

Should osteogenesis imperfecta be labeled as a low bone mass condition?

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INTRODUCTION: Osteogenesis imperfecta (OI) is a type I collagenopathy resulting in disordered connective tissue and bone fragility. Traditionally, OI has been considered a low bone mass disease. Robustness (total area/bone length) is a trait that describes the relationship between transverse expansion and longitudinal growth in long bones. Previous research examining 330 longitudinal pediatric hand radiographs has determined that bone growth in the average population falls over a wide range of robustness, from slender to robust (Figure 1). This study aims to establish the structural mechanism of low bone mass in OI and evaluate differences by sex, OI type, or bisphosphonate treatment.

METHODS: This IRB-approved retrospective study included 150 deidentified AP hand/wrist radiographs from 84 adults with OI (22M, 62F), 77 radiographs from 36 children aged 8-18 years old with OI (15M, 21F), and 52 radiographs from 28 children aged 0-8 years old with OI (11M, 17F). Radiographs were identified from patients at HSS and participants in the *Brittle Bone Disorders Consortium* (U54 AR068069). Second metacarpal length and midshaft width, cortical thickness, robustness (total area/length = $\frac{\pi(\frac{W}{2})^2}{L}$), and relative cortical area (RCA, cortical area/total area) were measured. Bisphosphonate treatment ≤ 2 years of the radiograph was noted. OI measurements were compared to those of age-matched controls using 63 radiographs from 63 adults (27M, 36F), 346 radiographs from 58 8-18-year-olds (29M, 29F), and 292 radiographs from 57 0-8-year-olds (33M, 24F). Groups were compared using non-parametric Kruskal-Wallis tests ($p < 0.05$).

RESULTS: The average age of the OI adult population was 42.7 ± 15.4 (18.12-87.69 years) and control population was 65.1 ± 20.17 (18-97 years). The average age of the OI 8-18-year-old population was 12.3 ± 2.55 (8.11 – 17.99 years) and control population was 12.4 ± 3.17 (8-18 years), and the average age of the OI 0-8-year-old population was 5.01 ± 2.13 (1.22 – 7.88 years) and control population was 3.77 ± 3.87 (0.25-7.99 years).

Overall, adult OI bones showed decreased robustness ($p < 0.001$) and increased RCA ($p < 0.001$) compared to controls. In the pediatric population, the bones of children aged 8-18 with OI demonstrated no difference in robustness but increased RCA ($p < 0.001$) compared to controls. Bones of female children aged 0-8 with OI displayed no difference in robustness and decreased RCA ($p < 0.001$), while bones of male children aged 0-8 with OI displayed decreased robustness ($p < 0.001$) and no difference in RCA compared to controls. Male adults and children 8-18 years old with OI displayed higher robusticity than age-matched females with OI ($p < 0.001$). However, there was no difference in robustness between males and females in children 0-8 years old with OI. Just around a quarter of the total OI cohort was treated with bisphosphonates (60/232, 25.7%). Treated individuals had significantly lower RCA ($p < 0.001$) than untreated individuals, with no significant difference in robustness. When comparing the effect of bisphosphonate treatment by OI type, individuals with type 4 had both lower RCA ($p < 0.001$) and lower robustness ($p < 0.05$) when treated; treated individuals with type 3 had lower RCA ($p < 0.001$), and people with type 1 displayed no treatment effect (Figure 2).

DISCUSSION: Compared to controls, adults with OI had decreased robustness indicating slender and structurally weaker bones. However, RCA was increased, which is the expected bone mass accrual for slender bones. This suggests that OI should not be considered to be a low bone mass condition, but rather the bones of individuals with OI tend to fracture due to other structural and material properties. Interestingly, we observed sexual dimorphism in the bone robusticity for the two older age cohorts, but not in children aged 0-8 years old, suggesting that the differences in robustness between males and females are likely due to the biological processes which occur during puberty. Furthermore, the significantly lower bone mass (i.e. decreased RCA) observed in individuals with OI after bisphosphonate treatment may explain why patients with OI do not respond as well to bisphosphonate treatment.

CLINICAL RELEVANCE: Our data is inconsistent with classifying OI as a low bone mass condition, which could have important clinical implications in treatment choices. This study provides greater insight into the patterns of bone morphology in OI by age and by sex, as well as the effect of potential treatments on bone morphology in OI, which may also extend to other osteopenic/osteoporotic populations.

Figure 1. Hand Radiographs of Slender vs. Robust bone (Control population)

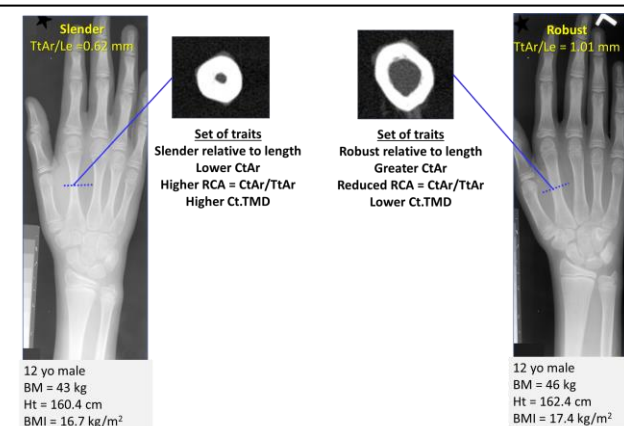


Figure 2. Comparing Average RCA and Robustness Between Treatment Groups and Types of OI

