Inhibition of tissue non-specific alkaline phosphatase, a novel therapy against arterial media calcification?†

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Abstract

Arterial media calcification refers to ectopic mineralization in the arterial wall and favors arterial stiffness and cardiovascular events. Patients with chronic kidney disease (CKD), diabetes, or osteoporosis are highly vulnerable to the development of arterial media calcifications. Tissue non-specific alkaline phosphatase (TNAP) is upregulated in calcified arteries and plays a key role in the degradation of the calcification inhibitor pyrophosphate into inorganic phosphate ions. A recent study published in The Journal of Pathology showed that an oral dosage of 10 or 30 mg/kg/day SBI-425, a selective TNAP inhibitor, inhibited the development of arterial media calcification in mice with CKD, without affecting bone mineralization. Their results indicated that SBI-425 is an effective and safe treatment for arterial media calcification. However, additional studies regarding the effect of TNAP-inhibitor SBI-425 on the progression and even the reversion of pre-existing pathological arterial media calcifications without affecting physiological bone mineralization are deserved. Furthermore, investigating the extent to which SBI-425 inhibits arterial calcification in a non-CKD context would be of particular interest to treat this comorbidity in diabetes and osteoporosis patients.

Keywords: arterial media calcification; alkaline phosphatase; pyrophosphate; chronic kidney disease; bone metabolism

Calcium phosphate crystals (i.e., hydroxyapatite) are released in the bone matrix to provide strength and hardness to the bone. However, a similar mineralization process also takes place in other tissues when certain molecular and cellular defense mechanisms fail. Elderly people and patients with chronic kidney disease (CKD) and/or diabetes are prone to develop calcification in the medial layer of the arteries, also called arterial media calcification, leading to increased arterial stiffness which in turn deteriorates peripheral blood circulation and favors cardiovascular events. Pyrophosphate (PPI) is a well-known calcification inhibitor through its binding to nascent hydroxyapatite crystals, whereby it inhibits further incorporation of inorganic phosphate into these crystals and thus prevents their growth. The bone and teeth co-express collagen I and tissue non-specific alkaline phosphatase (TNAP) in order to stimulate the mineralization process, since TNAP degrades the calcification inhibitor PPI into inorganic phosphate ions [1]. Under normal conditions, vascular smooth muscle cells (VSMCs), present in the medial layer of the vessel wall, do not express TNAP. However, in the presence of pro-calcifying factors such as uremic toxins, inflammation, high phosphate levels and so on VSMCs transdifferentiate into a bone-like cell phenotype going along with the upregulation of osteo/chondrogenic marker genes including TNAP. Moreover, the increased TNAP expression in calcified arteries of CKD patients may contribute to the observed reduced levels of plasma PPI, which negatively associate with arterial calcification in these patients [2].

In a recent issue of The Journal of Pathology, Tani et al reported that an oral dosage of the selective TNAP inhibitor SBI-425 (10 or 30 mg/kg/day during 6 weeks) was sufficient to inhibit the development of arterial media calcification in mice with CKD induced by a 0.2% adenine diet [3]. Because arterial media calcification resembles physiological bone mineralization, treatments that interfere with the calcification process in the vessel wall may also induce side-effects at the level of the bones. This is especially crucial for CKD patients as they already have disturbed mineral and bone metabolism, also called CKD-mineral and bone disorder (CKD-MBD). In their study, the authors provided strong evidence that SBI-425 is a safe and efficacious therapy for the prevention of arterial media calcification without...
affecting renal bone status in CKD mice, as evidenced by μCT imaging and evaluation of static and dynamic bone parameters by histomorphometric analysis of the femurs. The authors indeed observed no significant differences in bone mineral density, bone volume per tissue volume, trabecular thickness, osteoclast surface per bone surface, and mineral apposition rate between vehicle and SBI-425-treated CKD mice [3].

Other studies also showed that SBI-425 blocked arterial calcification in two mouse models overexpressing TNAP in either VSMCs or endothelial cells [4,5] without affecting bone metabolism. However, SBI-425 therapy has not yet been investigated in other species, that is, rats and large skeletally mature animals including dogs and rabbits, which are considered to be less resistant to effects on bone and have a bone structure/composition highly similar to that of humans [6]. A major limitation of using mice for evaluating effects on bone is the relative small size of the trabecular bone compartment, in which accurate quantitative histomorphometric evaluation is difficult. Moreover, this drawback hampers the measurement of important bone histomorphometric parameters related to bone formation/mineralization including mineralized area, osteoid width, osteoid and osteoblast perimeter, osteoid maturation time, and bone formation rate, which were not reported in the study of Tani et al [3]. For this reason, it would be interesting to evaluate the effects of SBI-425 in other species to provide an optimal clinical translation of its effects on both arterial media calcification and bone metabolism.
Aside from bone, the liver and kidneys are also two major sites of TNAP activity. The study of Tani et al [3] did not assess possible effects of SBI-425 on liver function, which would be of particular interest to analyze in further studies, as liver TNAP is responsible for lipopolysaccharide detoxification and is thus involved in inflammatory responses [7]. With regard to the kidney, the authors showed that a dose of 10 or 30 mg/kg SBI-425 did not aggravate chronic renal failure as indicated by the absence of significant differences in plasma urea, creatinine, and phosphate as well as for renal fibrosis between vehicle and SBI-425-treated CKD mice.

Furthermore, in the present study [3], mice developed only a mild to moderate chronic renal failure, as indicated by a 3.5-fold increase in plasma creatinine and phosphate values, comparable to those of CKD stage 3–4 patients. The widely used 0.75% adenine rat model shows a six-fold increase in serum creatinine levels, which is accompanied by severely disturbed bone turnover [8] and therefore enables investigations into whether SBI-425 treatment is sufficient to interfere with arterial media calcifications in a more advanced stage of CKD. Moreover, as most patients present in the clinic with a given degree of arterial calcification, it is imperative to study the TNAP inhibition on the progression, halting, or even reversion of already pre-existing arterial calcifications. On the other hand, testing the effect of the TNAP inhibitor SBI-425 in a non-CKD model for arterial media calcification, such as the warfarin rat model, would also be of interest, as vascular calcifications in the media also occur in non-CKD patient groups including the elderly and patients with diabetes and osteoporosis. This also offers the opportunity to investigate whether SBI-425 induces effects on the bone in a larger animal model and in a non-CKD context. To which extent co-administration of the TNAP-inhibitor SBI-425 in combination with its substrate PPi exerts a synergistic therapeutic effect on calcifications in the vessel wall without affecting bone metabolism is also worth considering. In this context, it should be mentioned that TNAP regulates only 50% of the PPi hydrolysis in aortic tissue, indicating that other sources must also play a role in PPi degradation. One study revealed that ectonucleotide pyrophosphatase/phosphodiesterase 3 (NPP3), expressed by VSMCs, also induces PPi hydrolysis [9]. An alternative therapeutic approach could thus consist of the prevention of total PPi hydrolysis in the arteries by not solely using a TNAP inhibitor but also targeting NPP3. However, a good balance between serum PPi and inorganic Pi is essential, as low levels of plasma PPi induce arterial calcification while high levels are linked to calcium pyrophosphate dehydrate deposition or the formation of insoluble calcium-PPi crystals in cartilage and joints (Figure 1) [10].

Taken together, the TNAP inhibitor SBI-425 seems to be a promising therapy against the development of arterial media calcification in a CKD setting. Further studies are required to investigate whether this treatment is also effective (1) in a non-CKD context, in particular in patients with diabetes and osteoporosis who are at high risk for the development of arterial media calcification; (2) to slow down the progression of already pre-existing arterial media calcifications; and (3) without inducing deleterious side-effects in other tissues.

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References