Microbiome Question 3: Do therapeutic modulations of the gut microbiome mitigate osteoarthritis from animal models to clinical efficacy?

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Response/Recommendation: Unknown. Preclinical and early clinical studies suggest that modulating the gut microbiome may help mitigate osteoarthritis.

Level of Evidence: Weak

Delegate Vote: Agree: %, Disagree: %, Abstain: %

Rationale:

The pathophysiology of knee osteoarthritis is multifaceted, driven by metabolic dysregulation and chronic inflammatory cascades **[4, 5]**. Recently, the "gut–joint axis" paradigm has emerged, illustrating how the gut microbiome may influence articular health **[6, 7]**. This framework suggests that the development of an adverse gut microbiota can trigger joint inflammation via immune-mediated pathways and the translocation of bacterial products to synovial tissues **[8, 9]**. Consequently, the therapeutic modulation of the gut microbiota to mitigate systemic low-grade inflammation represents a promising and novel frontier for the prevention, management, and clinical rehabilitation of OA.

Preclinical research utilizing diverse animal models has identified the gut microbiome as a potential therapeutic target. These studies demonstrate that manipulating the gut microbiota through prebiotic, probiotic, or symbiotic administration effectively mitigates osteoarthritis progression, protects joint tissues, and reduces pain **[10–12]**. Regarding prebiotics, pivotal studies by Schott et al. **[13]** and Rios et al. **[14]** demonstrated that oligofructose or prebiotic fiber (often combined with exercise) can restore protective *Bifidobacterium* populations within the gut and significantly reduce the histopathologic severity of OA. Further investigations on the administration of prebiotics in animals include quercetin **[15]**, chicken cartilage compounds **[16]**, and milk-derived extracellular vesicles **[17]**. These interventions are associated with increased levels of beneficial short-chain fatty acids (SCFAs), decreased levels of inflammatory cytokines (such as IL-1β and TNF-α), and reduced cartilage degradation by suppressing catabolic proteins. In terms of probiotics, research has highlighted the efficacy of specific strains in modifying disease outcomes: So et al. **[18]** and Lee et al. **[19]** found that strains of *Lactobacillus casei* (supplemented with collagen/glucosamine) and *L. acidophilus* (LA1) effectively reduce pain and cartilage destruction by inhibiting the NF-κB pathway. These findings are supported by Cho et al. **[20]** and O'Sullivan et al. **[21]**, who observed reduced chondrocyte inflammatory cell death and the suppression of systemic angiogenesis factors involved in disease progression. Other key probiotic studies show that *Clostridium butyricum* strains **[22, 23]** protect joint integrity via the gut–muscle–joint axis and the downregulation of COX-2, while *Lactobacillus* M5 **[24]** and multi-strain probiotics **[25]** reduce the severity of OA in both high-fat diet and surgically induced models. Additionally, *Bifidobacterium longum* **[26]**, *L. plantarum*, and *Streptococcus thermophilus* **[27, 28]** have been associated with decreased cartilage lesions and suppressed pain behavior. Notably, Yang et al. **[29]** found that recolonization of the gut by *Clostridium bolteae* alleviated OA through the formation of protective bile acids. Symbiotic strategies, such as those investigated by Kwon et al. **[30]** using a probiotic complex combined with rosavin and zinc, and Korotkyi et al. **[31, 32]** combining multi-strain probiotics with chondroitin sulfate, have demonstrated synergistic benefits in improving pain behaviors and amplifying chondroprotective signaling. Finally, metabolite supplementa-

tion with indole-3-propionic acid **[33]** or direct butyrate **[20]** has been shown to attenuate disease progression by inhibiting chondrocyte inflammation. Collectively, these animal studies provide strong evidence that targeted gut microbiome manipulation can protect joint integrity and restore metabolic homeostasis.

In clinical settings, consistent results show that the gut microbiome of patients with OA differs markedly from that of healthy controls. These alterations involve both taxonomic shifts and functional changes, where lower levels of certain taxa are associated with disease progression. Specifically, the *Methanobacteriaceae* family, *Desulfovibrionales* order, and *Ruminiclostridium-5* genus appear to have a protective effect **[34]**. Other beneficial taxa include *Bacteroides*, *Agathobacter*, *Faecalibacterium*, and *Roseburia*. The administration of probiotics and prebiotics shows promise in reversing these dysbiotic patterns and improving clinical outcomes. Administration of probiotics (e.g., *Lactobacillus*) decreases inflammatory factors and nociceptive mediators, leading to significant reductions in pain and symptoms. This was clinically observed in a case trial involving a 67-year-old female with OA of the lower back and ankle; after a daily intervention of *Lactobacillus rhamnosus*, *Saccharomyces cerevisiae*, and *Bifidobacterium animalis*, mean pain scores on the Visual Analogue Scale (VAS) dropped significantly from 4.9 ± 2.2 to 4.0 ± 1.7 compared to a placebo ($p = 0.04$, 95% CI [0.04, 1.77]). Beyond this numerical improvement, the participant reported a preference for the probiotic treatment, which was further supported by improved clinical scores and a notable reduction in rescue medication usage **[35]**. In a randomized, prospective, double-blind study, Shine et al. investigated the effect of *Lactobacillus sakei* LB-P12 in patients with knee OA. Patients receiving the probiotic experienced significantly greater pain relief and improvement in functional outcomes than those receiving a placebo **[39]**. No adverse events or clinically meaningful laboratory abnormalities were noted in patients receiving the live bacteria.

Furthermore, a recent meta-analysis indicates that oral probiotic intervention significantly improves clinical outcomes for patients with knee osteoarthritis (KOA), significantly reducing overall WOMAC scores and VAS pain scores. Despite high heterogeneity and a lack of statistical significance in specific high-sensitivity C-reactive protein (hs-CRP), broader findings suggest an ameliorating effect on inflammatory biomarkers **[36]**. Notably, using probiotics as an adjunctive therapy alongside conventional pharmaceuticals or chondroprotective agents may yield enhanced clinical outcomes by potentiating anti-inflammatory responses in clinical settings **[37, 38]**. However, it remains unclear what traits of probiotics are needed to ameliorate OA.

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