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

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\begin{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.
\end{abstract}

\begin{backmatter}
\section*{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 lifestyle 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-
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 × 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

Presentation of the hypothesis

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phytate in patients with renal impairment and phytate loss during dialysis, may contribute to the development of CVC and might require advice on phytate intake by modifying diets. Recommending commercially available phytate preparations requires caution as excessive oral intake can cause dietary deficiencies due to chelation of important nutrients such as vitamin D and iron in the gastrointestinal tract. We could find no publications documenting malabsorption due to excessive phytate intake. It should also be noted that calcium phytate is designated as a GRAS (Generally Regarded As Safe) substance by the FDA.19

• Phytate as a medicine: The bioavailability of phytate by the oral route is poor and we propose that supra-physiological phytate concentrations, only achievable by parenteral administration, could beneficially influence mortality and morbidity in severe forms of CVC such as seen in ESRD. Life-long intravenous phytate administration during dialysis sessions is a plausible approach in patients on haemodialysis, because of the easy availability of intravascular access during sessions. An intravenous phytate formulation (SNF472) is currently in the early stages of development [7] for the prevention of vascular calcification in patients on haemodialysis due to end stage renal disease or calciphylaxis. It should be pointed out that intravenous phytate has no effect on gastro-intestinal absorption of vit D and iron. Furthermore serum iron and vit D exposure are carefully controlled in ESRD patients on HD.

It seems logical that the earlier a preventive therapy is started in a pathological process, the greater the chance of success. It is therefore our opinion that the development of alternative parenteral routes of administration might extend administration to risk populations without easy regular intravenous access.

Conclusions

Our hypothesis suggests that adequate dietary intake of phytate could prevent mortality and morbidity in milder forms of CVC, particularly associated with ageing. We furthermore suggest that dietary restriction of phytate in patients with renal impairment and phytate loss during dialysis, may contribute to the development of CVC. We therefore propose 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.

Supra-physiological phytate concentrations that can potentially influence mortality and morbidity in severe forms of CVC require parenteral administration. To prevent the progression of CVC, an intravenous phytate formulation (SNF472) is currently under development for administration during HD sessions. It is also our opinion that the development of alternative routes of parenteral administration might extend administration to risk populations not on HD and without easy regular intravenous access.

Competing interests

SNF472 an intravenous phytate formulation, is in early stage clinical development by Laboratoris Sanifit for the prevention of vascular calcification in end stage renal failure patients, as well as in patients with calciphylaxis.

All the authors are full time or part-time employees or consultants at Sanifit and receive salaries, consultancy fees and/or stock options for their contributions.

References


