Medical Hypotheses 94 (2016) 89–92

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Hypothesis: Phytate is an important unrecognised nutrient and potential intravenous drug for preventing vascular calcification

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ARTICLE INFO

Article history:
Received 19 April 2016
Accepted 10 July 2016

Keywords:
Vascular calcification
Phytate
Hydroxyapatite
Haemodialysis
End stage renal disease
Calciphylaxis

ABSTRACT

Cardiovascular calcification (CVC) associated with conditions such as ageing, diabetes or renal impairment, results from the deposition of hydroxyapatite in the endothelium or media of blood vessels. Key medical management options are directed towards controlling plasma calcium and phosphate concentrations (e.g. parathormone inhibition, phosphate binders, dialysis), enhancing the effect of calcification inhibitors (e.g. fetuin-A, pyrophosphate, vitamin K, osteopontin, matrix Gla protein) and decreasing the effect of promoters of calcification (e.g. vitamin D, lipids, cytokines). Dietary phytate prevents the calcification of ageing in rats and epidemiological data suggest that phytate rich diets are associated with a lower incidence of CVC in the elderly. Intravenous phytate prevents aggressive CVC induced by vitamin D in rats. We propose that phytate should be added to the list of inhibitors of vascular calcification. We further suggest that adequate dietary phytate could prevent mild forms of calcification and that the low phytate content of diets for patients with renal disease can contribute to the increased risk of vascular calcification. It is also our contention that supra-physiological systemic phytate concentrations not achievable orally, might prevent aggressive vascular calcification. Appropriate epidemiological (to determine nutritional value) and clinical studies (evaluating safety and efficacy) are required to confirm, modify or reject our hypothesis.

Background

The influence of nutrition is widely recognised as crucial to understanding the pathophysiology, progression and prevention of disease This perception is evident from the impact of epidemiological data, such as from the Framingham study, on modern medical practice and a plethora of publications on the impact of dietary fat, carbohydrates and other life style factors on cardiovascular risk factors [1].

The current concept of the pathophysiology of cardiovascular calcification (CVC) is that an excess of calcium and/or phosphate results in CVC due to the formation of hydroxyapatite (HAP) crystals in the vascular endothelium and media [2–4]. There are several natural promoters of this process (e.g. vitamin D, lipids, inflammatory cytokines) and inhibitors (e.g. fetuin-A, pyrophosphate, vitamin K, osteopontin, matrix Gla protein). Current treatment options to prevent CVC are aimed at:

- reducing plasma calcium and phosphate (controlling the Ca × P product) [5];
- enhancing the effects of inhibitors or reducing the effects of promoters of CVC.

Although the pathophysiology of cardiovascular calcification is complex, the final common pathway in the process is the formation, irrespective of the main cause, of HAP crystals.

A few available published nonclinical studies, as well as a limited number of small epidemiological studies, have stimulated our interest in the impact of phytate on CVC. In a study in rats which lasted 76 weeks, the ageing-associated development of CVC was enhanced by dietary phytate deficiency and prevented by a phytate-rich diet [6]. When aggressive CVC is induced by vita-

Abbreviations: CAC score, coronary artery calcium score; CKD, chronic kidney disease; CVC, cardiovascular calcification; ESRD, end stage renal disease; HD, haemodialysis; IP6, myo-inositol hexaphosphate; MBD, mineral bone disorder.

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http://dx.doi.org/10.1016/j.mehy.2016.07.005
0306-9877/

min D administration in rats, intravenous phytate administration (producing supra-physiological phytate concentrations), reduced aortic and heart calcification by 60 and 70% respectively [7]. Urinary phytate appears to be a good indicator of dietary phytate intake [8]. Fernández-Palomeque et al. [9] studied 188 patients (mean age 68 years) who were referred to a cardiology centre for cardiac echocardiography and who had evidence of cardiac valve calcification. Patients with the presence of valvular calcification, showed lower urinary phytate concentrations, compared to patients with no valvular calcification. These findings suggested that adequate dietary phytate might protect against the CVC of ageing in humans as well as in rats. There is further support for our contention in a non-clinical study reported by Moe et al. [10] They developed a model of inducing slowly developing chronic kidney disease-mineral bone disorder (CKD-MBD) over a period of 38 weeks with protein-fed Cy/+ rats (a genetic strain that develops renal impairment due to polycystic kidneys) receiving a normal phosphorus intake. These animals develop typical CVC, hyperparathyroidism and bone demineralisation. The severity of CKD and its associated features was most profound when the source of dietary protein was casein based. When the protein source was grain-based, the CKD including calcification, was significantly attenuated. The authors attributed this to the poor bioavailability of phosphorous (mainly in the form of phytate) in grain-based protein. It should be pointed out that this paper describes an animal model for inducing CKD with similar features to CKD-MBD in humans and was not aimed at studying the effects of phytate. We accept that they describe a very useful animal model for studying CKD. We however propose that an additional or alternative explanation for the reduced severity of CKD in animals fed grain compared to animals fed casein, could be that the grain-fed animals were protected by the phytate content, whereas the animals fed casein, were phytate-deficient.

The degree and rate of progression of CVC are accepted predictors of cardiovascular risk. The CAC (coronary artery calcium) score derived from computerized tomography scanning, is a widely accepted tool for assessing vascular calcification. The relationship between CAC scores and mortality has been described in many settings including the general population [11], the elderly [12], diabetics [13] and patients with chronic kidney disease without [14] or on haemodialysis (HD) [15]. As the baseline CAC score and the rate of progression of CAC scores are the key determinants of cardiovascular events including mortality, we believe that CAC score determination should be a key parameter in early human studies of the effect of phytate on CVC.

It is interesting to note that although there have been no large scale epidemiological studies on the effect of dietary phytate on health, there are several large studies showing an inverse relationship between cardiovascular mortality and the intake of nuts [16]. Nuts, in common with other plant seeds, are a dietary source of phytate.

Presentation of the hypothesis

Phytate (myo-inositol hexaphosphate or IP6) is a polyphosphate and a normal dietary constituent found in seeds (e.g. whole grains, legumes, nuts and other seeds). Phytate is highly polar and therefore its absorption from the gastro-intestinal tract is limited. It prevents the formation of HAP crystals, the final common pathway in the pathophysiology of vascular calcification. In a paper on *in vitro* studies of the effects of polyphosphonates on hydroxyapatite crystals produced by solutions of calcium and phosphate ions, Francis [17] suggested that the chemisorption of polyphosphates on HAP might have a use in medical and dental conditions involving pathological calcium and phosphate metabolism.

Our hypothesis (Fig 1) is that dietary phytate deficiency is a key contributor to the CVC of ageing and that CVC can be attenuated by an adequate dietary intake of phytate. Furthermore we propose that patients with end stage renal disease (ESRD), particularly those on HD, have aggressive calcification due to a disturbed Ca $\times$ P product (whatever the aetiology), superimposed on the background calcification due to ageing. As phosphates, including phytate, are intentionally restricted in the diet of ESRD, we suggest that dietary deficiency of phytate contributes to the occurrence and progression of CVC. Furthermore, due to its high water solubility and its consequent dialysability, phytate deficiency could be accentuated by dialysis. We suggest that supra-physiological phytate plasma concentrations, higher than achievable by the oral route, can be obtained by intravenous infusion and may prevent aggressive CVC as seen in patients with ESRD. It is also possible that phytate could have a role in the treatment of calciphylaxis [18], a rare disease occurring predominantly in HD patients and associated with debilitating painful skin ulcers, severe vascular and soft tissue calcification and a high mortality.

Testing the hypothesis

Our contention that phytate has an important dietary role and has potential as an intravenous medication is an interesting hypothesis based on limited scientific information. There have been no large scale epidemiological studies on dietary phytate intake Testing the hypothesis however is possible, but presents many challenges because large, long term studies will be required. Potential studies include:

- Prospective epidemiological studies of the relationship between dietary phytate and the calcification of ageing (retrospective and prospective) and cardiovascular events and mortality.
- Controlled studies of the effect of long term dietary phytate supplementation on vascular calcification and cardiovascular events and mortality in an ageing population. Before embarking on such studies, further research is needed to clearly define an upper limit of intake to avoid an impact on the absorption of essential nutrients.
- Studies with supra-therapeutic phytate concentrations obtainable by intravenous infusion vs. placebo in conditions associated with aggressive calcification (e.g. ESRD, diabetes, calciphylaxis). Long term studies are only practical in patients on HD where the intravascular route is regularly available during dialysis sessions. Studies will be difficult, requiring large numbers of patients, long study duration and assessment of CVC-related events, including mortality, as an endpoint.
- Calciphylaxis might be a target for a study with smaller patient numbers and shorter study duration. As the condition is rare and associated with a high CVC-related mortality and morbidity, study logistics and design will be a challenge. If it can be shown in this population that reducing vascular calcification reduces mortality, calcification reduction could potentially be validated as an endpoint acceptable to regulatory authorities.

Implications of the hypothesis

- *Pathophysiology*: We suggest that current models of the pathophysiology of the development of CVC should be adapted to include phytate as a naturally occurring inhibitor of vascular calcification along with fetuin-A, pyrophosphate, vitamin K, osteopontin and matrix Gla protein.
- *Nutrition*: The medical community and the general population should be informed about the sources and the potential benefit of adequate dietary phytate. Furthermore dietary restriction of