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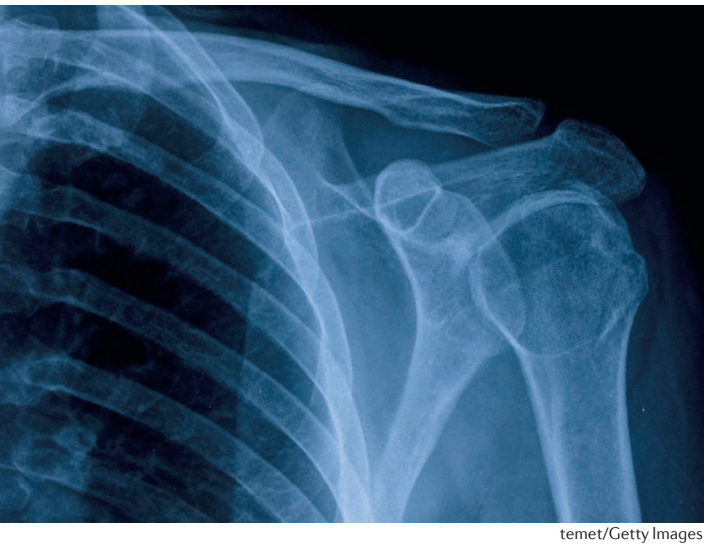
BONE

Gut microbiota promote bone growth via IGF1

Presence of the gut microbiota increases circulating levels of insulin-like growth factor 1 (IGF1) and supports bone growth, according to a new study in mice.

Bone mass is an important determinant of the increased risk of bone fracture with age. The gut microbiota exhibit enhanced diversity and reduced stability with age, but findings have conflicted whether the microbiota promote bone growth or resorption.

To resolve this contradiction, Jing Yan *et al*. investigated the short-term and long-term effects of the microbiota in mice. The team examined germ-free mice (which had no gut microbiota) and compared them with formerly germ-free mice that were colonised with the microbiota from conventionally raised mice at age 2 months. "We hypothesized that germ-free mice would be protected from age-related bone loss," explains corresponding author Julia Charles. "Our findings were not at all what we expected."



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Colonisation of germ-free mice was found to promote both bone formation and resorption after 1 month, with a reduction in trabecular bone mass compared with germ-free mice, but an increase in bone formation rate, as measured by dynamic histomorphometry. However, after 8 months of colonisation, trabecular bone mass was higher in colonised mice than in germ-free mice; longer femurs and L5 vertebrae were also observed in the colonized animals, suggesting that the bone-formation-enhancing effects of the microbiota become more prominent than the resorption-enhancing-effects during long-term colonisation.

Previously, circulating levels of IGF1, an important growth factor that regulates skeletal formation, were shown to be lower in germ-free mice than in conventionally raised mice, but whether colonisation is sufficient to increase IGF1 levels was not known. The team found that serum IGF1 levels were increased in colonised mice at both 1 month and 8 months after colonization, compared with germ-free mice. To discount potential developmental effects in the germ-free mice, the investigators treated conventionally raised mice with antibiotics for 4 weeks, and observed a reduction in serum IGF1 levels in antibiotic-treated mice compared with untreated mice.

Finally, to investigate the mechanisms for microbiota-mediated increases in IGF1, the team administered short-chain fatty acids (SCFAs; metabolites produced by the microbiota during fermentation of dietary fibre) to antibiotic-treated mice. SCFA supplementation reversed the changes in serum IGF1 levels that were observed in antibiotic-treated mice, indicating that microbiota-derived SCFAs are sufficient to mediate the observed changes in IGF1 levels in the host.

"This finding has potential implications for long-term antibiotic treatment, faecal transplants and the use of prebiotics and probiotics to modulate gut microbial communities," concludes Charles. Several questions remain regarding the mechanisms underlying the effect of the microbiota on IGF1. "Can the effect be mapped to a particular set of microbial species?" asks Charles. "Is the effect mediated solely by SCFAs or are other microbiota products or microbiota–host interactions important?"

Charlotte Ridler

ORIGINAL ARTICLE Yan, J. *et al.* Gut microbiota induce IGF-1 and promote bone formation and growth. *Proc. Natl. Acad. Sci.* http://dx.doi.org/10.1073/pnas.1607235113 (2016)