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ABCC6 deficiency and bone loss: A double benefit of etidronate for patient presenting with pseudoxanthoma elasticum?

ABCC6 transporter deficiency causes pseudoxanthoma elasticum (PXE), a rare disease associated with progressive calcification in the eyes, skin and arteries. Ectopic mineralization in PXE results from altered hepatic cellular ATP export.¹ Extracellular ATP serves as a substrate for ENPP1 ectoenzyme to produce pyrophosphate (PPi), a physiological calcification inhibitor. Deficiency in ENPP1 enzyme leads to general arterial calcification of infancy (GACI) another rare genetic disease presenting phenotypic overlapping with PXE.² These phenotypes advocate for the central role of PPi and the imbalance of its ratio with the procalcifying inorganic phosphate (Pi) to PPi ratio in the prevention of soft tissue mineralization. The importance of Pi to PPi ratio maintenance in bone homeostasis is however not known.

Investigating for potential intervertebral disc calcification in *Abcc6*^{-/-} murine model, Boneski et al., recently evidenced a progressive vertebral osteopenia in this animal model. This phenotype is essentially characterized by trabecular bone loss and likely linked to an increased osteoclastic activity.³ Our group, using a similar CT-scan approach⁴ in 2-year-old *Abcc6*^{-/-} mice,⁵ evidenced a similar bone loss of the tibiae characterized by decreased trabecular bone percentage, trabecular number and increased inter trabecular spacing (see Figure 1). This phenotype was not observed in 6-month-old animals. These results, obtained by two independent laboratories with different *Abcc6*^{-/-} mouse strains show clearly that *Abcc6* transporter deficiency results in trabecular bone alteration with ageing. Importantly, they suggest that in concert with other pathways such as RANK/RANK-L, OPG and Wnt, the Pi/PPi imbalance could play a role in the bone/vascular axis in PXE and beyond. Moreover, in virtue of the fair fidelity of *Abcc6*^{-/-} model phenotype relative to human pathophysiology, these results also suggest that human PXE might impact bone homeostasis with ageing and result in bone fragility. In a pilot study, we did not observe obvious bone loss in human PXE patients.⁶

This apparent discrepancy may be linked to the relative youth of the human population studied (47-year-old) in regard to 2-year-old mice, which are senescent animals (\approx 80-year-old). Moreover, this osteopenic phenotype might be limited to specific morphologic parameters (i.e. trabecular bone) or subject to gene modifiers and restricted to certain subset of patients. In agreement with this hypothesis, a subset of adult GACI patients (16.7%), with mutations in *ABCC6* gene suffered from hypophosphatemic rickets.⁷ Hence, the real impact of PXE on bone fragility and potential fracture propensity still remains to be established, in particular in elderly and postmenopausal patients. Of note, those patients are remarkably absent of PXE patient series in the literature. This is also our clinical experience that aged PXE patients often disappear from routine follow-up and if they experience clinical events late in life remains unknown.

In this context, although clear overviews of long-term adverse events (e.g. osteomalacia, osteonecrosis) and of risk/benefit ratio are mandatory, treatment with first-generation bisphosphonate such as etidronate could benefit patients with PXE. Indeed, this analogue of PPi was shown to display efficacy in preventing ectopic calcification in murine models⁸ through inhibition of hydroxyapatite crystals growth and is considered to treat human patients affected by PXE with encouraging preliminary results.⁹ Etidronate may then display the double benefit of both counteracting ectopic mineralization and preventing bone loss in the long term through anti-osteoclastic effect. These new data provided by Boneski and ours should encourage clinicians to further investigate the role of *ABCC6* and PPi on the bone structure throughout the natural evolution of PXE and in particular in the context of hormones deprivation. Before innovative therapies, such as TNAP inhibitors and ENPP1 replacement enzyme therapy emerge,¹⁰ first-generation bisphosphonates are the only drugs to date to counteract ectopic mineralization in PXE patients with the potential advantage of preventing bone loss.

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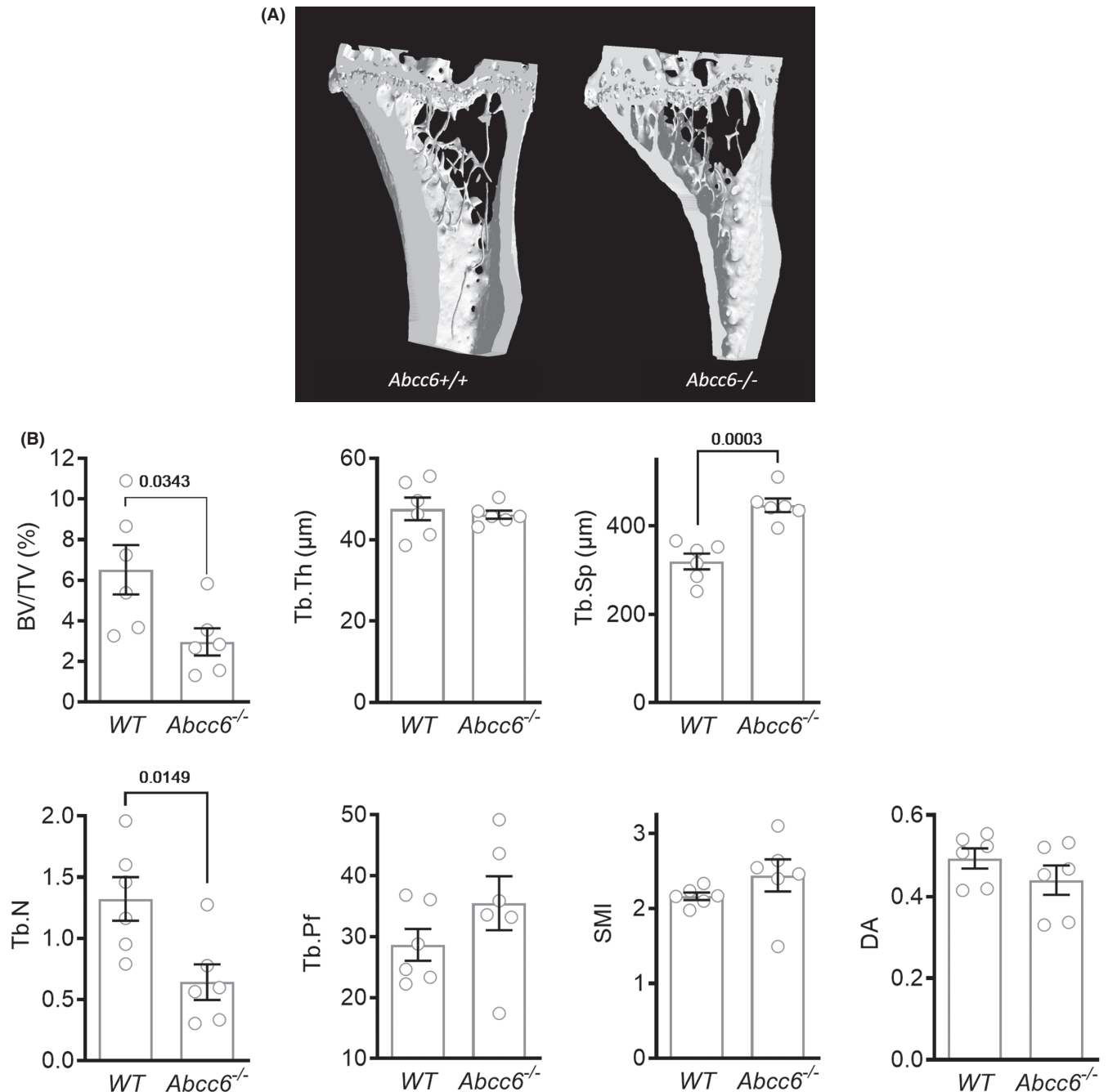


FIGURE 1 Altered trabecular bone volume in 2-year-old *Abcc6*^{-/-} mice. (A) Representative CT-scan image of wild type and *Abcc6*^{-/-} tibiae. (B) Morphometric analysis (BV/TV, Trabecular Bone Volume; DA, degree of anisotropy; SMI, structure model index; Tb.N Trabecular number; Tb.Pf trabecular bone pattern factor; Tb.Sp Trabecular separation; Tb.Th Trabecular thickness). Data represent the mean \pm SEM of 6 independent acquisitions. Results of unpaired t-test are specified when reaching significance ($p < 0.05$)

AUTHOR CONTRIBUTIONS

GK performed the research and wrote the paper; DC performed the research, analysed the data and edited the manuscript; GL edited the manuscript; LM edited the manuscript and designed the research study.

KEYWORDS

ABCC6, ageing, bone loss, PXE, pyrophosphate

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CONFLICT OF INTEREST

None to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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