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The Gut–Musculoskeletal Axis: Reframing Orthopaedic Disease Through the Microbiome Lens

Bibek Banskota

Editor-in-Chief

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Introduction

Orthopaedic practice has traditionally focused on mechanical injury, degeneration, and localized inflammatory processes. Emerging evidence suggests that musculoskeletal health may be significantly influenced by systemic biological networks. Among these, the gut microbiome has gained attention as a key regulator of immune, metabolic, and endocrine pathways influencing bone and joint biology.[1,2] The human gut harbors trillions of microorganisms that function as a metabolically active organ. Once considered peripheral to musculoskeletal science, the microbiome is now recognized as a central modulator of systemic inflammation and skeletal homeostasis. This evolving understanding introduces the concept of the gut–musculoskeletal axis, which may reshape our understanding of many orthopedic pathologies.

Microbiome regulation of bone biology

Bone is a dynamic tissue regulated by continuous osteoblastic bone formation and osteoclastic resorption. This balance is highly sensitive to immune signaling and systemic inflammation, both of which are strongly influenced by gut microbial composition. Microbial metabolites such as short-chain fatty acids (SCFAs), particularly butyrate, regulate bone metabolism through epigenetic and immune-mediated mechanisms. These metabolites enhance regulatory T-cell differentiation and suppress osteoclast activation, thereby promoting bone formation.[3,4] Conversely, dysbiosis increases pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which accelerate bone resorption and impair skeletal integrity.[5]

Experimental models further demonstrate that gut microbiota directly influence insulin-like growth factor-1 (IGF-1), a key regulator of bone growth and remodeling, highlighting a mechanistic link between intestinal health and skeletal development.[6]

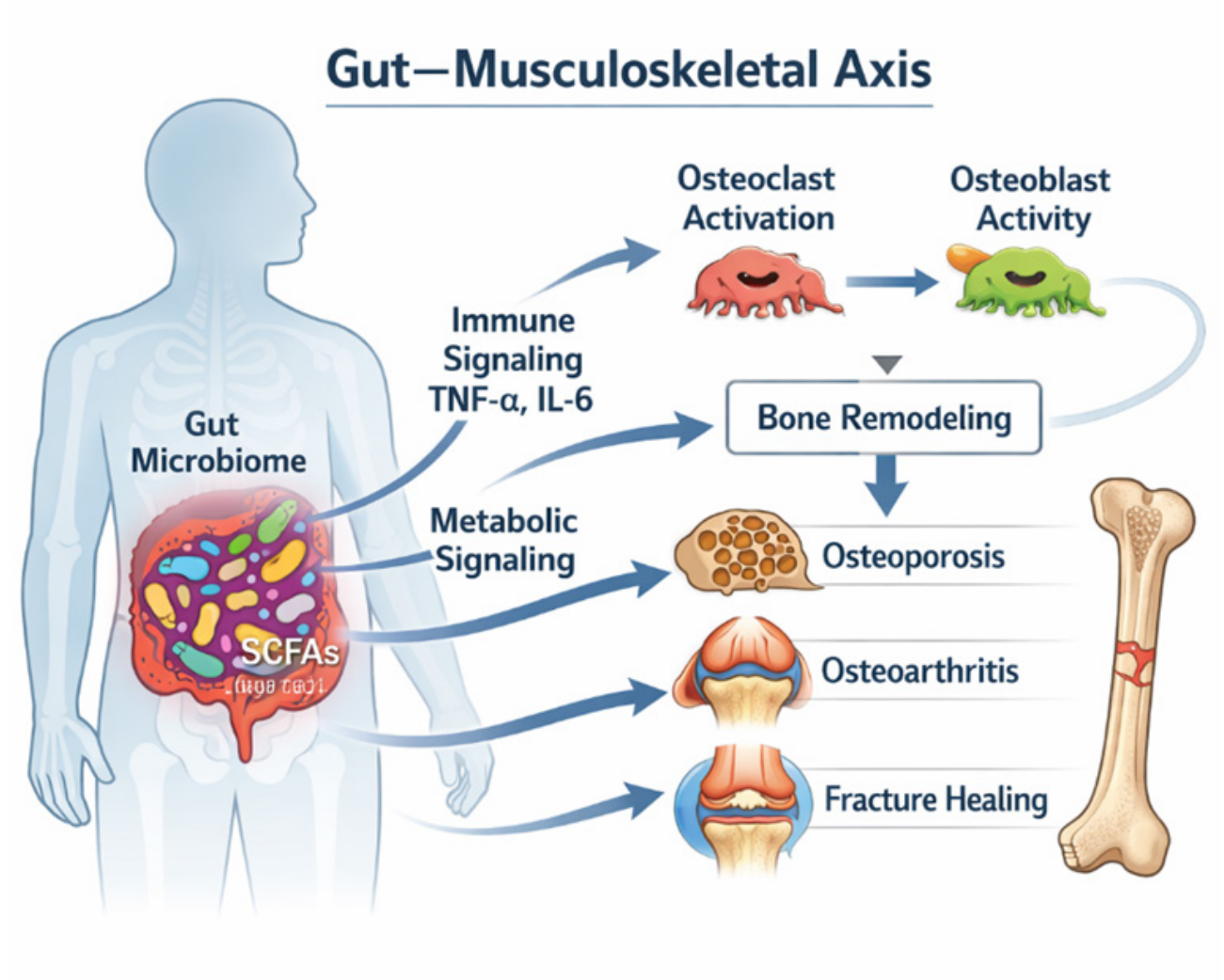

Figure 1 Gut Microbiome Regulation of Bone Biology via the Gut–Musculoskeletal Axis

Orthopaedic diseases and gut dysbiosis

Osteoporosis

Alterations in gut microbial diversity have been associated with reduced bone mineral density and increased fracture risk, particularly in postmenopausal women.[3,7] The microbiome influences calcium absorption, hormonal regulation, and systemic inflammation, all of which contribute to skeletal fragility.

Osteoarthritis

Osteoarthritis, traditionally considered a degenerative joint disease, is increasingly recognised as having an inflammatory component. Gut dysbiosis may contribute to chronic low-grade systemic inflammation, accelerating cartilage degradation and synovial changes.[1,5]

Fracture healing

Animal studies suggest that microbiome composition affects bone regeneration, influencing callus formation and mechanical strength during healing. Germ-free or dysbiotic models demonstrate impaired fracture repair compared to microbiome-balanced controls.[4,8]

Musculoskeletal infections

Although indirect, gut microbiome–mediated immune modulation may influence susceptibility to infections, including periprosthetic joint infections (PJI), through systemic immune regulation and barrier integrity.[2]

Clinical implications

Recognition of the gut–musculoskeletal axis expands orthopaedic practice beyond structural pathology. It introduces biologically modifiable factors that may influence disease prevention and recovery. Potential clinical implications include:

- Nutritional optimisation to support bone metabolism
- Probiotic and prebiotic interventions as adjuncts in musculoskeletal care
- Rational antibiotic use to preserve microbiome integrity
- Perioperative optimisation strategies incorporating gut health assessment

While these approaches remain largely experimental, they represent a shift toward integrative musculoskeletal medicine that bridges microbiology, immunology, and orthopaedics.

In Nepal, orthopaedic disease burden is significantly influenced by late presentation, nutritional deficiencies, infectious complications, and limited preventive health access. Osteoporosis-related fractures, neglected trauma, and delayed fracture healing are common clinical challenges in both urban and rural settings. Nutritional insecurity and dietary fibre deficiency in many populations may contribute to altered gut microbiota, potentially exacerbating bone fragility and impairing recovery outcomes.

Moreover, widespread empirical antibiotic use in peripheral healthcare settings may further disrupt microbiome balance, indirectly affecting immune-mediated bone healing and infection risk. Integrating dietary counselling, infection prevention strategies, and rational antibiotic stewardship into orthopaedic care pathways may improve long-term musculoskeletal health outcomes in resource-limited settings.

Conclusion

The gut microbiome represents a previously under-recognized regulator of musculoskeletal health. The emerging gut–musculoskeletal axis challenges traditional orthopaedic paradigms by linking intestinal microbial ecology with bone metabolism, joint disease, and recovery processes. For orthopaedic practice, including in Nepal, this evolving framework opens new approaches to musculoskeletal care.

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