Probiotics and Microbiota: Can They Modulate Fracture Healing?

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Purpose: Fractures remain a huge burden and their management adversely affects individuals' function and productivity during the lengthy healing period. Gut microbiota exert a systemic influence on diverse aspects of host physiology, including bone. The objectives of this study were to evaluate the administration with oral probiotics prior to a fracture (prevention) and after a fracture (treatment) in a preclinical mouse model. The primary outcome was to determine the regulation of cytokines and biomarkers essential for bone healing in osteoblasts and the impact on the biomechanical properties of the healed callus.

Methods: Right femur open osteotomy and intramedullary pinning were performed on C57BL/6 mice. The first cohort of mice received either control PBS (phosphate buffered saline) or probiotic VSL#3 via oral gavage for 5 weeks before fracture. Similarly, the second cohort of mice was treated only after fracture for 4 weeks. Fracture calluses were harvested, and RT-qPCR (quantitative reverse transcription polymerase chain reaction) analysis was performed to quantify messenger RNA expression of osteogenic-related inflammatory markers. Both fractured and contralateral intact femurs were evaluated 4 weeks post-fracture with stereologic analysis (μCT) and biomechanical (torsion) testing.

Results: The prevention cohort with a 5-week administration of probiotic before fracture showed a significant increase ($P<0.05$) in gene expression on day 3 of cytokines transforming growth factor (TGF)- β, interleukin (IL)-6, and IL-17F compared to untreated controls. This corresponded to an increase on day 7 of Col1 and Runx2. At day 28, stereologic μCT analysis of the harvested fractured callus confirmed significantly higher bone mineral density, tissue mineral density, and bone volume fraction ($P<0.05$) for probiotic-treated compared to untreated controls. Biomechanical testing also showed significantly higher maximum yield torque, strain energy and torsional stiffness ($P<0.05$). The treatment cohort with administration of probiotic after fracture for 4 weeks demonstrated no changes in cytokine or bone marker gene expression on day 3 or 7. However, significant increases ($P<0.05$) were seen in twist angle and strain energy in the probiotic treatment group compared to untreated controls, with a corresponding significant reduction in torsional stiffness ($P<0.05$). No differences were seen in the stereological parameters in the treatment cohort.

Conclusion: Our results suggest that oral probiotic administration had the greatest effect on modulating fracture healing when given prior to fracture. However, even when administered post-fracture, it sufficiently altered the gut flora microenvironment to improve the bone healing biomechanical properties. The use of probiotics may provide a cost-effective and low-risk adjunctive therapy to improve bone fracture healing.