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Plant-based diets relatively low in bioavailable phosphate and calcium may aid prevention and control of prostate cancer by lessening production of fibroblast growth factor 23

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ABSTRACT

Fibroblast growth factor 23 (FGF23), a hormonal regulator of phosphate and vitamin D metabolism produced primarily in bone by osteocytes and mature osteoblasts, is now known to have growth factor activity for many prostate cancers. In some of these cancers, autocrine production of FGF23 drives their proliferation. FGF23 synthesized within bone likely promotes the expansion of prostate cancer bone metastases. Hence, dietary or lifestyle factors which boost bone's production of FGF23 may encourage the induction and spread of prostate cancer. High dietary intakes of bioavailable phosphorus and of calcium have been found to boost FGF23 levels, and this accords well with prospective epidemiology pointing to high intakes of both phosphate and calcium as risk factors for aggressive prostate cancer. Hence, prospective studies correlating baseline FGF23 levels with subsequent risk for prostate cancer, or advanced prostate cancer, are needed. Natural plant-based diets, though not inherently low in calcium or phosphorus, provide forms of these that are less bioavailable than those in animal products, and hence may be expected to down-regulate bone's production of FGF23. This may play a role in the lower risk for clinical prostate cancer observed in vegans and quasi-vegan cultures. Other factors, such as decreased IGF-I levels and mTORC1 activity, may also play a role in this regard.

A role for FGF23 in promotion and spread of prostate cancer

Fibroblast growth factor 23 (FGF23) is a hormone, produced primarily in bone by osteocytes and mature osteoblasts, that functions to regulate phosphate and vitamin D metabolism [1]. There is recent evidence that FGF23 may act as autocrine, paracrine, and systemic growth factor for many prostate cancers [2–4]. Many prostate cancer cell lines can produce FGF23; they also express alpha-klotho and a range of FGF receptors capable of interacting with it to generate a membrane receptor that responds to FGF23 stimulation [2]. In these cell lines, exposure to exogenous FGF23 boosts proliferation, invasiveness, and anchorage-independent growth; signaling via Akt and ERK is observed. Also speaking for a role of FGF23 in prostate cancer induction is a study demonstrating increased risk for prostate cancer associated with certain single-nucleotide polymorphisms of the FGF23 gene [4]. Evidently, nested case-control studies in prospective data bases are needed to determine whether higher FGF23 levels are indeed associated with increased risk for prostate cancer and aggressive prostate cancer.

It is therefore reasonable to postulate that dietary and lifestyle measures which up-regulate bone secretion of FGF23 play a role in the induction and progression of prostate cancer. Moreover, such measures could be expected to accelerate the expansion of prostate cancer bone metastases, owing to FGF23 of paracrine origin [2,3]. Indeed, dovitinib, a monoclonal antibody targeting FGF receptors – which would be expected to block FGF23 signaling – has been found to be clinically useful in prostate cancer patients with bone metastases [5]. Likely, the impact of systemic or paracrine FGF23 on prostate cancer progression would be less important for cancers whose autocrine production of FGF23 is high.

Dietary determinants of FGF23 production – focus on calcium and phosphorus

Studies with cultured osteocytes and mature osteoblasts obtained from fetal rat calvaria have examined the direct impact of various factors on their production of FGF23. The most dramatic boost in production was produced by calcitriol, the hormonally active metabolite of vitamin D; this is a transcriptional effect mediated by the activated vitamin D receptor [6]. A high-normal phos-

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phate level had a much more modest impact on FGF23 production, but notably potentiated the response to calcitriol. Homeostatically, it makes perfect sense for both calcitriol and phosphate to boost FGF23 production, since this hormone acts on the kidneys to increase phosphate clearance while suppressing conversion of 25-hydroxyvitamin D to calcitriol [7]. A rise in serum phosphate can also boost FGF23 production indirectly: phosphate promotes the parathyroid's secretion of PTH either directly, or by decreasing serum levels of ionized calcium; PTH acts on the kidney tubules to boost synthesis of calcitriol [8]. This calcitriol then acts directly on osteocytes to promote FGF23 synthesis.

Several controlled clinical studies have indeed shown that acute or chronic increases in phosphate intake, or of phosphate + calcium intake, can increase plasma levels of total or intact FGF23 [9–11]. Using data from the Health Professionals Follow-Up Study, Guiterrez and colleagues found that dietary phosphorus, as well as plasma phosphate levels, correlated positively with plasma FGF23 [12]. However, an analysis of EPIC-Germany study failed to demonstrate a correlation between dietary phosphorus and plasma FGF23 [13]. A factor which might confound such correlations is the considerable difference in bioavailability of phosphorus from animal and plant sources. Much of the phosphorus in plant products is in the form of phytates; this phosphorus is poorly absorbed owing to a lack of phytase activity in the intestine [14,15]. In one recent study, patients with advanced chronic kidney disease were sequentially fed two diets for a week, each with comparable macronutrient composition; however, one diet featured animal protein, while in the other protein from plant sources predominated [16]. Although the diets were nearly identical in phosphorus content, urinary phosphorus output was about 29% lower on the vegetarian diet, and plasma FGF23 was about 40% lower. While the magnitude of these effects might not have been replicated if the study had enrolled subjects with normal renal function, this study does highlight the impact of dietary source of phosphorus as a key determinant of FGF23 production. Likewise, in a cross-sectional study enrolling over 2000 patients with chronic kidney disease, the percentage of dietary protein provide by plant sources was found to correlate inversely with plasma levels of FGF23 [17].

In one study examining osteocytes and osteoblasts from fetal rat calvaria, neither parathyroid hormone, nor other measures which boost intracellular cAMP levels, influenced FGF23 production in this system [6]. However, another study with osteocytes from rat calvaria did report a direct stimulatory effect of PTH [18]; the reason for the disparity in these results is not clear.

Some studies have reported that low iron status – reflecting either low body iron stores, or an acute reduction in plasma iron owing to systemic inflammation - raises FGF23 levels [19–21]. However, these studies employed the C-terminal assay for FGF23, which measures both intact, hormonally active FGF23, and the proteolytically cleaved inactive form produced in a regulated matter within osteocytes. Cell culture studies show that low iron status activates hypoxia-inducible factor-1 (HIF-1), which in turn promotes transcription of FGF23 [22,23]. However, HIF-1 activity likewise promotes synthesis of the furin protease which cleaves FGF23 [24]. The net result is that low iron status increases plasma levels of the cleaved form of FGF23, while having little impact on circulating levels of the intact hormone [25]. This presumably is why iron deficiency is not typically associated with hypophosphatemia.

Fortunately, the fact that calcitriol promotes FGF23 transcription does *not* imply that increased intakes or endogenous synthesis of vitamin D will boost FGF23 production. Except very transiently, or in special circumstances such as primary hyperparathyroidism or sarcoidosis, an increased intake of vitamin D does not increase systemic calcitriol levels, owing to rapid compensatory down-regulation of PTH secretion [26]. (Indeed, toxic levels of vitamin D ingestion do not produce toxicity by boosting calcitriol production, but by displacing bound calcitriol from the vitamin D-binding protein [27].)

One way to lower calcitriol levels is by increasing dietary calcium intake. It might therefore seem logical to conclude that an increased calcium intake could decrease FGF23 production, and thereby aid prevention/control of prostate cancer. In fact, experimental evidence suggests precisely the opposite: high-calcium diets are associated with increased bone production of FGF23 and increased plasma levels of this hormone [7] – whereas calcium/vitamin D deficiency in rats suppresses plasma FGF23 levels despite concurrent increases in calcitriol and PTH levels [28]. These findings suggest that high-normal levels of free calcium may act directly on osteocytes to promote FGF23 production; however, this author has not located any cell culture studies assessing this.

Correlative epidemiology

These considerations thus raise the possibility that high dietary intakes of bioavailable sources of both calcium and of phosphorus might increase prostate cancer risk, and/or encourage its spread by boosting systemic and paracrine production of FGF23. Indeed, prospective epidemiology has linked increased dietary intakes of both phosphorus and calcium to increased risk for prostate cancer, and, most notably, for aggressive prostate cancer. In a fully adjusted regression analysis (accounting for many pertinent covariates, including daily calorie intake) of data from the prospective Health Professionals' Follow-Up Study, men in the top quintile of phosphorus intake were over 50% more likely to develop high-grade prostate cancer as compared to those in the bottom quintile (RR = 1.56; CI 1.20–2.20; p = 0.0002) [29]. (No association was seen with low-grade cancer.) In the same data base, daily calcium intakes of 2000 mg daily or more, were associated, after appropriate multivariate adjustment, with significant and notable increases in risk for high-grade and lethal prostate cancer [29]. Relative to a calcium intake of 500–750 mg daily, men ingesting at least 2000 mg calcium daily from all sources experienced a relative risk for advanced-grade prostate cancer of 1.88 (CI 1.13, 3.12; p = 0.01); there is little clear trend for intakes below 2000. Another prospective study likewise found increased prostate cancer risk in men ingesting over 2000 mg calcium daily [30]. A recent meta-analysis of prospective studies evaluating the associated of dietary calcium with prostate cancer risk has concluded that increased intakes of total calcium, dairy calcium, and certain dairy products were indeed associated with increased prostate cancer risk [31]. Non-dairy and supplemental calcium per se did not show such as association, possibly owing to lesser absorption from these sources (oxalate complexes impede the bioavailability of calcium in green leafy vegetables [32–34], and some tablets do a poor job of providing soluble calcium); also, dairy products are also rich in bioavailable phosphorus, so the impact of high dairy consumption of on prostate cancer risk may represent a joint effect of calcium and phosphorus. Findings to date suggest that the threshold beyond which calcium intake represents a risk is close to 2000 mg daily, so only men who are taking multiple servings of dairy products daily may be putting themselves at increased risk; calcium supplementation has not been implicated in this regard [35].

In regard to iron status, despite that fact that iron status does not appear to notably modulate systemic levels of intact FGF23, it is curious that newly diagnosed prostate cancer patients tend to have lower body iron stores than matched controls, as judged by serum levels of transferrin receptor and ferritin [36,37]. It is unlikely that occult bleeding could account for this at an early stage of this cancer. One conceivable explanation could be that increased HIF-1 activity in prostate cancer cells, reflecting lower iron status, is increasing autocrine production of FGF23 in the can-