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Review Article

Gut Microbiome, Probiotics and Bone: An Updated Mini Review

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Abstract

The gut microbiome is now considered as a large organ that has a direct effect on gastrointestinal tract, immune and endocrine system. There is no evidence that gut microbiota regulates the immune system and is responsible for bone formation and destruction. Probiotics have been shown through the gastrointestinal tract to have a positive effect on the management of the healthy bone. This article discusses the latest data available from PubMed and Scopus databases regarding gut microbiome, probiotics and bone briefly.

Introduction

Gut microbiome (GM) is the largest one that includes trillions of bacteria, fungi and viruses that live in the intestinal tract. These *bacteria* have been found to modulate immune responses that are associated with many diseases such as Crohn's, irritable bowel syndrome, celiac, cardiovascular, and rheumatic [1]. GM is a major regulator of bone mineral density via the effects of the immune system [2], [3].

It has been reported by several clinical trials the association of low intestinal bacteria and decreased bone mineral density [4]. There is no convincing evidence of the role of GM in the development of bone formation and destruction [4]. Very recently the importance of microbiome health has become now clear; many consider it as a new large organ, while specific strains have been identified to affect immune cells [5].

Review of Text

Osteoporosis is a major public health burden in our ageing population [6]. Bone undergoes turnover continuously, and the immune system is regulating this process since 1980 [7]. This chronic progressive bone disease is mainly due to the natural cessation of endogenous estrogen marked by the onset of menopause and characterised by decreased bone mineral density (BMD) and negative changes in bone microarchitecture [8]. Estrogen cessation gives rise to two stages of bone loss: an early rapid loss of trabecular and cortical bone due to increased osteoclast activity and decreased osteoclast apoptosis, and a second slower prolonged loss due to decreased osteoblast activity [9]. This notable imbalance between bone formation and bone resorption increases the risk of fractures among postmenopausal women [10], [11]. Although estrogen therapy (ET) was shown effective in the prevention and treatment of estrogen-deficient osteoporosis in

postmenopausal women, its use remains controversial due to its association with increased risk of breast, endometrium and ovaries cancer [12].

Recently, alternative and complementary therapies such as dietary supplements have become the preferred prophylactic treatment of clinicians and patients in the prevention and management of osteopenia [13]. Meta-analyses have shown that daily intake of 1200 mg Calcium (Ca) and 20–25 mg vitamin D (D) can reduce total- and hip-fracture risk by 15% and 30%, respectively, [14], hence, it seems that Ca and D supplementation alone is not sufficient to fully prevent the menopausal bone loss.

In the past decade, a growing body of evidence suggests that probiotics may have favourable effects on bone health. Probiotics are living microorganisms that could influence the GM composition and exert positive effects that have been attributed to several complex mechanisms, including enhanced mineral absorption, beneficial anti-inflammatory pathways [15] and many more. Probiotic strains differ significantly in genotype and phenotype, and they may show different metabolic functions, particularly with regards to immune function [16].

In earlier reports, various strains of Lactobacillus and Bifidobacterium were shown to prevent and even restore bone loss related to estrogen deficiency [17], they were also shown to cause a 45% increase in femoral and vertebral trabecular bone volume fraction in mice [18]. More recently, a randomized, double-blind, placebo-controlled study [19] revealed that multispecies probiotic supplementation (7 specific strains: *Lactobacillus casei, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Bifidobacterium breve* and *Streptococcus thermophiles*) among postmenopausal osteopenic women diminished bone resorption through significant effects on serum concentrations of bone biomarkers, such as serum bone-specific alkaline phosphatase (s-BALP) and serum C-terminal telopeptide of type I collagen (CTX). Decreased serum levels of BALP, the marker of bone turnover and CTX-produced by osteoclasts during the bone resorption process- compared to the placebo group, suggest a protective effect of this multispecies probiotic against bone resorption. These results are consistent with earlier studies using *Bifidobacterium subtilis* (CH201) [20], *Bifidobacterium longum* [21] and *Lactobacillus reuteri* [22].

The beneficial effects of probiotics on nutrients absorption were highlighted in several recent reports. Various strains of Lactobacillus and Bifidobacteria were shown to influence the pH of the gut and the metabolism of bile acids [23], important factors in the control of nutrients absorption, especially calcium. Lactobacillus helveticus fermented milk exhibited an acute positive effect on calcium metabolism. Thus, in addition to the well-established benefits of calcium and vitamin D content of milk, it is possible that some types of probiotics may aid in the breakdown of proteins contained in milk to biologically active peptides [24]. Furthermore, elevated concentration of Lactobacillus reuteri and *Bifidobacterium longum* in the gut may be involved in promoting mineral (calcium, magnesium, and phosphate) absorption resulting in an increased BMD. Probiotics were also shown to play an essential role in the synthesis of vitamin B and vitamin K, which are critical for the regulation of bone health [25].

On another note, various strains of probiotics were shown to affect bone health via the production of short-chain fatty acids (SCFA). SCFA are byproducts produced by the microbiota during fermentation of dietary fibre and were reported to have direct effects on osteoclasts and osteoblasts. For example, butyrate is an SCFA known to reduce osteoclastogenesis by suppressing the receptor activator for nuclear factor κB ligand signalling pathway [26]. More recently, SCFA were shown to have indirect effects on endocrine factors such as peptide YY and glucagon-like peptide 1 Peptide YY is a gastrointestinal hormone secreted from the endocrine L cells and is negatively associated with the total body and hip BMD in premenopausal women [27]. Glucagon-like peptide 1, an amino acid hormone that is also secreted from the endocrine L cells, has been shown to act as a regulator of bone metabolism by altering the balance between osteoblast and adipocyte differentiation from bone mesenchymal stem cells [28].

When it comes to the immune-modulatory properties, probiotic administration was shown to reduce the expression of several pro-inflammatory and osteolytic cytokines such as Tumor Necrosis Factor-α (TNF -α) and Interleukin-1b (IL-1b) [29]. *Lactobacillus reuteri, Lactobacillus rhamnosus* and *Lactobacillus paracasei* [30] were shown to decrease osteoclastogenesis and bone resorption significantly. *Lactobacillus reuteri* enhanced the suppression of pro-inflammatory cytokines TNF-mediated bone resorption in mice [19] and enhanced the reduction of the percentage of CD4C T cells in bone marrow [22]. The treatment was able to improve bone health in healthy male mice [19]. Similarly, decreased TNF-α and IL-1b, along with increased anti-inflammatory cytokine IL-10 also resulted from oral administration of Saccharomyces cerevisiae [31].

One of the recent applications of probiotics is the incorporation of *Bacillus spp.* in birds' feeds to promote growth, as an alternative to the harmful antibiotic growth promoters (AGP). Several studies show that certain strains of Bacillus subtilis also promote the growth of chickens to a greater extent than AGP [32].

On the other hand, it is important to note that, in contrast with the reported benefits of probiotics on bone health, a recent study [6]

showed that dietary enrichment with powdered whole grape and probiotics (composed of equal parts *Bifidobacterium bifidum, B. breve, Lactobacillus casei, L. plantarum*, and *L. bulgaricus*) exerted either no effect on bone microarchitecture in a mouse model of age-related osteoporosis. However, this negative effect was attributed to possible differences in probiotic strains, the small sample size and the duration of the supplementation.

Conclusions

Current research efforts, although varied, mostly indicate favourable effects of probiotics on bone metabolism. Therefore, long-term investigations with different strains of probiotics are needed to dissect the mechanisms and effects on bone formation and resorption, especially in humans.

This relationship is a promising area of investigation, which potential outcomes could lead to physicians directing their therapeutic efforts to probiotics, among dietary supplements, for most effective treatments for bone-related ailments.

Future directions are focused now on the major role of the gut microbiome in rheumatic disease, and a lot of interest is growing in the gut microbiome manipulation as a therapeutic tool for bone diseases. Preclinical models may also be a future promise for the treatment of bone disease.

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