and whites had the lowest\(^{158}\).

When additionally considering calcium intake, the combination of higher vitamin D and calcium were associated with higher BMD in young adults\(^{159}\) and reduced osteoporosis risk in postmenopausal women\(^{92}\), with the optimum dose for fracture reduction being 700-800IU/d vitamin D3 with 500-1200mg/d calcium\(^{153}\). Animal studies confirm that a diet deficient in calcium and vitamin D lowers BMD and increases urinary excretion of markers of bone resorption, not seen in calcium or vitamin D deficiency alone\(^{160}\). In humans, BMD and BMC loss and fracture risk were more consistently inversely associated with calcium intake and serum 25(OH)D taken together among all agegroups than either nutrient taken alone\(^{150,155}\). Three recent reviews and meta-analyses of intervention studies found that vitamin D supplementation alone did not prevent fractures or increase BMD; the two reviews found a protective effect of vitamin D with calcium but results of the meta-analysis depend on the authors’ “futility boundary”\(^{161-163}\). A further meta-analysis found that in older adults, supplementation of 800IU/d could significantly reduce hip fractures and associated deaths over one year\(^{164}\).

**Other multinutrient interactions**

Lappe and Heaney point out that nutrient trials may fail because of inadequate attention to co-nutrient optimisation, including protein\(^{152}\). One of the most important mineral partnerships is that of calcium and phosphorus, with the calcium/phosphorus ratio in bone being 2.2:1\(^{156}\). An intake ratio of <1.0 was associated with nephrocalcinosis in rats but increasing the ratio to 1.3 inhibited calcification development\(^{156}\), while a low intake ratio increased osteoporosis risk in Koreans\(^{166}\) and increased bone resorption markers\(^{159}\) but a ratio of at least ≥0.74 benefited bone among younger females\(^{89,170}\). Although phosphorus restriction increases serum ionised calcium\(^{152}\), phosphorus supplementation was also associated with decreased urinary calcium excretion\(^{156,171}\), suggesting that calcium is retained to bind the phosphorus. There is also a strong interaction between calcium and magnesium, with low magnesium intake in animals increasing serum calcium, the calcium/phosphate ratio and calcium deposition in bone\(^{172-175}\) but with high calcium intake, serum and tissue magnesium was lower, suggesting decreased absorption\(^{174}\). High magnesium intake in calcium sufficiency, however, significantly improved all bone parameters compared to calcium insufficiency and when supplemented together, there was a significant improvement to all bone parameters\(^{175}\). There is competitive inhibition of gradient-dependent intestinal absorption, not only between magnesium and calcium\(^{97,94}\) but also between magnesium and phosphorus provided calcium is adequate but magnesium absorption may increase at the expense of phosphorus when serum calcium is low\(^{29}\). Magnesium depletion is associated with increased serum ionised magnesium and calcium and decreased ionised phosphate\(^{101,102}\). Magnesium also interacts with vitamin D, such that magnesium deficiency impairs the synthesis of 1,25(OH)2D even during dietary calcium deprivation\(^{176}\) and can lead on to resistance to 1,25(OH)2D\(^{177}\).

**Mechanisms**

As well as vitamin D, additional regulators of CV calcification and bone mineralisation include parathyroid hormone (PTH)\(^{178}\) and fibroblast growth factor 23 (FGF23), a phosphotin secreted from bone, which appears to be a counter-regulatory hormone for vitamin D\(^{179}\). Figures 1-3 demonstrate how all three are involved in the regulation of serum calcium, phosphate and magnesium. Optimal PTH concentrations have been found when 25(OH)D ≥80nmol/l\(^{151,156}\), while elevated FGF23 was associated with the CAC score in haemodialysis patients\(^{162}\) and even among healthy subjects, the highest FGF23 quartile was associated with higher CAC scores and greater risk of heart failure and CHD\(^{183}\). Elevated serum phosphate can impair endothelial function, as evidenced by decreased vasodilatation, and may promote transdifferentiation of VSMCs to osteoblast-like cells\(^{17}\).

**Discussion**

Although most studies show little association between calcium intake and CV calcification or BMD and fracture risk, the large study showing a positive correlation between higher intake and absence of AAC and the review showing an association between low intake and osteoporosis indicate that a higher intake is preferable. BMD studies indicate that this should be ≥800mg/d, with 1100mg/d for postmenopausal women, although larger doses were required for fracture prevention. Possibly the studies show a lack of association because even in the higher quartiles, intake is still too low. Serum calcium studies also generally show no association with CV calcification or bone, although a few show a positive association with AAC, but an association between serum calcium and bone would not be expected, since bone is a calcium reservoir to maintain serum levels. Bone studies also highlight the fact that ethnicity may distort results, which may be equally applicable to CV studies. There is no evidence that calcium supplementation increases CV risk; in fact calcium appears beneficial for prevention of CV events and mortality and can lower cholesterol and blood pressure.

Higher dietary and serum phosphorus may promote CV calcification even when serum phosphate is within normal range. Results of phosphorus intake and bone studies are mixed, possibly because phosphorus is necessary for healthy bone but the phosphoric acid in colas may pose a particular risk for bone loss in women. It appears that healthy individuals can adjust to a wide range of phosphorus consumption but have little adaptive ability for low calcium intake, indicating that the calcium/phosphorus intake ratio is more critical than the absolute phosphorus intake\(^{184}\); any detrimental effect of high phosphorus intake can be negated by increasing calcium intake. Dietary and serum magnesium intake shows a strong inverse correlation with CV calcification, osteoporosis and bone loss, as well as with stroke incidence, cIMT and conventional risk factors; CV calcification is minimised with intake in the quartile ranging from 384-669mg/d but this association may only apply to Caucasians. Calcification resulting from a low magnesium intake is particularly severe in animals when combined with high phosphorus intake. Although human trials are lacking, magnesium supplementation in animals significantly lowered CV calcification. In bone, magnesium supplementation increased BMD and improved markers of bone turnover.
Although human observational studies for vitamin D intake and CV calcification are lacking, animal studies show a U-shaped dose/response curve for intake, while bone studies found that intake of >400IU/d is required to reduce bone loss. Serum 25(OH)D is generally not correlated with CV calcification, except in CKD and other already-diagnosed conditions, where it is inversely associated, but in bone, serum 25(OH)D is positively associated with BMD. Intervention studies show reduced CV calcification in CKD, improved ventricular function in heart failure and lower mortality in longer term studies but no effect on CV calcification in healthy postmenopausal women, either alone or when accompanied by calcium, although the vitamin D dose was low (400IU/d). The vitamin D/calcium combination is beneficial to bone, however, provided the vitamin D dose is adequate. Bone studies indicate that supplementation of >800IU/d is required to bring serum 25(OH)D up to 50nmol/l in healthy adults or >75nmol/l in the fragile elderly. Ethnicity may again affect results, with higher 25(OH)D giving a higher fracture risk in black and Asian women. It is difficult to assess the CV or bone effects of vitamin D alone, since its predominant function is to maintain serum calcium homeostasis and it will do this to the detriment of bone or arteries if necessary; baseline serum calcium is seldom measured in these studies.

These studies highlight the interactions between the different micronutrients and point up the need for a calcium phosphorus intake in the ratio of >1 for bone health, which may also translate to arteries. Because of the competitive inhibition of absorption if intake of one mineral is imbalanced, it is important that adequate, but not excessive, intake of all bone minerals is maintained for both artery and bone health.

Conclusion

This review has firstly demonstrated that a mineral and vitamin D intake that is beneficial for bone is also generally protective against CV calcification. In principal this involves ensuring an adequate intake through diet or supplementation of each mineral and, in particular, supplementing sufficient calcium to balance any increased phosphorus intake to avoid upregulating PTH and to prevent a catabolic effect of vitamin D supplementation on bone to maintain serum calcium. These relationships may, however, not hold among African Americans and Asians. It has secondly shown the striking inter-relationship between the three bone minerals and vitamin D. This is particularly true with calcium, magnesium and vitamin D, where one can, to a certain extent, substitute for the other in the short term in maintaining bone health. Bone studies showed limited effect when considering calcium and vitamin D separately but when supplemented together there is a significant protective effect. The competitive inhibition of absorption between all three minerals further emphasises that the diet should contain adequate levels of all three. The concern over the effect of supplemental calcium and CV events appears unnecessary since there is no evidence of any significant detrimental effects, whereas calcium supplementation may in fact be protective.

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Abstract

Coronary artery disease (CAD) has an important impact on the morbidity and mortality in the West and health service resources worldwide. It is therefore crucial to accurately diagnose CAD early, in an attempt to limit its burden on patients and society, potentially by optimum risk stratification, accurate diagnosis and management. Invasive coronary angiography (ICA) is the conventional gold standard imaging investigation for the coronary circulation and assessment of disease severity. However, it is an invasive procedure and is associated with risks, although rare. In addition, it detects luminal stenosis but not the functional importance of those anatomical lesions. Therefore, a wide variety of non-invasive imaging developed to evaluate the presence and severity of CAD, including anatomical techniques e.g. coronary CT that assesses coronary stenosis, and quantities coronary calcium, hence the burden of atherosclerotic plaques and functional imaging e.g. stress echocardiography, nuclear imaging by SPECT and PET and stress CMR. Selection of the most appropriate imaging, therefore, is challenging and requires knowledge of patients’ pre-test probability and prevalence of disease, their advantages and limitations, cost and availability. This review attempts to provide an overview of the current supporting evidence of the role of non-invasive imaging in diagnosing CAD, in addition to its prognostic value, limitations and advantages.