

Reduced middle ear bone fractures in the *oim* mice treated with alendronate

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Progressive hearing loss is a common clinical hallmark of people with osteogenesis imperfecta (OI, or brittle bone disease), a genetic disease caused mainly by mutations in collagen type I. There is no cure for OI, and treatments for its hearing loss rely on conventional treatments for the general population, with low success rates in OI. To date, the pathological hearing mechanisms in OI remain poorly elucidated. Similarly, little is known about the effect of bisphosphonates treatment - the golden standard treatment for children with OI - on their auditory system. This study examines the morphometric-volumetric parameters of the middle ear of the *oim/oim* mouse model of OI treated with bisphosphonates.

The middle ears of 14-week-old control (CTR) and bisphosphonates-treated (BP) *oim/oim* and wild-type (WT) mice (N=6/group) were imaged using synchrotron microtomography at 1.6 μm resolution. We determined the volume of the malleus, incus, and stapes, and the total volume of the ossicles. We assessed the interconnected canals volume in the malleus, and morphometrical parameters in the stapes: total height, footplate height, and crura and head height. A statistical analysis was conducted in all the parameters to identify significant differences between groups. The presence of fractures in the ossicles was quantified.

The total volume of the ossicles was significantly ($p < 0.05$) smaller in the CTR- and BP-*oim/oim* groups compared to their respective WT groups, with the *oim/oim* group having a smaller malleus (Table 1). The stapes footplate height was significantly smaller in the CTR-*oim/oim* group compared to the CTR-WT group, and it was comparable between the BP groups. Compared to the BP-WT malleus, the BP-*oim/oim* incus was smaller, and the malleus had a higher volume density of interconnected canals. There were no significant differences between the BP and CTR groups in the volumetric-morphometric parameters. However, half of the CTR-*oim/oim* incudes had localized fractures, whereas none of the BP-*oim/oim* incudes presented any fractures.

Results from the volumetric-morphometric analysis of the *oim/oim* ossicles suggest a state of compromised middle ear that might affect hearing function in OI. Bisphosphonates treatment had no effect on the volumetric-morphometric parameters. However, the absence of fractures in the BP-groups suggests an implication of bisphosphonates on reducing incus fractures possibly due to changes in intracortical architecture and/or in composition.

	Total vol. (mm ³)	Malleus vol. (mm ³)	Incus vol. (mm ³)	Footplate height (mm)	Malleus C. V. (%)
CTR-WT	0.180 $\pm$ 0.005	0.123 $\pm$ 0.003	0.047 $\pm$ 0.002	0.148 $\pm$ 0.004	2.089 $\pm$ 0.265
CTR-<i>oim/oim</i>	0.164 $\pm$ 0.011*	0.110 $\pm$ 0.008*	0.045 $\pm$ 0.003	0.136 $\pm$ 0.008*	2.020 $\pm$ 0.155
BP-WT	0.180 $\pm$ 0.005	0.121 $\pm$ 0.005	0.049 $\pm$ 0.001	0.148 $\pm$ 0.007	1.963 $\pm$ 0.220
BP-<i>oim/oim</i>	0.166 $\pm$ 0.009\$	0.110 $\pm$ 0.005\$	0.046 $\pm$ 0.003\$	0.139 $\pm$ 0.007	2.403 $\pm$ 0.358\$

Table 1. Ossicles' parameters in control (CTR) and bisphosphonates-treated (BP) WT and *oim/oim*. Statistically significant difference ($p < 0.05$) are reported with * between the CTR groups, and with \$ between the BP groups.