Ectopic calcification and bone: a comparison of the effect of dietary carbohydrates, sugars and protein

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Abstract

A number of studies have shown that severe calcification of the arteries, heart and kidneys commonly coexists with osteoporosis, particularly in renal disease. We have already shown that with respect to dietary fats, those that promote ectopic (mainly cardiovascular) calcification are also detrimental to bone, with a similar relationship seen in fats which inhibit ectopic calcification. This review of dietary carbohydrates, sugars and protein has shown a similar correspondence of effect, with protein proving protective against ectopic calcification, at least in animals, and beneficial to bone. There appears to be an interaction with calcium intake, with the beneficial effects of high protein being negated in a calcium deficiency, while a high calcium intake enhances the dangers of a low protein intake; the cut-off for calcium intake may be around 800mg/d for bone health. The results of studies on carbohydrates are unclear. Although there are no human studies on ectopic calcification and intake of sugars, diabetes mellitus, insulin resistance and high blood glucose are known risk factors and are also detrimental to bone. Fructose consistently promotes ectopic calcification in animals and is detrimental to bone in both animals and humans, although the results for sucrose, glucose and lactose are mixed. Protein and prebiotics, both protective against ectopic calcification and beneficial to bone, appear to act by increasing calcium absorption. Mechanisms of action shared between inhibition of ectopic calcification and increased bone mineral density (BMD) include insulin-like growth factor (IGF)-1, which can be directly induced by protein and glucose, and advanced glycation end products (AGEs), which decrease expression of IGF-1 and generate reactive oxygen species, promote ectopic calcification and increased bone resorption.

Introduction

Cardiovascular (CV) calcification presence, extent and progression has been shown in several studies to correlate with fracture or low bone mineral density (BMD), particularly in older men and women¹⁻³. CV calcification shares some similar properties with cortical bone⁴ and, when severe, can manifest as bone formation in both arteries and valves⁵⁻⁶. CV calcification and impaired bone metabolism are particularly prevalent in chronic kidney disease (CKD), where the condition has become known as mineral-bone disorder (MBD)⁷. The association between bone and CKD calcification has been shown in several studies to correlate with the aortic calcification score¹⁷ or CAC score¹⁸. Nevertheless, a number of studies have considered dietary intake and bone parameters show mixed results²⁹⁻³⁰, with several comparison studies of carbohydrates, proteins or fats showing no difference in markers of bone formation or resorption²⁹⁻³¹. However, can reduce CV and renal calcification²⁵⁻²⁶. Likewise, in vitro studies have shown that a high glucose medium enhances calcification of vascular smooth muscle cells (VSMCs) and increased expression of markers of bone formation, confirming a cell-mediation process characterized by the trans-differentiation of VSMCs to osteoblast-like cells²⁷.

Carbohydrates and sugars

Ectopic calcification

In a prospective study of premenopausal women, carbohydrate intake was inversely associated with coronary artery calcification (CAC) five years after menopause but was not associated with aortic calcification or carotid artery plaque¹⁰ and a large cross-sectional study showed that whole grain intake was not associated with two measures of subclinical atherosclerosis: carotid intima-media thickness (CIMT) and CAC¹¹. Although there are no studies considering dietary intake of sugars, diabetes mellitus, metabolic syndrome, insulin resistance and high blood glucose, HbA1C and triglycerides are known risk factors for the presence of aortic calcification, breast¹³, carotid¹⁴ and coronary artery calcification and may also correlate with the aortic calcification score or CAC score. The relationship between CAC presence and blood glucose levels was found particularly among men¹⁷ and may be nonlinear²⁶, with low insulin levels, as well as hyperinsulinaemia, independently predicting CAC presence. Similarly in animals, a high carbohydrate diet appears to facilitate nephrocalcinosis, while starch or any form of sugar can result in increased incidence of CV or renal calcification, particularly in magnesium deficiency, Galactooligosaccharides or a high phytate diet, however, can reduce CV and renal calcification. Likewise, in vitro studies have shown that a high glucose medium enhances calcification of vascular smooth muscle cells (VSMCs) and increased expression of markers of bone formation, confirming a cell-mediation process characterized by the trans-differentiation of VSMCs to osteoblast-like cells²⁷.
Dietary fibre is generally inversely associated with BMD\textsuperscript{33}. Type 2 diabetes and insulin resistance are strongly associated with impaired bone strength and quality\textsuperscript{34}, although there may be less correlation with BMD\textsuperscript{35} and bone formation\textsuperscript{36} or resorption\textsuperscript{37}; some have suggested that it may be hyperinsulinaemia, rather than hyperglycaemia, that underlies the relationship\textsuperscript{38}. The effect of sugar intake depends upon the type, with sucrose or fructose intake correlated with increased bone resorption markers\textsuperscript{39}, adversely affecting mineral homeostasis\textsuperscript{40}, while higher glucose intake decreased bone resorption markers\textsuperscript{41}. Low lactose intake reduced calcium absorption and BMD\textsuperscript{42} and increased fracture risk\textsuperscript{43}. Prebiotics, such as inulin or fructans, increased mineral absorption in humans but results on bone parameters were not always positive\textsuperscript{44,45}.

In animals, both high\textsuperscript{46} and low\textsuperscript{47} carbohydrate intake can have a detrimental effect on bone formation, while higher dietary fibre from legumes can increase calcium absorption, bone calcium content and BMD\textsuperscript{48}. High glucose, sucrose and fructose generally result in lower BMD, particularly in magnesium deficiency, probably through reduced calcium absorption\textsuperscript{49}. Lactose again appears to be beneficial for bone\textsuperscript{50}, while xylitol can slow bone resorption, increasing BMD, BMC and biomechanical properties\textsuperscript{51}. Manitol and prebiotics can improve bone mineral absorption by increasing gut fermentation, resulting in greater mineral uptake in bone and improved BMD and bone strength\textsuperscript{52}.

**Dietary protein**

**Ectopic calcification**

There have been no human studies investigating protein intake and CV calcification and in animals they focus almost exclusively on nephrocalcinosis, with the majority showing that increased dietary protein reduced renal calcification in rats with or without CKD with frequent reduction in urinary calcium excretion\textsuperscript{53,54}. Likewise, a low protein intake induced more severe renal calcification, with decreased glomerular filtration rate and enhanced urinary albumin loss, suggesting kidney damage\textsuperscript{55}. In a study which considered both nephrocalcinosis and bone health, krill protein produced lower renal tubular calcium deposition than casein, but had no effect on BMC or bone strength\textsuperscript{56}; although this shows a positive benefit of krill protein, this may in part be due to the omega-3 fatty acid content. A high calcium, high phosphorus or low magnesium intake can enhance the detrimental effect of low protein intake on renal calcification\textsuperscript{57,58}, while a calcium deficiency combined with high protein intake also enhanced the rate of ectopic calcification\textsuperscript{59}.

**Bone**

Bone is 50% protein and 50% mineral\textsuperscript{60} and consequently dietary protein is essential for bone formation\textsuperscript{61} but it has nevertheless been considered detrimental to bone since protein induces urinary calcium excretion thought to derive from bone resorption\textsuperscript{62,63}. Some recent studies, however, suggest that increased calcium excretion may derive from increased absorption, possibly through elevated gastric acid production\textsuperscript{64}, higher glomerular filtration rate or decreased renal calcium reabsorption\textsuperscript{65}. This is born out in a 2009 systematic review and meta-analysis of protein intake studies and protein supplementation trials, which found a small positive association with BMD and no detrimental association with fracture risk\textsuperscript{66}. Recent studies have generally shown that, although there may be little short term effect\textsuperscript{67}, long term high protein intake is positively associated with BMD, BMC and decreased fracture risk\textsuperscript{68} and slowed bone turnover\textsuperscript{69}. Similarly, animal studies have generally shown that while high protein diets certainly increase urinary calcium excretion, they either have no effect on bone\textsuperscript{70} or bone calcium content and bone mass is improved\textsuperscript{71}. In fact, it is generally low protein diets that are harmful to bone, particularly after ovariectomy\textsuperscript{72,73}. There has been concern that a high animal/vegetable protein ratio may be detrimental to bone\textsuperscript{74}. Despite this, a 2009 meta-analysis showed that BMD was around 4% lower in vegetarians than in omnivores\textsuperscript{75}, although it was noted that key confounding variables had not been taken into account\textsuperscript{76}. Since then a large study found no association between hip fracture and the animal/plant protein ratio\textsuperscript{77}, while animal protein was found to increase calcium absorption to a greater extent than soy protein\textsuperscript{78}.

There may be an interaction with calcium status in humans. Sahni et al found that when calcium intake was <800 mg/d, there was a three-fold increase in fracture risk with a high animal protein intake, while in those consuming ≥800 mg/d calcium those with a high animal protein intake had an 85% reduced risk of hip fracture\textsuperscript{79}. Nevertheless, the body is clearly attempting to compensate since among postmenopausal women, a high protein intake increased calcium retention only in those with a low calcium intake\textsuperscript{80}. Supplemeting both protein and calcium significantly reduced bone loss in elderly hip fracture patients\textsuperscript{81}, while protein intake was associated with BMD increase over three years in subjects aged ≥65 receiving calcium and vitamin D\textsuperscript{76,77}. A high protein diet in calcium repletion can also protect against the bone loss of weight reduction\textsuperscript{82}. Age may also play a role; a large study showed that increased protein intake was associated with a decreased risk of osteoporotic hip fracture in subjects aged 50-69 years but not in those aged 70-89, regardless of calcium intake\textsuperscript{83}. Nevertheless, other prospective studies of the elderly have shown a clear relationship between low protein intake and...
IGF-1 83, while blood glucose and insulin levels are important for bone metabolism 84. A diet high in carbohydrates appears to increase ectopic calcification, a diet high in protein may inhibit it, possibly through induction of IGF-1 85. Dietary protein intake was generally inversely correlated with renal calcification in animals with and without CKD, although there were no human studies of protein intake and ectopic calcification. In both animals and humans, there is a modest positive association between protein intake and BMD and an inverse association with fracture risk; there appears to be little difference between animal and plant proteins. There may be a strong synergistic interaction with calcium, with low calcium and high protein intake significantly increasing fracture risk and enhancing renal calcification, while a high protein and calcium intake significantly reduces fracture risk and ectopic calcification. Increased protein is known to increase urinary calcium excretion but rather than being taken from bone, this seems more likely to be due to increased intestinal absorption and/or decreased renal reabsorption, although this may only occur in calcium deficiency. In general, therefore, a diet high in carbohydrate and sugars and low in protein is detrimental to both arteries and bone. This finding accords with our previous review, which concluded that the dietary fats which are beneficial or harmful for arteries are also beneficial or harmful for bone 90.

### References


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