**RESEARCH TOPIC CLI21**

# Diving into the Gut-Bone Axis: Microbiota-Bisphosphonate Interplay in Human Osteporosis and How It Is Affected By Chronic Intestinal Inflammation

**Research area**
Medical Area

**Clinical Unit name**
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**Abstract**
Background: Osteoporosis and fragility fractures represent a major public health burden, driven by several not fully clarified mechanisms (1). Increasing evidence suggests that the gut microbiota could play a key role in bone metabolism, through the production of bioactive metabolites, modulation of immune pathways, and regulation of intestinal barrier function (2-4). However, the functional relationship between gut microbiota and bone health in humans is still poorly characterized, and its clinical implications for osteoporosis treatment are largely unexplored. Current approach in osteoporosis management mainly relies on oral bisphosphonates, but their response is highly variable. Given that bisphosphonates are minimally absorbed and could reside in the gut lumen for extended period, their interaction with the intestinal microbiota, may represent a plausible explanation to this variability of response (5-7). In this scenario, Inflammatory Bowel Disease (IBD) may offer a unique human model to better evaluate microbiota-bone interactions, given their inherent enhanced gut dysbiosis, increased intestinal permeability, and a relevant higher risk of osteoporosis (8).
Aim: The main aim of this project is to investigate the role of gut microbiota in bone metabolism, and therapeutic response to oral bisphosphonates, addressing the unmet need for more precise and biologically targeted management. This project will address the following research questions: (i) how gut microbiota composition, functional pathways, and metabolite profiles change during bisphosphonate therapy; (ii) whether microbiota-driven pathways and mechanisms influence bisphosphonate transformation and intestinal absorption; and (iii) whether these features are associated with variability in treatment response. The ultimate aim is to identify integrated clinical, biochemical and microbiota-based predictors of response and potential microbial targets for future therapeutic intervention.
Methodology: To address these questions, a 3-year longitudinal clinical–translational study will be conducted, enrolling 100 patients with IBD and 100 non-IBD patients with newly diagnosed osteoporosis, initiating bisphosphonate therapy, alongside a historical cohort of 50

IBD patients without osteoporosis. Participants will undergo several clinical, instrumental (DEXA) and biological assessment (including microbiota profiling and metabolomic, intestinal permeability and bone turnover markers). Longitudinal data will be analyzed using mixed-effects models. In parallel, mechanistic studies will be performed using anaerobic colonic bioreactor systems seeded with patient-derived microbiota to evaluate microbial effects on bisphosphonate transformation, together with epithelial models to evaluate how intestinal permeability influences drug translocation. Finally, integrative and interpretable machine learning models will be used to predict signatures of bisphosphonates response and side-effect risk, that may be potentially modifiable by microbial targeted interventions.
Conclusion: In conclusion, this project will be the first human-focused longitudinal characterization of the functional relationship between gut microbiota and bisphosphonate therapeutic response, using IBD as a model of gut dysbiosis to generate insights applicable to osteoporosis management in the broader population.

**Scientific references**


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**Type of contract**

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