Etidronate halts systemic arterial calcification in pseudoxanthoma elasticum

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HIGHLIGHTS

- Pseudoxanthoma elasticum results in extensive arterial calcification.
- Etidronate halts systemic arterial calcification in pseudoxanthoma elasticum.
- Further studies must assess the efficacy of etidronate on clinical outcomes.

ARTICLE INFO

ABSTRACT

Background and aims: In pseudoxanthoma elasticum (PXE), low levels of inorganic pyrophosphate result in extensive arterial calcification. Recently, the treatment of ectopic mineralization in the PXE (TEMP) trial showed that one year of treatment with etidronate halts progression of femoral artery calcification in PXE patients. The aim of this study was to test the efficacy of etidronate on calcification in different vascular beds.
Methods: In this prespecified *post-hoc* analysis of the TEMP trial, arterial calcification mass was quantified in the carotid siphon, common carotid artery, thoracic and abdominal aorta, coronary arteries, iliac arteries, and the femoropopliteal and crural arteries using CT at baseline and after one year of etidronate treatment or placebo. In addition, a total arterial calcification score was calculated. The difference in calcification progression was compared between the etidronate and placebo group.
Results: 74 PXE patients were enrolled and randomized. Etidronate significantly halted progression of calcification in all vascular beds except for the coronary arteries. For the total arterial calcification score, the median absolute increase in mass score was −63.6 (−438.4–42.2) *vs.* 113.7 (9.4–377.1) ($p < 0.01$) and the median relative increase was −2.4% (−10.3–3.8) *vs.* 6.3% (0.2–15.8) ($p < 0.01$) in the etidronate and placebo arm, respectively.
Conclusions: Etidronate treatment halts systemic arterial calcification in PXE. Further research must assess the long term safety and efficacy of etidronate on clinical outcomes in PXE.

1. Introduction

Medial arterial calcification is a distinct type of vascular disease from the more generally known atherosclerosis [1]. Atherosclerosis, a disease of the intimal vascular wall, is associated with traditional cardiovascular risk factors like, hypercholesterolemia, hypertension, and smoking [2] and results in narrowing and obstruction of the arteries. Medial arterial calcification is a consequence of aging, but is accelerated in common diseases like diabetes mellitus and chronic kidney disease (CKD) [1]. In contrast to atherosclerosis, it results in circular calcifications in the medial layer of the arterial wall that cause arterial stiffening and systolic hypertension [1]. The subsequent increased pulse pressure is thought to induce damage especially in high-flow, low impedance organs such as the kidney and the brain [3]. These medial calcifications might therefore contribute to the high residual risk for recurrent vascular events in patients with vascular disease [4],

but also to critical limb ischemia and loss of function in organs such as the heart, kidney, and the brain [5].

Pseudoxanthoma elasticum (PXE, OMIM #264800) is an autosomal recessive disorder in which mutations in the *ABCC6* gene result in low levels of inorganic pyrophosphate (PPi) [6]. PPi is one of the strongest inhibitors of ectopic calcification and therefore PXE results in extensive calcification of the elastic fibers in the skin, the Bruch's membrane of the eyes, and the peripheral arteries [7]. The arterial phenotype involves medial arterial calcification of predominantly the intracranial arteries and the arteries of the legs, but other arteries, including the carotid arteries, aorta and iliac arteries are also affected by vascular calcifications [8,9]. PXE can therefore be used as a model disease to investigate the role of relatively isolated medial arterial calcification on vascular physiology and function and the effect of arterial stiffness on end organ damage [10].

The bisphosphonate etidronate is a molecular homologue of PPi and has the potential to inhibit progressive calcification in PXE and generalised arterial calcification of infancy (GACI, OMIM#208000) syndrome [11] and it is currently being tested in arterial calcification due to a deficiency in CD73 (ACDC, OMIM #211800, trials.gov: NCT01585402). Since etidronate predominantly binds to hydroxyapatite crystals, its potential to inhibit ectopic mineralization is larger than newer bisphosphonates like alendronate, which primarily inhibit osteoclasts [12]. Recently, we conducted the treatment of ectopic mineralization in PXE (TEMP) trial in which we showed that one year of etidronate treatment reduces progressive calcification in the femoral arteries in PXE when compared to placebo, without important safety issues [13]. This proof of principle study confirmed that etidronate influences the calcification process, but its effect on different vascular beds, that are less susceptible to medial arterial calcification, remains to be established. In this post-hoc analysis of the previously described TEMP trial, we therefore aimed to investigate the effect of etidronate on arterial calcification in different vascular beds on whole body computed tomography (CT) scans.

2. Patients and methods

2.1. Study design and participants

This study is a prespecified post-hoc analysis of the TEMP trial [13]. The TEMP trial was a single-center, randomized, placebo-controlled trial conducted at the University Medical Center Utrecht, Utrecht, the Netherlands to test the safety and efficacy of one year of etidronate treatment in PXE patients (Netherlands Trial Register NL4956). The methods of this study have been reported previously [13]. In short, all participants had a confirmed clinical diagnosis of PXE and evidence of arterial calcification in the arteries of the legs. PXE was diagnosed if two of the following three signs were present: skin involvement (pseudoxanthomas), eye involvement (peau d'orange, angioid streaks) and/or biallelic *ABCC6* mutations [7]. Patients were randomized in a 1:1 ratio to a cyclical regimen of 2 weeks 20 mg/kg etidronate or placebo every 12 weeks. Exclusion criteria were severe renal impairment, known abnormality of the oesophagus, known sensitivity to etidronate, bisphosphonate use in the past five years, osteomalacia, chronic diarrhoea, pregnancy, claustrophobia, hypocalcaemia (calcium < 2.20 mmol/L) and vitamin D deficiency (25-OH vitamin D < 35 nmol/L). Randomization with random permuted blocks for sex was performed using a random number generator at the pharmacy department. This study was approved by the institutional review board of the University Medical Center Utrecht (number 15/522). All participants gave written informed consent.

2.2. CT imaging and quantification

All patients underwent an unenhanced, low-dose, whole body CT scan (120 kVp, mAs dependent on body weight) at baseline and after 12

months on a Siemens Biograph 40, Siemens Healthcare, Erlangen, Germany. In all scans calcification mass was quantified with an in house developed software tool (iX Viewer). Calcifications were defined as hyperdense arterial wall lesions with a density above 130 Hounsfield (HU) units. Calcification mass scores were computed as the product of the volume of the lesion in ml and the mean attenuation in HU of the lesion [14]. We measured calcification mass in the carotid siphon, common carotid arteries (CCA), coronary arteries, thoracic aorta, abdominal aorta, the iliac arteries (common, internal and external), and the arteries of the legs (femoral and crural arteries). All measurements were performed blinded for patient characteristics and treatment. The femoral artery calcification mass has previously been published [13]. Due to the difficult anatomical localization of the carotid siphon, all scans were scored by two investigators (JB, AH) and calcification scores were averaged. The total arterial calcification score was calculated by summing the calcification mass in all vascular beds. In addition, 25 randomly selected scans were scored by two investigators (AH, PdJ) blinded for all characteristics and the intraclass correlation coefficient (ICC) was assessed (Supplemental Table 1).

2.3. Statistical analysis

The sample size calculation was based on the primary outcome of the TEMP trial, which was ^{18}F sodium fluoride PET target-to-background ratio (TBR) in the femoral artery [13]. Assuming a mean TBR of 1.96, a standard deviation of 0.58 [15] and anticipating 6 drop outs or lost to follow ups, 74 participants were required to detect 20% change in TBR with 80% power and a 2-sided alpha of 0.05. Descriptive data are presented as mean ± standard deviation (SD) for normally distributed continuous variables, median (interquartile range (IQR)) for non-normally distributed continuous variables or number (%) for categorical variables. The difference in absolute and relative change in calcification mass score between the treatment and placebo group was analysed with the Mann-Whitney *U* test. A *p* value < 0.05 was regarded statistically significant.

3. Results

3.1. Baseline characteristics

77 patients were screened between July 2015 and June 2016, and 74 eligible patients were enrolled and randomized between October 2015 and June 2016. One participant in the placebo group declined further participation after severe uveitis developed following a vascular endothelial growth factor (VEGF) injection. One participant in the etidronate group discontinued treatment because of a hypersensitivity skin reaction at month 6 but remained in the study. Baseline characteristics and calcification mass scores per vascular bed are shown in Table 1. In both groups, mean age was 57 years and 51% was male.

3.2. Change in calcification mass in different vascular beds

The ICC was excellent for all arteries except for the coronary arteries where it was moderate (Supplemental Table 1). Except for the coronary arteries, etidronate significantly halted calcification progression in all vascular beds (Table 2 and Fig. 1). For the total arterial calcification score, the median absolute increase in mass score was −63.6 (−438.4–42.2) *vs.* 113.7 mg (9.4–377.1) (*p* < 0.01) and the median relative increase was −2.4 (−10.3–3.8) *vs.* 6.3% (0.2–15.8) (*p* < 0.01) in the etidronate and placebo arm, respectively (Table 2 and Fig. 1).

4. Discussion

In this prespecified *post-hoc* analysis of the TEMP trial, we showed that one year of etidronate treatment halts progressive arterial

Table 1
Baseline characteristics of study population and baseline calcification mass in different vascular beds.

	Etidronate (n = 37)	Placebo (n = 37)
Age, years	57 ± 9	57 ± 8
Male, n	19 (51%)	19 (51%)
Diabetes mellitus, n	3 (8%)	1 (3%)
Systolic BP, mmHg	142 ± 20	138 ± 18
Diastolic BP, mmHg	81 ± 9	80 ± 11
Body mass index, kg/m^2	26.7 ± 4.6	25.6 ± 3.5
LDL cholesterol	3.0 ± 1.1	3.2 ± 1.1
Non-HDL cholesterol, mmol/L	3.6 ± 1.1	3.8 ± 1.2
Total cholesterol	5.2 ± 1.3	5.4 ± 1.3
Triglycerides	1.2 (0.9-1.7)	1.3(1.0-1.6)
Calcification mass score		
Carotid siphon	14.9 (3.5–61.1)	28.1 (5.2–88.6)
Common carotid artery	10.4 (0.0–122.4)	5.5 (0.0–58.0)
Coronary arteries	32.1 (0.0–228.8)	11.4 (0.0–63.4)
Thoracic aorta	61.8 (12.1–495.0)	35.9 (15.7–118.5)
Abdominal aorta	706.5 (42.3–2284.9)	331.9 (94.6–913.8)
Iliac arteries	402.4 (32.4–1874.7)	216.9 (19.2–540.8)
Arteries of the legs	1272.8 (352.1–2314.5)	1453.1 (590.6–2306.7)
Total arterial calcification	3023.3 (1295.6–7003.8)	2388.4 (1330.5–4251.2)

BP blood pressure. Values are mean ± SD, median (IQR) or n (%) as appropriate.

calcification systemically. This confirms the previous observations in the femoral artery, a vascular bed that is susceptible to the development of medial arterial calcification [16]. The effect of etidronate also occurs in arteries that are less commonly involved in medial arterial calcification such as the common carotid artery, the aorta, and the iliac arteries. A larger study with longer follow-up is needed to show the effect of etidronate treatment on clinical outcomes in PXE.

These systemic findings are in line with findings of other studies into etidronate for arterial calcification. In GACI syndrome, severe deficiency of plasma PPi results in extensive arterial calcification already at birth. Most patients die within the first six months of life and bisphosphonate use is associated with prolonged survival in these patients [17]. Several case reports into GACI show that arterial calcification in the common carotid artery, coronary arteries, aorta, pulmonary, renal, iliac and femoral arteries decreases and even resolves after etidronate treatment[11,18–23], although regression without etidronate has also been described [24–26]. PPi is one of the strongest calcification inhibitors in the human body. The consequences of disorders associated with low plasma PPi are convincingly shown in PXE, GACI and ACDC, but it might also be involved in vascular calcification in more prevalent diseases such as chronic kidney disease (CKD) and diabetes. In patients with CKD, low levels of PPi have been found which were shown to decrease even further after hemodialysis [27]. Several small clinical trials in patients with CKD have shown stabilization and regression of calcification in the aorta[28–30] and the coronary arteries

on ECG-gated CT scans after treatment with etidronate [31]. The high prevalence of medial calcification in diabetes mellitus[1,32,33] makes it likely that PPi is also involved in this disease, but this remains to be established.
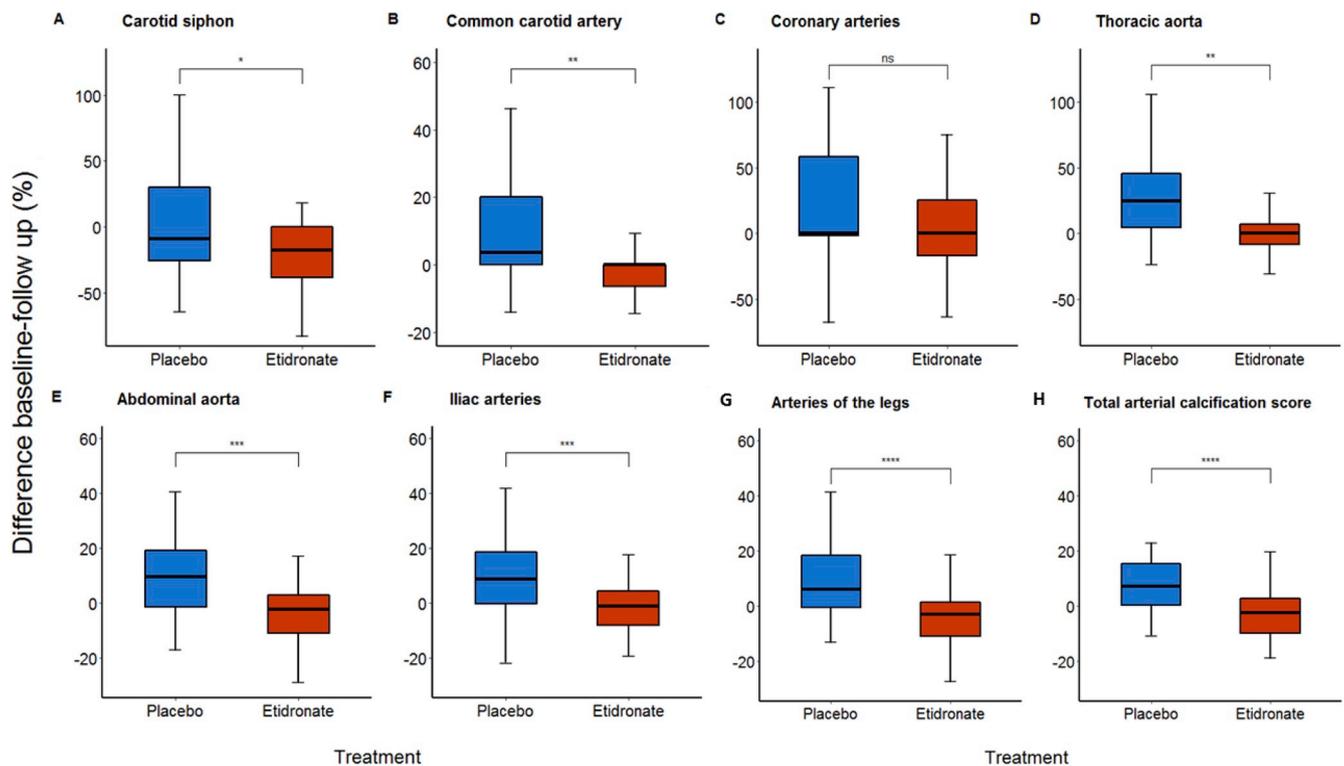
Arterial stiffness in the aorta and carotid arteries is independently associated with microvascular damage in the brain, risk of dementia and cognitive decline [34–37]. In normal physiology, the difference in impedance between the arterial branches from the heart to the brain allow for the transition from pulsatile to laminar flow [3]. Stiffening of the arteries reduces this impedance mismatch and allows for the pulsatile energy to penetrate into and damage the brain [37]. Arterial stiffness is the result of several processes including the remodelling and degradation of elastin and increased collagen deposition in the arterial wall [3]. Calcification increases arterial stiffness [38] and calcification of the aorta and the carotid and intracranial arteries are indeed associated with microvascular brain damage and dementia [39,40]. Halting the calcification process might therefore slow progression of microvascular brain damage and cognitive decline. Evidence in the literature suggests that the brain is also involved in PXE patients, as small studies and case reports suggest an association with infarctions and white matter lesions [41–44]. This brain damage might be caused by the progressive calcification [8] and stiffening [10] of the arteries. Etidronate treatment might therefore reduce progression of microvascular brain damage in PXE.

4.1. Strengths and limitations

Strengths of this study include the – for a rare disease – large number of PXE patients included in the trial, the availability of full body scans, and the low drop-out rate during follow-up. Limitations are the short follow-up time, which made it impossible to thoroughly investigate clinical outcome and long-term safety. These aspects, including generalizability beyond PXE, would require further studies. In contrast to a previous study performed in patients with CKD, we did not find an effect of etidronate on the coronary arteries [31]. We investigated these arteries with non-triggered scans. Although the calcification mass could be measured with acceptable accuracy, it could be considered to use triggered scans or more advanced motion and partial volume correction [45,46] in the future to further improve the reproducibility of the total arterial calcification score and more reliably investigate the effect of etidronate on coronary artery calcification. Finally, in our experience it was difficult to quantify siphon calcifications on the CT scans that we used and it may be beneficial to increase spatial resolution and/or reduce noise around the skull base to improve this measurement.

4.2. Conclusions

Etidronate treatment halts progressive systemic calcification in PXE, also in arteries that are not typically affected by medial arterial calcification. Therefore, clinical benefits of etidronate in PXE may be more

Table 2
Change in calcification after one-year etidronate treatment or placebo in different vascular beds in PXE.

	Absolute change in calcification mass score			Relative change in calcification mass (%)		
	Etidronate (n = 37)	Placebo (n = 36)	p	Etidronate (n = 37)	Placebo (n = 36)	p
Carotid siphon	−3.8 (−14.3–0.0)	−1.3 (−9.1–5.4)	0.14	−17.5 (−39.0–0.0)	−9.1 (−26.6–33.0)	0.05
Common carotid artery	0.0 (−5.2–0.1)	0.4 (0.0–8.3)	0.01	0.0 (−7.1–0.2)	3.7 (0.0–23.9)	< 0.01
Coronary arteries	0.0 (−18.7–6.1)	0.0 (−0.7–17.4)	0.35	0.0 (−17.4–26.1)	0.0 (−2.0–66.4)	0.26
Thoracic aorta	0.0 (−8.1–5.9)	14.8 (1.7–32.6)	< 0.01	0.0 (−8.5–16.8)	24.5 (4.0–46.0)	< 0.01
Abdominal aorta	−2.0 (−126.5–6.8)	18.0 (−5.7–59.6)	< 0.01	−2.2 (−11.2–3.8)	9.6 (−1.6–19.8)	< 0.01
Iliac arteries	−3.2 (−142.5–7.8)	19.3 (−0.9–39.7)	< 0.01	−1.1 (−8.7–5.1)	8.7 (−0.6–19.8)	< 0.01
Arteries of the legs	−36.3 (−83.6–24.3)	64.3 (−6.6–216.6)	< 0.01	−3.0 (−11.2–3.1)	6.2 (−0.6–18.7)	< 0.01
Total arterial calcification score	−63.6 (−438.4–42.2)	113.7 (9.4–377.1)	< 0.01	−2.4 (−10.3–3.8)	6.3 (0.2–15.8)	< 0.01

Data is presented as median (interquartile range). Data were analysed with the Mann-Whitney U test, p < 0.05 was regarded as statistically significant.

Fig. 1. Effect of etidronate on arterial calcification in different vascular beds.

Data is presented as the percentage difference in calcification mass after one year etidronate treatment (red box) or placebo (blue box) in the carotid siphon (A), common carotid artery (B), the coronary arteries (C) the thoracic aorta (D), the abdominal aorta (E), the iliac arteries (F), the arteries of the legs (G) and the total arterial calcification score (H). Calcification mass decreased by 9.1% (−26.6-33.0) *vs.* 17.5% (−39.0–0.0), $p = 0.05$ in the carotid siphon, increased 3.7% (0.0–23.9) *vs.* 0.0% (−7.1–0.2), $p < 0.01$ in the CCA, 0.0% (−2.0-66.4) *vs.* 0.0% (−17.4–26.1), $p = 0.26$ in the coronary arteries, 24.5% (4.0–46.0) *vs.* 0.0% (−8.5-16.8), $p < 0.01$ in the thoracic aorta, 9.6 (−1.6-19.8) *vs.* −2.2 (−11.2–3.8), $p < 0.01$ in the abdominal aorta, 8.7 (−0.6-19.8) *vs.* −1.1 (−8.7–5.1), $p < 0.01$ in the iliac arteries, 6.2% (−0.6-18.7) *vs.* −3.0% (−11.2–3.1), $p < 0.01$ in the arteries of the legs and 6.3% (0.2–15.8) *vs.* −2.4 (−10.3–3.8), $p < 0.01$ in the total arterial calcification score in the placebo and etidronate group respectively. Data was analysed with the Mann-Whitney *U* test, a $p < 0.05$ was regarded statistically significant, ns = not significant, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

systemic and not only involve the legs. Further research is needed to assess the long-term safety and the efficacy of etidronate on clinical outcomes and its generalizability.

Clinical trial registration

https://www.trialregister.nl/trial/4956, Netherlands Trial Register NL4956.

Author contributions

All authors have made substantial contributions to 1) the conception and design of the study, or acquisition of data, or analysis and interpretation of the data, 2) drafting or critically revising the article for intellectual content, 3) final approval of the manuscript.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.10.004.

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