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See related article on page 370

COMMENTARY

A Link between the Gut and Bone

Bone Health Impacted by Changes in Gut Microbiota

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The skeleton undergoes constant remodeling by the balanced and coordinated activity of bone-forming osteoblasts and bone-resorbing osteoclasts.[1] Physiologic bone remodeling occurs in response to many factors including hormonal influences and mechanical forces. However, numerous pathological conditions induce significant imbalances between bone formation and bone resorption that result in net bone loss. Indeed, there are so many scenarios of chronic or acute inflammation that have been associated with bone loss that the accumulated studies have defined an exciting new and growing field termed osteoimmunology. It is now widely accepted that the skeletal and immune systems are functionally linked, sharing common cells and cytokine signaling pathways that if activated result in aberrant osteoclast differentiation and bone resorbing activity. The gut microbiota has the potential to exert both pro- and anti-inflammatory responses, and the balance within the resident community of gut bacteria may be intimately linked to the proper function of the immune system.[2] The strong connection between the immune system and bone (osteoimmunology) also links systemic effects driven by the immune system and mediated by gut microbiota with changes in bone remodeling.

It is clear that there is a wide-ranging impact of the gut microbiota on host physiology. This occurs locally, where nutrient and energy extraction as well as gut barrier function can be affected, and systemically, where the gut microbiota may shape immune homeostasis.[3] In the manuscript by Hathaway-Schrader et al,[4] a series of elegant experiments extend the breadth of putative regulatory osteoimmunology pathways to include antibiotic disruption of the gut microbiota altering post-pubertal skeletal development.

In compelling and well-designed studies, using 6-week–old sex-matched post-pubertal C57BL/6T mice, the authors identify the connection between the microbiota of the gut and systemic immune responses. The animals were treated with broad-spectrum antibiotics [vancomycin (500 mg/L), imipenem/cilastatin (500 mg/L), and neomycin (1 g/L)] or vehicle-control in the drinking water from six to 12 weeks of age to deplete or disrupt bacterial communities in the gut.[5] Antibiotic administration–related alterations in the gut bacterial composition resulted in small but significant decreases in the trabecular bone volume fraction and the bone mineral density in male mice (but not females). Interestingly, antibiotic administration began at 6 weeks of age when the murine immune system is considered mature,[6] which is likely not be the case for the skeleton. Almost certainly, the skeletons of both male and female mice were still actively growing. Indeed, whether the mice are at peak adult bone mass at this age was not determined in this study and, if not, may be confounding the interpretation of any sex-dependent effects.

Despite the relatively small effects on trabecular bone architecture in the long bones and no changes in the cortical geometry, there were robust changes in parameters of osteoclast number and activity (*in vivo* and *in vitro*). The changes in osteoclast parameters induced by antibiotic administration occurred in the absence of any discernible changes in osteoblastogenesis or endochondral bone formation. A likely contributor to these male-specific cellular changes may also be related to the size and continued growth of the skeleton, there is simply more bone in males at this age that can be lost, compared with the females of the same age.

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The cellular changes in osteoclast parameters that elicit the significant decrease in bone volume are rightly suggested to be the result of significant increases in two serum cytokines, macrophage inflammatory protein 1α (MIP-1α) [CC chemokine ligand 3 (CCL3)] and tumor necrosis factor α (TNFα). Both of these cytokines are known to be potent osteoclastogenic agents.[7,8] CCL3 may mediate changes in T-cells, B-cells, macrophages (M2 and M1), and myeloid-derived suppressor cells via the sequential release of TNFα, as has been reported.[9] Even with the significant elevations in circulating cytokines and the strong activation of immune cell populations in the bone marrow, these effects are secondary to the initial immune response. The pro-inflammatory changes in adaptive and innate immune cells reported to be induced by antibiotic administration primarily occurred in the mesenteric lymph node and spleen, suggesting that the elevated systemic pro-inflammatory cytokines are due to hyper-immune response effects at secondary lymphoid tissues draining the local gut and systemic circulation.

Hathaway-Schrader et al's investigation is the first to determine that antibiotic-mediated disruption of the gut microflora in C57BL/6T mice elicits a broad immunosuppressive effect that is prevalent in the bone marrow and results in sex-specific decreases in bone accrual.[4] If these studies are reproduced, the sex-dependent effects of antibiotics would add yet another important wrinkle to our growing understanding of the regulation of bone cell function. Indeed, the data strongly support the evolving notion of an important and powerful role for the immune system in mediating local changes in bone cell function and overall skeletal development. Although more work is required to determine the breadth of immune responses induced by the regulation of the gut microbiota (beneficial or not), it is interesting to consider the events reported here as perhaps similar to the well-documented abscopal effects of radiation on bone.[10] In both cases, changes in the gut cellular milieu have the ability to alter bone cell function and bone mass.

The notion that indigenous bacteria somehow impact bone-to-immune system crosstalk to support normal bone homeostasis and perhaps fortify the bone marrow niche is certainly worthy of continued interrogation. The reported findings[4] may lay the foundation for unraveling evolutionary and mutually beneficial alliance between mammals and gut bacteria that is apparently critical in maintaining the long-term health of the skeleton.

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