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The Microbial Revolution in the World of Joint Replacement Surgery

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Background: The prevalence of revision surgery due to aseptic loosening and periprosthetic joint infection (PJI) following total hip and knee arthroplasty is growing. Strategies to prevent the need for revision surgery and its associated healthcare costs and patient morbidity are needed. Therapies that modulate the gut microbiota to influence bone health and systemic inflammation are a novel area of research.

Methods: A literature review of preclinical and clinical peer-reviewed articles relating to the role of the gut microbiota in bone health and PJI was performed.

Results: There is evidence that the gut microbiota plays a role in maintaining bone mineral density, which can contribute to osseointegration, osteolysis, aseptic loosening, and periprosthetic fractures. Similarly, the gut microbiota influences gut permeability and the potential for bacterial translocation to the bloodstream, increasing susceptibility to PJI.

Conclusions: Emerging evidence supports the role of the gut microbiota in the development of complications such as aseptic loosening and PJI after total hip or knee arthroplasty. There is a potential for microbial therapies such as probiotics or fecal microbial transplantation to moderate the risk of developing these complications. However, further investigation is required.

Clinical Relevance: Modulation of the gut microbiota may influence patient outcomes following total joint arthroplasty.

The number of total knee arthroplasty (TKA) and total hip arthroplasty (THA) procedures in the United States is projected to surpass 1 million annually by 2030[1,2]. The economic cost of osteoarthritis is estimated to be up to 2.5% of the gross domestic product (GDP) of high-income countries[2-4]. Revision surgery, with aseptic loosening of implants and periprosthetic joint infections (PJIs) as the leading causes, accounts for 10% of these costs[2,5]. Implant failures requiring revision cause pain and require hospital stays for patients[1,6,7]. Consequently, strategies to reduce aseptic loosening and PJIs are needed.

One of the most fascinating developments in science and medicine over the past 2 decades has been the study of the gut microbiota. With the numbers of microbes dwarfing the totality of cells in the human body they inhabit, this ecosystem of microbes populating our gastrointestinal tract has been implicated in an array of conditions, including metabolic disorders such as diabetes and obesity, cancers, and depression[8,9]. Treating diseases via the manipulation of the gut microbiota has thus gained tremendous interest.

In the past decade, the so-called "gut-bone axis" has been hailed as a key mediator in bone health[10]. Healthy host bones are needed for implant osseointegration and to avoid aseptic loosening and periprosthetic fractures following THA and TKA[11]. Emerging research has also implicated the gut microbiota in PJIs[12]. Therefore, this review will focus on the potential for interventional microbial therapies that may one day reduce the need for revision surgery following THA and TKA.

The Gut-Bone Axis: A Brief Overview

Bone metabolism is primarily mediated by osteoclasts and osteoblasts, which resorb and install new bone matrix, respectively. The contribution of the gut microbiota to this process is complex (Fig. 1). Germ-free mice were found to have increased bone mass, due to a reduced number of osteoclasts, compared with conventionally raised mice[13]. Disruption of the microbiota via antibiotics reduces bone quality and strength[14]. Additionally, the microbiota is a key mediator of bone metabolism in fracture healing, osteoporosis, inflammatory bowel disease, and rheumatoid

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arthritis. The gut microbiota communicates with distant sites of bone metabolism through immune mediators, regulation of hormones, extracellular vesicles, short-chain fatty acids (SCFAs), vitamins, and aromatic amino acids, among other mechanisms[15-19].

An example of the role of the microbiota is the important contribution made by the segmented filamentous bacteria (SFB) in the gut to fracture healing[20]. Fracture healing requires an inflammatory phase, and the SFB induce the production of the proinflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-17 from Th (T helper) 17 cells, aiding in this healing process. Accordingly, the administration of broad-spectrum antibiotics disrupts this pathway and severely blunts the bone healing response[20,21]. SFB and their downstream proinflammatory cytokines also stimulate osteoclast activity, contributing to osteoporosis. Inflammatory bowel disease (IBD), characterized by an increased profile of proinflammatory bacteria and gut dysbiosis, elevates osteoporosis fracture risk by 40%, with the prevalence of osteopenia and osteoporosis being up to 77% in patients with IBD[22-24].

SCFAs, which are the byproducts of indigestible carbohydrates metabolized by microbes, improve bone mineral density (BMD) by promoting osteoblast numbers[25]. Production by microbes or delivery of SCFAs to parts of the digestive tract promote beneficial bacteria such as *Akkermansia muciniphila*[26]. Such organisms have been shown to be critical in metabolism, weight control, and response to immunotherapies in oncology[27-32]. Extracellular vesicles from *A. muciniphila* improve bone strength and mass in osteoporotic mice[19]. The production of vitamins and other important nutrients by the gut microbiota also likely plays an important role in bone health. The absorption of vitamin D, important for bone health due to its role in calcium acquisition and storage, can be increased with the administration of the probiotic bacteria *Limosilactobacillus reuteri*[33]. Vitamin K2 is produced by the gut microbiota and inhibits osteoclast differentiation while

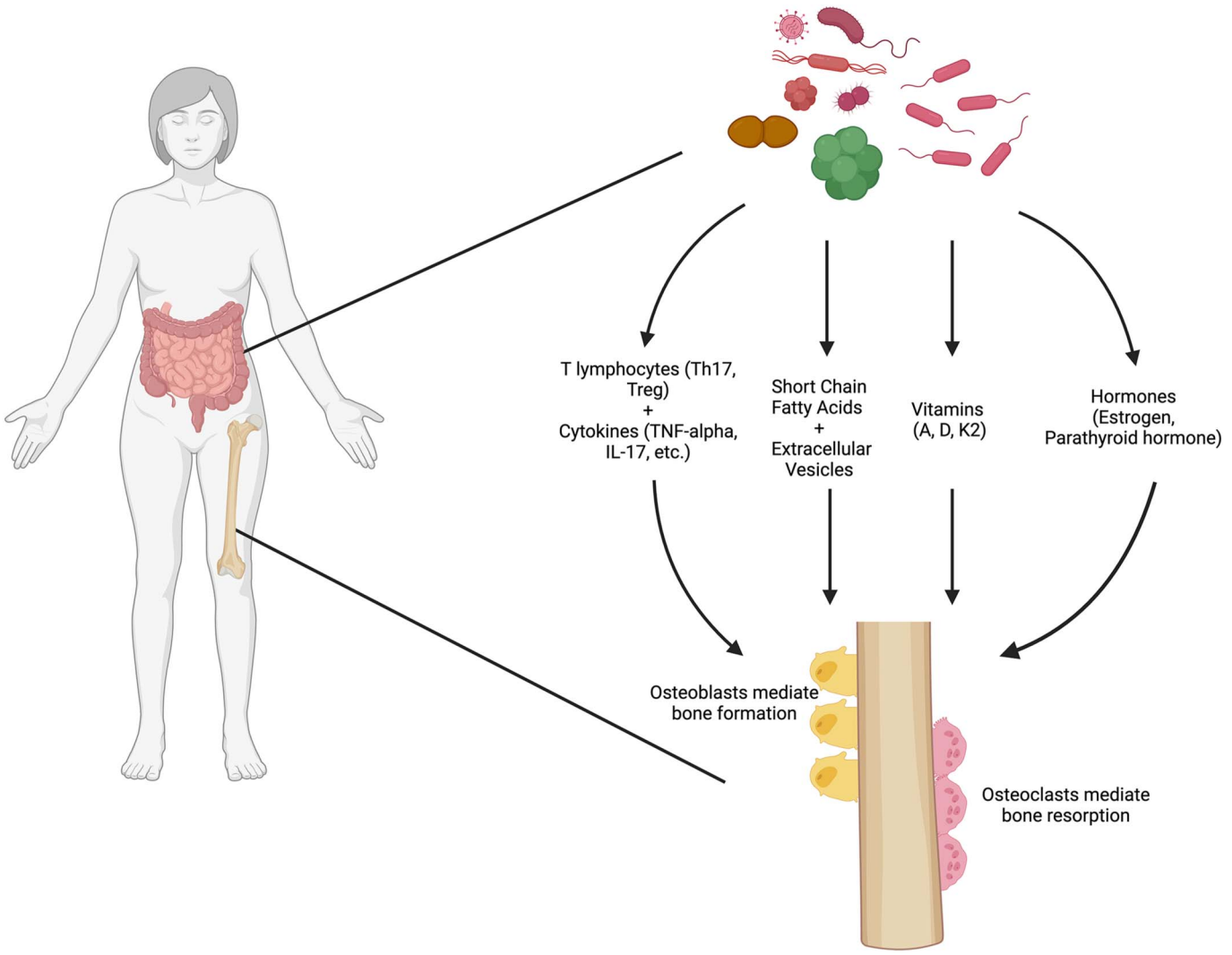

Fig. 1

Microbial involvement in bone homeostasis. Well-known mediators of the gut-bone axis involve the immune system, microbial metabolites such as SCFAs and vitamins, and hormones.

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stimulating osteoblast activity and numbers[34-37]. Parathyroid hormone (PTH)-induced bone loss is also microbiota-dependent, with germ-free mice and antibiotic-treated mice protected from the effects of the hormone[38]. Bone health depends on gut barrier integrity as well, and bacteria within the Clostridium, Enterococcus, and Streptococcus genera have been implicated in the metabolism of vitamin A, which is known to improve barrier function[18]. Finally, proinflammatory bacteria such as Streptococcus species are postulated to contribute to joint pain by the secretion of immunologic factors that pass from the gut into the circulation[39].

Given the intimate involvement of the gut microbiota with bone health, manipulating the gut microbiota to achieve better outcomes prior to and following joint arthroplasty is an exciting possibility.

Aseptic Loosening

Aseptic loosening of implants is one of the most common reasons for revision total joint arthroplasty[40]. The production of wear debris at the joint interface causes inflammation[41-43]. Wear debris stimulates macrophages to produce proinflammatory cytokines, which increase osteoclast numbers and activity, causing osteolysis (Fig. 2)[44]. Manipulation of macrophages to an anti-inflammatory state may reduce osteolysis and improve implant longevity[45]. Suboptimal osseointegration predisposes patients to aseptic loosening[46]. Low BMD delays osseointegration and reduces the initial stability of the implants[46]. Poor bone quality also increases implant migration and heightens the risk of revision surgery[47,48]. This decreases patient satisfaction and slows recovery after the surgery[11,49]. While use of bisphosphonates such as zoledronic acid reduces implant migration, it is associated with many side effects[50-53]. Poor bone quality and osteolysis also increase the risk of periprosthetic fractures and are a common cause of revision surgery[54,55]. Mortality rates following periprosthetic femoral fractures have been reported to be 15.8% (at 18 months) and 16.5% (at 12 months), respectively, with enduring pain and decreased ambulatory function several years after revision surgery[54,56-58]. While poor surgical technique and the use of cementless implants increase the risk of periprosthetic fractures, implant loosening is a very common cause of these fractures, with up to 66% of patients presenting with implant loosening at the time of their fracture[59,60].

Altering the gut microbiota could affect osseointegration and the risk of aseptic loosening and periprosthetic fracture.

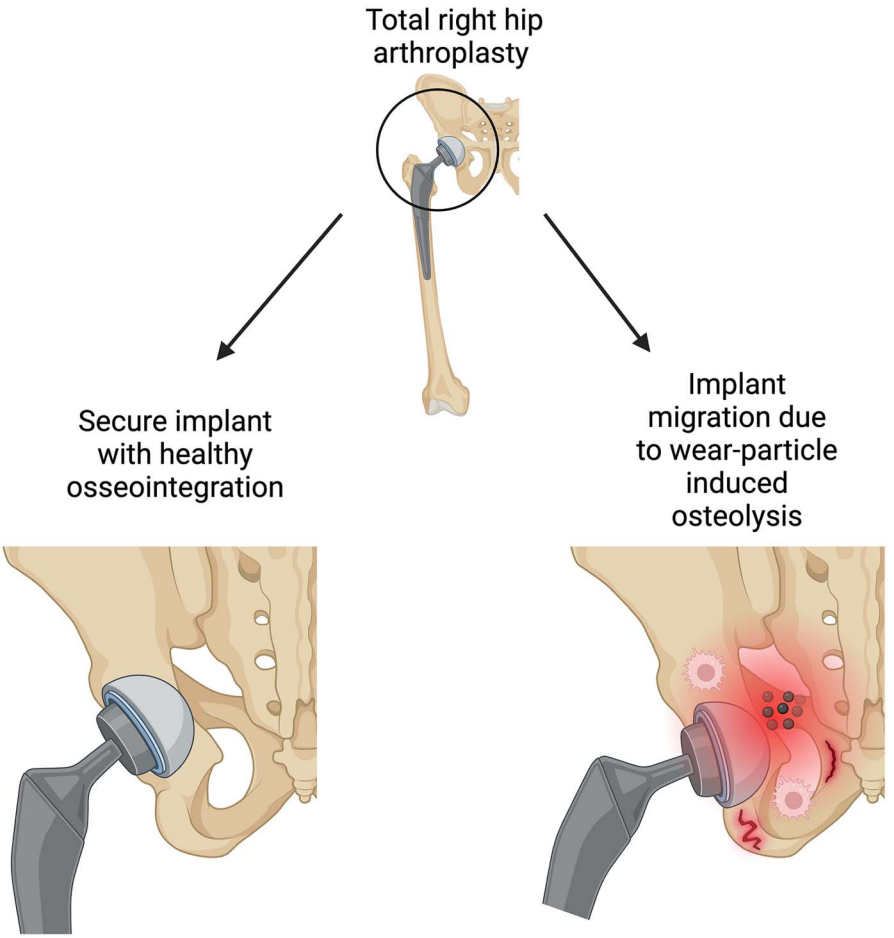

Fig. 2

Mechanism of wear particle-induced osteolysis. Pathophysiology includes debris (pictured as green circular particles) causing macrophage recruitment and inflammation, and concurrent osteolysis (the red lesion in the bone).

The gut microbiota influences the inflammatory capacity of the immune system, which is a key mediator of wear particle-induced osteolysis[61-65]. The gut microbiota of rats with wear particle-induced osteolysis had an increased Firmicutes-to-Bacteroidetes ratio and a reduced abundance of SCFA-producing bacteria, both of which are associated with an increased inflammatory profile[61]. The administration of the probiotic *Lacticaseibacillus casei,* known for its immunomodulatory and anti-inflammatory properties, protected mice from wear particle-induced osteolysis while also reducing inflammatory markers and osteoclast number[62,63]. SCFAs such as propionate and butyrate also inhibited wear particle-induced osteolysis in a mouse calvarium via multiple mechanisms, one being the negative regulation of osteoclast differentiation[64]. The probiotic *Lactobacillus reuteri* prevented bone loss in estrogen-depleted mice[66], likely by increasing 25-hydroxyvitamin D levels to aid in the absorption of calcium necessary for bone growth[33]. The treatment of 75 to 80-year-old women presenting with low BMD with the same strain of *L. reuteri* decreased tibial bone loss over a span of 12 months[67]. In contrast, supplementation with a multispecies probiotic formulation that included various Lactobacillus and Bifidobacterium species had no effect on the hip and spine BMD of patients 50 to 72 years of age with osteopenia; however, outcomes were measured only at 6 months[68]. The levels of the inflammatory cytokine TNF-α and of osteoclast-inducing PTH were significantly reduced in the serum, indicating that the multispecies probiotic might play a positive role in bone quality in the long term[68]. While 4 species of Lactobacillus were used, *L. reuteri* was not part of the formulation, suggesting that treatment effectiveness could depend on the species and strains of probiotics.

Use of anti-inflammatory probiotics should be evaluated for its potential to protect against osteolysis and aid in increasing BMD, allowing for proper osseointegration and the avoidance of aseptic loosening. Longitudinal clinical trials studying the prevalence of aseptic loosening in patients given probiotics containing the Lactobacillus and Bifidobacterium species before, during, and after arthroplasty are indicated. Fecal microbial transplantation (FMT) may also be considered as an intensive option to protect high-risk patients, given its ability to produce persistent changes in the gut microbiota[69]. Preclinical animal data show that FMT can help treat osteoporosis, but data on its efficacy and concurrent risks are still lacking[70,71]. Even with the advent of oral capsules, which are more easily administered than an enema or nasal gastric delivery, FMT remains unpopular for patients without life-threatening conditions, given its expense and required screening of both the donor and the recipient[69,72,73].

Periprosthetic Joint Infections

Although its prevalence is <2%, the impact of PJI on the individual patient is severe, with a 5-fold increase in mortality, a higher risk of morbidity, and a reduced quality of life due to repeat surgical procedures and loss of ambulatory capacity[74]. Treatment of PJI entails a combination of antibiotic therapy and surgery, but up to 35% of these interventions fail[75,76]. Bacteria can adhere to and colonize the implant, forming a biofilm that is challenging to disrupt via conventional antibiotic courses[77,78]. While bacterial colonization and subsequent PJI were previously thought to occur solely due to contamination from skin during the initial surgical procedure, recent work has revealed the presence of microbes in the joints of patients even prior to surgery[12]. This section of the review will focus on the lesser-known sources of microbes within joint spaces: the oral and gut microbiota (Fig. 3)[12,79-82].

It was postulated that 6% to 13% of PJIs are caused by bacteria resident in the oral cavity and saliva[83]. The oral bacterial species *Fusobacterium nucleatum* and Peptostreptococcus have been reported to cause PJI in patients following dental surgery[84,85]. Oral bacteria such as *Prevotella intermedia* and *Porphyromonas gingivalis* have been found in both the subgingival dental plaques and the synovial fluid of patients with both rheumatoid arthritis and periodontal disease[81]. Additionally, identical clones of the oral bacterial species *F. nucleatum* and *Serratia proteamaculans* were found in both dental plaques and synovial fluid of patients with both rheumatoid arthritis and periodontal disease[82]. The 2 diseases are thought to have similar pathophysiological mechanisms, and since rheumatoid arthritis has been associated with an increased risk of PJI, the identification of oral microbiota constituents in these joints causes considerable concern[86,87]. Despite this, no association between antibiotic prophylaxis and the incidence of PJI following dental procedures has been found[88,89]. The American Academy of Orthopaedic Surgeons recommends antibiotic prophylaxis only in immunocompromised patients, patients with poor glycemic control, those who have had an arthroplasty within the past year, and those with a history of PJI[90].

Similarly, enteric pathogens from the gut can spread to joint spaces via the hematogenous route to seed and infect implant sites. This is thought to be the mechanism of the increased PJI risk in patients with IBD[91,92]. The dysregulated and inflamed intestinal microbiota paves the way to a disrupted gut barrier, leading to bacterial translocation into the bloodstream. Since only a small amount of bacteria is required to establish a PJI, this phenomenon puts patients at high risk for implant failure[93]. Patients with IBD are often on immunosuppressive therapies, which may also increase their risk of PJI. While the most recent guidelines for prophylactic antibiotic therapy provide recommendations for immunocompromised patients and those who have obesity, liver cirrhosis, type-2 diabetes, and other conditions associated with gut dysbiosis must also be considered in the decision whether to administer such therapy[8,9,94-96]. Prophylactic antibiotic therapy in patients with those conditions may contribute to dysbiosis and worsen the risk of PJI in immunocompetent patients with gut dysbiosis. The duration of treatment also matters, as the long-term use of antibiotics in women >60 years of age was shown to significantly increase the risk of all-cause mortality, while treatment for <2 months did not[97]. Persistent changes in the microbiota have been documented following even short-term antibiotic use[98]. For example, a 7-day course of clindamycin caused reductions in the Bacteroides species that persisted for 2 years, while a 10-day course reduced Bifidobacterium to levels that could not be restored until 1 year post-treatment[99-101]. Although the link has yet to be explored, such profound

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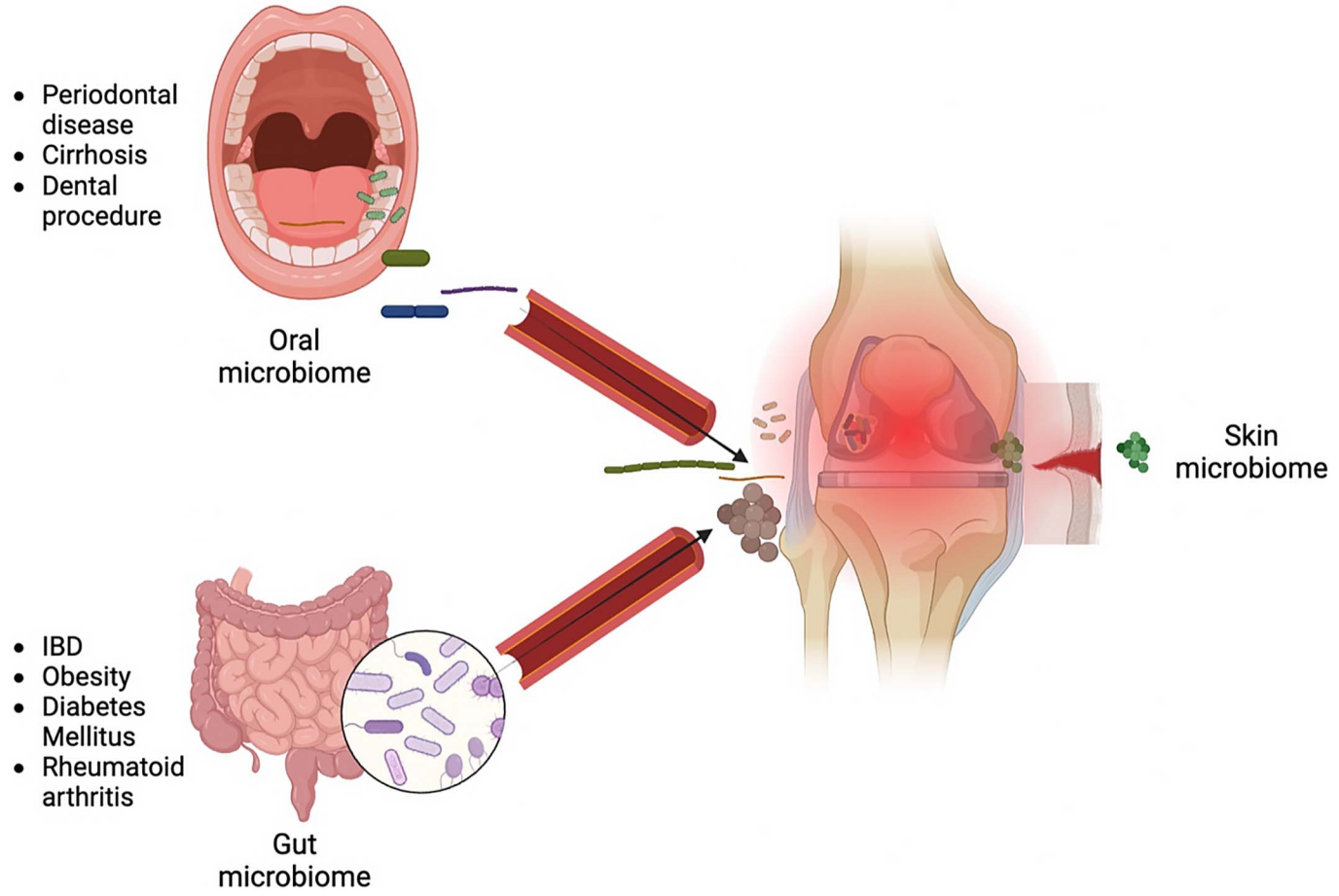

Fig. 3
Three sources of bacteria in periprosthetic joint infections and risk factors.

disturbances in the enteric microbiota might predispose patients with comorbidities to altered gut microbial homeostasis, further compromised barrier function, and a subsequently increased risk of PJI. Comorbidities such as congestive heart failure, diabetes, obesity, renal disease, rheumatoid arthritis, and liver cirrhosis are just some of the many risk factors for the development of PJI[102-104]. Many of these comorbidities are also associated with gut microbiota perturbation that may increase these patients' susceptibility for PJI[39,94].

Use of probiotics to alter gut microbiota composition, improving the gut barrier and decreasing bacterial translocation to the bloodstream, is an area requiring further research. For example, obesity is strongly associated with an increased abundance of the Firmicutes phylum at the expense of Bacteroidetes within the gut of patients, with this shift reversed by weight loss[95]. Mice with this shift in their microbiota composition after antibiotic therapy are more vulnerable to PJI than mice with normal microbiota[78]. Likewise, patients with IBD are at a higher risk for PJI. However, their microbiota has the opposite shift: an increased abundance of Bacteroidetes compared with Firmicutes[91,105]. As such, use of specific probiotics to restore a healthy Firmicutes-to-Bacteroidetes balance for patients at higher risk for PJI could be explored.

Limitations in the Field

Although an ample number of studies indicate a strong possibility of microbial therapies in the future of orthopaedics, presently this field does have some limitations. Most microbial therapeutic modalities such as FMT, prebiotics, and fermented food remain greatly understudied regarding their direct impact on human bone health[70,106,107]. Moreover, the long-term efficacy of probiotics in functionally altering the gut microbiota remains controversial, with most studies demonstrating no substantial changes in overall microbial diversity following probiotic supplementation in humans[108]. Since PJIs can occur anytime during the life of an arthroplasty recipient, the therapy's inability to be efficacious over a patient's lifespan could be a limitation[108-110]. If probiotics fail, FMT or other microbial therapeutics (prebiotic, phage, defined microbial consortia, fermented food, and fermentation products) may be explored as an alternative; FMT has been shown to produce persistent changes in the recipient microbial signature[69]. However, since it remains unknown whether FMT will help or worsen the incidence of aseptic loosening and PJI, exploration of probiotics continues to be the preferred route.

It is also possible for probiotic therapies to have functional effects without creating major alterations in the microbial ecosystem, making their mechanism of action challenging to

study[105,106,111]. Consequently, the reliability of probiotic treatment in humans with differing basal microbial signatures can become hard to predict[105,106,111]. The present literature also has scant information on the appropriate dosages of microbial therapies for the bone health of humans. This is primarily because studies in this developing field have largely employed preclinical animal models, indicating the need for future studies in humans[106].

Conclusions

The involvement of the gut microbiota in the body's physiology and pathophysiology has made it a target in the treatment of various diseases. Its effect on bone and joint conditions, especially with respect to its control of systemic inflammation, should not be ignored. Probiotics are presently being investigated to treat a wide range of conditions, ranging from bloating and traveler's diarrhea to atopic dermatitis and clinical depression[112,113]. Presently popular and available probiotic formulations include the Lactobacillus and Bifidobacterium genera of bacteria, and emerging research shows that various other bacteria such as *A. muciniphila* and other species could be promising, with multifarious health effects[19,112-114]. Given the contributions of the gut microbiota to bone health, probiotics are a potential future therapeutic option in populations of patients requiring or living with hip and knee implants. However, dosages and therapeutic timelines are far from being elucidated, and the ability of probiotic interventions to cause long-term changes in the gut microbiota remains controversial[108-110,113]. Finally, nonspecific probiotic treatment may worsen gut health in certain circumstances, highlighting the need for personalized therapies in the future[115]. Still, with preclinical and clinical studies strongly suggesting that the manipulation of the gut microbiota may reduce the incidence of aseptic loosening and potentially even PJIs, further investigation of probiotic supplementation in this patient population is supported. ■

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