Increased ossicle volume and reduced fractures in osteogenesis imperfecta mice treated with bisphosphonates

Maialen Ugarteburu, Annalisa De Paolis, Anxhela Docaj, Michael Doube, Christoph Rau,
Luis Cardoso, Claus-Peter Richter and Alessandra Carriero
The City College of New York, City University of Hong Kong, Diamond Light Source, Northwestern University

Introduction: Hearing loss is a common clinical hallmark of osteogenesis imperfecta (OI), also called brittle bone disease. Progressive hearing loss affects about 70% of the OI population, and it can be sensorineural, conductive, or mixed. There is no cure for OI and treatments for their hearing loss are those used for the general population with low success rates in OI [1]. To date, the mechanisms of hearing loss in OI are unknown. Similarly, unknown is the effect of bisphosphonates, a group of antiresorptive drugs and golden standard treatment for children with OI, on their hearing function. To date, only two studies have examined the effect of bisphosphonates on OI patients: one reported no effects of bisphosphonates on hearing function [2], the other was observational and suggested a possible implication of bisphosphonates in the reduction of hearing loss [3]. We recently reported altered morphology and intracortical porosity in ossicle and otic capsule of the homozygote *oim* mouse model of OI suffering from hearing loss [4]. Specifically, we found an increased otic capsule cortical thickness, with higher intracortical porosity with more and highly branched canals in the *oim/oim* mice [4]. In the middle ear we found smaller ossicles volume, with a smaller malleus, and smaller footplate's height in the *oim/oim* mice [5]. In this study, we examine the morphometry of the middle ear in the *oim/oim* mice treated with bisphosphonates.

Methods: The middle ears of 14-week-old control (CTR) and bisphosphonates treated (BP) *oim/oim* and wild-type (WT) mice (N=5/group) were imaged using synchrotron microtomography at a resolution of 1.6 µm. We determined the volume of the malleus, incus, and stapes, and the total volume of the ossicles. We assessed the stapes total height, the height of the stapes footplate, and the stapes crura and head height (Fig. 1). Statistical analysis was conducted to assess differences between the groups. The presence of fractures in the ossicles was examined.

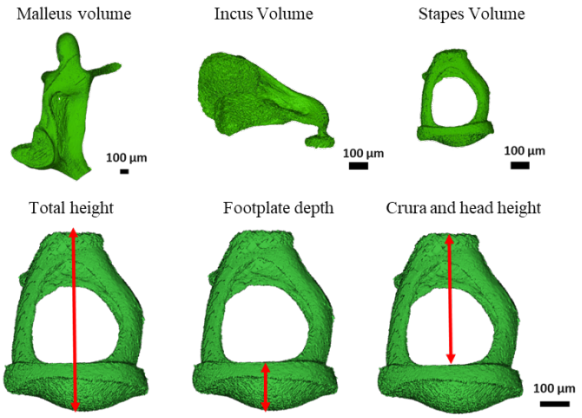

Figure 1. Volumetric and morphometric parameters quantified in the ossicles.

Results: The total volume of the ossicles was significantly smaller in the CTR- and BP-*oim/oim* groups compared to their respective WT groups, with a smaller malleus (Table 1). The stapes footplate height was smaller in the *oim/oim* mice. The total volume of the ossicles was smaller in the BP-WT mice compared to the CTR-WT mice but was bigger in the BP-*oim/oim* compared to the CTR-*oim/oim*, with a bigger stapes volume. Only three CTR-*oim/oim* incudes were fractured at the facet for the malleus (Fig. 2).

	Total vol. (mm^3)	Malleus vol. (mm^3)	Footplate height (mm)	Stapes vol. (mm)
CTR-WT	0.183 ± 0.006	0.125 ± 0.004	0.148 ± 0.005	0.00973 ± 0.0009
CTR-*oim/oim*	0.168 ± 0.013*	0.112 ± 0.009*	0.134 ± 0.008*	0.00914 ± 0.0008
BP-WT	0.180 ± 0.005	0.121 ± 0.005	0.150 ± 0.005	0.00995 ± 0.0007
BP-*oim/oim*	0.169 ± 0.004$^{\$\&}$	0.115 ± 0.003$^{\$}$	0.141 ± 0.005$^{\$}$	0.00991 ± 0.0003$^{\&}$

Table 1. Ossicles volume in WT and *oim/oim* control (CTR) and bisphosphonates-treated (BP). Statistical significant difference ($p < 0.05$) are reported with * between the CTR groups, with $ between the BP groups, and with & between the CTR and BP within the same mouse strain.

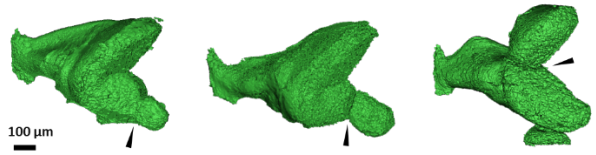

Figure 2. Fracture sites (arrow) in CTR-*oim/oim* incudes.

Conclusions: Our results report for the first time on the volumetric morphometric parameters of the middle ears of the BP-treated *oim/oim* mice model of OI. The differences encountered with BP treatment in the *oim/oim* volumetric ossicles suggest that bisphosphonates may be effective in reducing the number of fracture and partially restoring the bone morphology in the *oim/oim* ossicles. Our future research will investigate morphometrical parameters describing the shape of the incus, and malleus, and the intracortical canal porosity for each ossicle. Possible dislocations of the ossicular chain should also be assessed. Finally, since people with OI are treated with bisphosphonates at already young ages, the effects of bisphosphonates on the mechanics of the middle ear should further be investigated.

References:

1. Ugarteburu, M., et al. ARO. 2021
2. Ting, T.H., et al. Clin. Otol. 2012. 37:223-244
3. Brodd, I., et al., Klinic Och Vetenskap, 2011. 108(39)
4. De Paolis A. et al. J Struct Biol. 2021;213(2):107708
5. Ugarteburu, M., et al. ARO. 2022

Acknowledgements: This work was supported by the National Science Foundation (1829310) and Diamond Light Source.