Probiotics increase bone volume in healthy mice

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A widely-used probiotic stimulates bone formation in young female mice, according to a study published November 13th in the journal

Immunity. In response to treatment with *Lactobacillus rhamnosus* GG (LGG), other intestinal microbes produced a metabolite called butyrate, which in turn activated bone-enhancing immune cells, including regulatory T cells.

"The significance of the study is that probiotics are, at least in mice, an effective means to increase bone density," says senior study author Roberto Pacifici of Emory University. "Clinical trials are in progress to validate the efficacy of probiotics in humans."

Fractures due to osteoporosis can have devastating consequences. For example, complications of hip fractures lead to mortality rates of 24%-30% during the first year following injury, and almost 50% rates of permanent disability. Unfortunately, most cases of osteoporosis remain untreated or ineffectively treated due to the cost and side effects of currently available drugs. There is an urgent need to identify and develop inexpensive, safe, and effective interventions for both the prevention and treatment of osteoporosis.

Small-scale studies in patients with osteoporosis have reported positive results from dietary supplementation with probiotics. In animals, probiotics can prevent disease-related bone loss, but their influence on the healthy skeleton remains less clear. "Because their mechanism of action in bone is unknown, they are regarded as some kind of alternative, esoteric, unproven treatment," Pacifici says. "Our goal was to identify a biological mechanism of action of probiotics, a mechanism that makes sense to traditional scientists, hoping that this will make probiotics a mainstream treatment."

In the new study, Pacifici and colleagues found that oral LGG supplementation for four weeks increased bone formation in female mice by stimulating the growth of butyrate-producing gut bacteria, including Clostridia. Notably, LGG supplementation did not increase

bone mass in mice raised in a germ-free environment, suggesting that this probiotic indirectly exerts its effects through the metabolic activity of other microbes that normally inhabit the intestines.

Supplementation with either LGG or butyrate induced the expansion of regulatory T cells in the intestine and in bone marrow—the spongy tissue inside some bones. This caused T cells in the bone marrow to secrete a protein called Wnt10b, which is known to be critical for bone development. By contrast, treatments that inhibited the expansion of regulatory T cells prevented bone formation induced by LGG and butyrate.

"We were surprised by the potency of the gut microbiome in regulating bone and by the complexity of the mechanism of action of probiotics," Pacifici says. "In general, there is a lot of interest in the concept that the gut bacteria regulate the function of distant organs. How this happens is largely unknown. We described a detailed mechanism by which changes in the composition of the gut microbiome induced by probiotics affect a distant system like the skeleton."

Lactobacillus is the most common genus of bacteria with reported probiotic activities. According to the authors, the findings are likely to generalize beyond LGG to other bacteria that also produce lactic acid. But it remains to be determined whether other types of probiotics work in the same way.

"The controversies about probiotics are: Do they work for real, and which one is the best?" Pacifici says. "We show that they work for real in bone. Which one is the best remains unknown. However, the emerging concept is that the number of bacteria in a dose of probiotic may be as important or even more important than the type of probiotic used. It is possible that the response to probiotics might be influenced by mouse strain, gender, and age."

Moving forward, the researchers will explore the role of the microbiota in bone diseases other than osteoporosis. They also plan to determine whether butyrate supplementation could prevent and treat osteoporosis, and whether probiotics could improve skeletal health in various disease states. In the future, the use of probiotics or butyrate to increase the number of regulatory T cells may find wider applications, such as in transplant medicine or as a treatment for inflammatory and autoimmune conditions.

"Our findings will need to be validated in human studies," Pacific says. "If successful, this research could substantiate the use of butyrate or probiotics as a novel, safe, and inexpensive treatment for optimizing skeletal development in young people and to prevent osteoporosis in older people."

More information: *Immunity*, Tyagi and Yu et al.: "The Microbial Metabolite Butyrate Stimulates Bone Formation via T Regulatory Cell-Mediated Regulation of WNT10B Expression" www.cell.com/immunity/fulltext … 1074-7613(18)30478-3 , DOI: 10.1016/j.immuni.2018.10.013

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