Current Reviews in Musculoskeletal Medicine (2024) 17:37–46
https://doi.org/10.1007/s12178-023-09878-4

The Role of the Gut Microbiome in Orthopedic Surgery—a Narrative Review

David M. Hiltzik[1] · Alyssa M. Goodwin[1] · Steven S. Kurapaty[1,2] · Jacqueline E. Inglis[1] · Manasa S. Pagadala[1] · Adam I. Edelstein[1] · Wellington K. Hsu[1]

Accepted: 7 December 2023 / Published online: 22 December 2023

Abstract

Purpose of Review The importance of the gut microbiome has received increasing attention in recent years. New literature has revealed significant associations between gut health and various orthopedic disorders, as well as the potential for interventions targeting the gut microbiome to prevent disease and improve musculoskeletal outcomes. We provide a broad overview of available literature discussing the links between the gut microbiome and pathogenesis and management of orthopedic disorders.

Recent Findings Human and animal models have characterized the associations between gut microbiome dysregulation and diseases of the joints, spine, nerves, and muscle, as well as the physiology of bone formation and fracture healing. Interventions such as probiotic supplementation and fecal transplant have shown some promise in ameliorating the symptoms or slowing the progression of these disorders.

Summary We aim to aid discussions regarding optimization of patient outcomes in the field of orthopedic surgery by providing a narrative review of the available evidence-based literature involving gut microbiome dysregulation and its effects on orthopedic disease. In general, we believe that the gut microbiome is a viable target for interventions that can augment current management models and lead to significantly improved outcomes for patients under the care of orthopedic surgeons.

Keywords Gut microbiome · Dysbiosis · Gut flora · Commensal bacteria · Orthopedic surgery · Osteoarthritis · Osteoporosis · Osteomyelitis · Fracture healing · Degenerative disc disease · Spinal cord injury · Athletics · Probiotic

Introduction

The gut microbiome refers to the populations of bacteria found within the human intestine. Normally, the gut microbiome consists primarily of the phyla *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*, with *Firmicutes* and *Bacteroidetes* comprising about 90% of all gut bacteria [1]. The phylum *Firmicutes* includes a number of species that produce butyrate, a short-chain fatty acid (SCFA) that acts as a fermentable energy source in the colon. Butyrate has been shown to be crucial for gut homeostasis by way of immune system regulation, mucosal barrier improvement, reductions in oxidative stress, and anti-carcinogenic properties [2]. Other symbiotic gut flora include the genera *Lactobacillus* and *Bifidobacterium*, which are known to have antimicrobial, antioxidant, and anti-carcinogenic influence upon the enteric system [3, 4].

Dysbiosis, or gut microbiome dysregulation, describes a reduction in these beneficial flora and/or proliferation of strains that pose dangers to host health. Dysbiosis is a well-established risk factor for disorders such as diabetes, obesity, and inflammatory bowel disease [5–8], and recent literature has described complex consequences of dysbiosis beyond the enteric system such as the gut-liver-muscle axis [9]. These interactions are multifactorial, but one widely accepted model purports that alterations in the gut microbiome can compromise mucosal defenses and increase intestinal permeability, resulting in a higher degree of bacterial translocation into the blood and chronic increases in systemic inflammation [10]. Chronic inflammation alone has been shown to play a role in the pathogenesis

✉ Manasa S. Pagadala
Manasa.pagadala@northwestern.edu

[1] Department of Orthopaedic Surgery, Northwestern University, 303 E Chicago Ave, Chicago, IL 60622, USA

[2] Department of Orthopaedic Surgery, Howard University, Washington, DC, USA

and progression of a variety of problems within the field of orthopedic surgery, often involving age-related changes (or "inflammaging") [11]. While dysbiosis is associated with advanced age [11], the gut microbiome itself is emerging as an independent contributor to orthopedic disease processes, regardless of patient age.

The gut microbiome can be altered in various ways including diet changes and oral antibiotic use. Common supplements for gut health include "probiotics"—live cultures of beneficial flora—and "prebiotics" that stimulate proliferation of these flora. Fecal microbial transplantation (FMT), another potential intervention, involves stool transfer from a healthy donor and has been associated with significant benefits in IBD, diabetes, allergic diseases, neurological diseases, and obesity [12, 13].

As the gut microbiome is modifiable, it may represent a target for new interventions to augment the management of orthopedic conditions. The purpose of this review is to examine the relationship between dysbiosis and the development of various orthopedic disease processes, and discuss existing evidence for the effectiveness of the gut microbiome as a target for intervention.

Osteoarthritis

The associations between the gut microbiome and development or progression of osteoarthritis (OA) have been extensively studied, with some experts proposing that joint damage and an adverse gut microbiome constitute a "two-hit" model of OA [14]. Meniscus or ligament destabilizing procedures in animal models to induce knee OA have demonstrated significant associations between particular gut microbes and severity of OA [14, 15]. Collins et al. utilized this animal model divided into groups that received a high-fat diet with or without fat transplantation compared to healthy controls. In fecal sample analysis, they identified nine bacterial genera significantly associated with severity of cartilage damage, independent of diet or adiposity. These findings included two genera, *Rikenella* and *Kingella*, which were associated with a protective effect [15]. OA severity has also been directly correlated with *Fusobacterium* and *Faecalibacterium* abundance, and inversely correlated with *Ruminococcaceae* [14]. Furthermore, when mice received FMT from humans with OA and metabolic syndrome, Huang et al. found that these mice developed significantly worse OA following knee destabilization compared to those who received FMT from healthy humans. However, no difference was found between mice with FMT from OA patients without metabolic syndrome and those with FMT from healthy humans [14]. Nevertheless, this indicates that OA in humans, especially in the setting of metabolic syndrome, is tightly associated with changes in the gut microbiome that can further exacerbate OA.

Other studies in human subjects further support these associations. Holub et al. found that significant levels of peptidoglycan, a bacterial cell wall component, can be seen in synovial fluid in 59% of individuals with a history of total knee arthroplasty (TKA) without history of joint infection. Notably, there was an inverse correlation between peptidoglycan levels and age at time of TKA, indicating a potential relationship between dysbiosis (resulting in impaired intestinal barrier integrity and increased bacterial translocation into the bloodstream) and early development or rapid progression of OA [16]. A large retrospective study ($n = 1388$) by Wei et al. demonstrated that these associations are not limited to OA of weight-bearing joints. Beta diversity, a measure of similarity between microbial populations of two separate samples, was found to correlate with symptomatic OA of the hand, indicating that atypical composition of the gut microbiome is associated with poorer functional outcomes. The study also identified *Bilophila* and *Desulfovibrio* as correlates with symptomatic hand OA, and a protective effect associated with *Roseburia* [17].

Multiple large systematic reviews have likewise concluded that dysbiosis influences OA, generally via increased systemic inflammation as a result of increased intestinal permeability. One such review of 37 studies by Bonato et al. determined that *Clostridium*, *Streptococcus*, *Bacteroides*, and *Firmicutes* were frequently reported to be more abundant in OA patients [18]. However, another systematic review noted that the results of composition analysis were not consistent among the included studies, attributing the differences to the vast variability in factors that influence gut microbiome composition such as geography and genetics [19•]. This conclusion is supported by findings in this review—for example, *Roseburia* is rarely discussed in literature originating in the USA but appears to be common in China, Japan, Turkey, and Ireland [17, 20, 21]. This indicates that data regarding specific gut microbes implicated in dysbiosis may have limited generalizability across individuals and populations.

Both human and animal research provide evidence for the gut microbiome as a viable target for intervention in the management of OA. In the aforementioned systematic review by Bonato et al., *Lactobacillus* and *Bifidobacterium* were associated with more favorable outcomes in the literature [18]. Both are commercially available in over-the-counter probiotic supplements, representing an accessible potential augment in the management of OA. The mechanism of *Lactobacillus* effect on OA was characterized in an animal model by Cho et al., who demonstrated that the supplement reduced inflammation and cartilage damage in rat joints. The study elucidates that *Lactobacillus* administration increased the abundance of *Faecalibacterium*, a

member of the *Firmicutes* phylum that produces SCFAs including butyrate. The authors found that these SCFAs, in addition to known systemic anti-inflammatory effects, also regulate autophagy as a response to impending necroptosis, a form of aberrant cell death [22]. This implies that modification of the gut microbiome with *Lactobacillus* can effectively reduce inflammatory cell death that contributes to worsening OA.

Broadly, the gut microbiome is implicated in the OA disease process; however, variable gut composition limits direct correlation of specific bacterial species with OA development. Furthermore, the exact mechanisms by which gut dysbiosis leads to OA remain to be elucidated.

Osteoporosis

Osteoporosis and osteopenia are particularly well-associated with changes in the gut microbiome. Das et al. used statistical models to identify six genera that were significantly altered in abundance in osteoporotic or osteopenic groups compared to age- and gender-matched controls, and these findings are supported by those of He et al. who described a number of significant differences in bacterial community structure among postmenopausal patients with and without osteoporosis [20–23]. Li et al. further explored this idea by comparing operational taxonomic units (OTUs, a measure of diversity describing the number of populations with discrete taxonomy), taxa with altered abundance, and specific functional pathways in low bone mass density (BMD) patients of the elderly Chinese population. The low-BMD individuals had a smaller number of OTUs and bacterial taxa at each level. Functional prediction on fecal microbiota revealed that 93 metabolic pathways significantly differed between the two groups (FDR-corrected $p < 0.05$). Most pathways, especially pathways related to LPS biosynthesis, were more abundant in low-BMD individuals than in healthy subjects, which indicates an association between endotoxin production in the gut and reduction in BMD [24]. Wang et al. explored beta diversity of microbiota and found it to be increased in the osteoporosis and osteopenia groups compared with healthy controls, indicating that individuals with gut microbiome composition that differs significantly from typical composition may be more predisposed to bone loss [25]. Overall, strong evidence exists in human models of a relationship between the microbiome and osteoporosis.

Many of these findings have been explored and supported by experiments with animal models. Using ovariectomized rats as a postmenopausal model, Ma et al. demonstrated that the number of taxonomically discrete microorganisms significantly increased in ovariectomized rats compared to controls. In particular, *Ruminococcus flavefaciens* was highly varied in abundance and was associated with histomorphometry findings consistent with osteoporosis, as well as osteoclastic indicators such as collagen I carboxy-terminal peptide [26]. In another study, the same group compared the gut microbiota of an aged rat model to that of adult controls, and found that the taxonomy of microbiota in aged animals with bone histomorphometry consistent with osteoporosis differed significantly from controls. At the genus level, *Helicobacter* emerged as the bacterium most tightly associated with osteoporosis [27]. These findings indicate that both senile osteoporosis and postmenopausal (i.e., steroid-deficiency-induced) osteoporosis are associated with gut flora alterations in rats, as well as a potential role of gut biomarkers to assess bone health.

One such biomarker that has received attention in the literature is the ratio of *Firmicutes*-to-*Bacteroidetes* (F/B ratio) at the phylum level, with a low F/B ratio representing a specific indicator for osteoporosis [28]. *Firmicutes* encompasses many butyrate-producing species, and animal models have demonstrated that *Firmicutes* and *Bacteroidetes* have opposite effects on the regulation of glutathione synthesis, osteoclast differentiation, and mitochondrial biogenesis [28]. This is supported by the findings of Li et al., who examined fecal samples from 102 male and female adults over the age of 60 and found that BMD and T-score were positively correlated with *Firmicutes* and *Actinobacteria* and negatively correlated with *Bacteroidetes* in all subjects [24]. Ozaki et al. similarly examined dominant strains in the gut microbiota of postmenopausal women and found significantly increased populations of the family *Rikenellaceae* (phylum *Bacteroidetes*) in subjects with low bone mineral density. However, the same study found a 5.6 relative risk for fracture associated with low *Bacteroides*, a genus of *Bacteroidetes*, in the gut microbiome ($P = 0.0049$) [29]. Thus, the utility of high F/B ratio as a general correlate to bone health may be limited, as the effects of individual families or genera within these phyla are complex. Nevertheless, these findings indicate that the negative influence of gut health on BMD may have significant consequences on patient morbidity.

There is also evidence that microbiome composition can be reciprocally influenced by changes in bone metabolism. Zhou et al. demonstrated that intermittent parathyroid hormone administration, in addition to its benefits on bone mineral density, improved diversity and complexity in the gut microbiota of ovariectomized rats [30]. The intervention increased populations of bacteria associated with higher bone mineral density such as *Lactobacillus*, *Muribaculaceae*, *Ruminococcaceae*, and *Clostridia*, and reduced populations of *Rikenellaceae* which was shown in the aforementioned study by Ozaki et al. to be strongly associated with osteoporosis in elderly humans [29, 30]. Of note, *Lactobacillus*, *Ruminococcaceae*, and *Clostridia* belong to the *Firmicutes* phylum and *Rikenellaceae* to the *Bacteroidetes* phylum; thus, these findings largely support the concept of

F/B ratio as a biomarker for osteoporosis. These reports indicate strong feedback and feedforward effects in the association between dysbiosis and osteoporosis.

Human and animal data have demonstrated promising evidence for the utility of gut interventions on bone mineral density. Ma et al. showed that fecal microbiota transplantation from young subjects can ameliorate bone loss in an aged rat model [31]. In a postmenopausal rat model, Yuan et al. similarly demonstrated that supplementation of animals with *Firmicutes* probiotics prevented the development of osteoporosis, and germ-free mice did not develop osteoporosis in response to ovariectomy [28]. Various randomized clinical trials have been performed in humans as well: A meta-analysis of 5 such trials ($n = 497$) concluded that probiotic supplementation was associated with significantly higher BMD in the lumbar spine, although other metrics (BMD in hips, collagen I C-terminal peptide, ALP, OPG, osteocalcin, and TNF) showed no differences [32••].

Frailty and Sarcopenia

Existing literature has demonstrated a complex link between gut health and muscle mass. Bacterial endotoxins (e.g., LPS) and various proinflammatory cytokines (e.g., TNF-a, IL-1B, IL-6, TWEAK) have been shown to induce muscle atrophy, and it is well-known that dysbiosis can lead to increased systemic circulation of these factors [33, 34]. It has been demonstrated that abundance of beneficial gut flora such as *Bifidobacterium*, which is associated with lower circulating LPS levels, decreases with age [11]. van Tongeren et al. demonstrated significant reductions in *Lactobacilli*, *Bacteroides*, *Prevotella*, and *Faecalibacterium* and significant increases in *Ruminococcus*, *Atopobium*, and *Enterobacteriaceae* specifically in elderly individuals with high frailty scores [35].

However, the associations between sarcopenia and dysbiosis are not limited to age-related changes. In a 2014 case-control study, Ponziani et al. examined the role of microbiota in patients with sarcopenia with and without cirrhosis [9]. The gut microbiome of sarcopenic patients showed reduced populations of *Methanobrevibacter*, *Prevotella*, and *Akkermansia*, all of which are associated with robust physical function [35, 36], and increased populations of *Eggerthella*, which has been associated with frailty [37]. These findings were independent of the presence of cirrhosis, indicating a stronger association with sarcopenia than cirrhosis. Sarcopenic subjects without cirrhosis also demonstrated a statistically significant difference in calprotectin and ZO1 (indirect markers of intestinal barrier integrity) compared to healthy controls, while this difference was not found within the cirrhosis patients. This indicates a specific association between sarcopenia and dysbiosis in noncirrhotic patients. The authors also reported correlations between gut flora and features of sarcopenia including independent associations between poor handgrip strength, increases in ethanol-producing bacteria (e.g., *Klebsiella*), and decreases in bacteria involved in ethanol clearance (e.g., *Prevotella*) [9]. This represents evidence for the importance of the gut-liver-muscle axis, as ethanol in the digestive tract is known to contribute to protein catabolism and muscle autophagy in liver disease [38].

Sarcopenic patients have also been shown to exhibit compensatory mechanisms involving the gut microbiome. This includes upregulation of populations of various bacterial species that produce antioxidants, branched chain amino acids, and intermediates of glycolysis/gluconeogenesis and other metabolic pathways (e.g., xylose and arabinose). These metabolites are theorized to counteract sarcopenia, maintain muscle homeostasis, and protect against consequences of increased muscle wasting by scavenging ammonia produced by protein catabolism in the setting of advanced liver disease. In particular, butyrate-producing bacteria such as *Ruminococcus* and *Oscillospira* are often found to be abundant in individuals with sarcopenia [9].

Data regarding the potential benefit of gut flora interventions on sarcopenia are limited. However, increases in muscle mass have been demonstrated after *Lactobacillus* probiotic supplementation in healthy adults [39••]. Additionally, a randomized controlled trial demonstrated that daily supplementation with the *Bifidobacterium*-associated prebiotics inulin and fructooligosaccharide resulted in significantly reduced frailty index scores in nursing home residents at 13-week follow-up [40••]. Other interventions on diet and exercise, known to improve functional status in sarcopenic patients, have also been shown to have a beneficial effect on gut microbiome composition [41•]. However, a notable caveat described in the BIOSPHERE study by Picca et al. is that high-protein diets, often recommended for sarcopenic patients, may ultimately have a detrimental effect on amino acid absorption by upregulating protein consumption by gut flora [41•].

Overall, sarcopenia is related to dysregulation of intestinal composition through age-related changes as well as a complex gut-liver-muscle axis. Further research is warranted to examine and optimize treatments targeting gut health to improve sarcopenic symptoms.

Osteomyelitis and Periprosthetic Joint Infection

Numerous reports have demonstrated a link between dysbiosis and infection susceptibility in humans [42, 43], as well as risk factors associated with periprosthetic joint infection (PJI) such as diabetes [44], obesity [45], inflammatory

arthritis [46], and anemia associated with malnutrition [47]. While the nature of the gut microbiome's influence on host health is complex, there is ample evidence that poor gut health increases the risk of developing infections.

While human studies directly investigating the links between dysbiosis and infection of bones and joints are sparse, Chisari et al. confirmed translocation of gut bacteria to the site of PJI in humans undergoing revision arthroplasty. The study also examined markers of intestinal permeability (Zonulin, sCD14) and found increased sCD14 in patients with PJI compared to those with aseptic failure, as well as increased Zonulin in patients found to have gut commensal species present at the site of PJI [48]. These findings support a direct link between dysbiosis and risk of remote infections. The authors went on to describe a proposed mechanism for these findings known as the "Trojan Horse" theory, which hypothesizes that virulent microbes in the gut can cause remote infections by traveling intracellularly in neutrophils and macrophages [48].

Animal models have also demonstrated these associations. Hernandez et al. created a compromised microbiome in a mouse model by chronic oral antibiotic use and revealed increased risk of developing PJI as well as a reduced local and systemic response. Mice underwent arthroplasty with a titanium proximal tibial component and concurrently received an intra-articular inoculation of methicillin-sensitive *Staphylococcus aureus*. The dysbiosis group developed PJI in 29 subjects (72.5%) compared to 21 (50%) in the control group ($P = 0.03$). The dysbiosis group was also shown to have significantly lower levels of serum amyloid A (a mouse equivalent of CRP), which represents an association between dysbiosis and impaired generation of acute phase reactants in response to immune threat. Flow cytometry performed on splenic samples and ipsilateral popliteal lymph nodes demonstrated no increase in local or systemic neutrophils, monocytes, or T cells in the dysbiotic subjects with PJI, indicating that dysbiosis contributes to impaired or delayed systemic immune response. Of note, 14 of the animals in the study died prematurely, of which 13 belonged to the dysbiosis group [49].

Since then, other animal models have further elucidated the impact of microbiome alterations secondary to chronic antibiotic use on perioperative complications. Zhao et al. utilized an animal model of chronic osteomyelitis to demonstrate that mice with dysbiosis had poorer survival and higher intraosseous bacterial loads than those with normal gut flora. Subjects received an intramedullary injection of *Staphylococcus aureus* after 5 weeks of oral antibiotics to induce dysbiosis. Survival rate at 30 days was 70% for the dysbiosis group and 90% for the control ($P = 0.002$) [50]. This is evidence that given identical perioperative infections, individuals with dysregulated gut flora may suffer significantly poorer outcomes.

Bone Formation and Fracture Healing

Numerous studies have explored the complex role of the microbiome in fracture healing and bone growth, with implications that the relationship may be reciprocal. Carson et al. examined the effects of the antibiotic minocycline on skeletal maturation. As minocycline is commonly used in adolescents for the treatment of acne, this study focused on pubertal and postpubertal skeletal maturation in mice. Specific pathogen-free mice exposed to minocycline demonstrated gut microbiome shifts, with reductions in *Actinomycetota* and *Bacteroidota*, and disruption to gut-liver endocrine homeostasis. Osteoblast function was consequently suppressed via antagonism of farnesoid X receptors in bone marrow by conjugated serum bile acids. The study also concluded that upregulation of serum bile acids dysregulates bone microarchitecture and fracture resistance [51].

In addition to skeletal maturation, alterations in gut flora also have a complex effect on both growth and repair. Luna et al. examined the effect of various antibiotics on bone properties such as mechanical strength in a mouse model. Whole bone strength, determined by bone geometry and tissue strength, was decreased by 28% ($P = 0.002$) in the group receiving neomycin, and increased by 39% ($P < 0.001$) in the group given artificial sweetener without antibiotics. Corresponding with these findings, microbiome fecal analysis of the neomycin group demonstrated differences in 7 taxonomic features; conversely, fecal analysis in those with greater bone strength showed a differential abundance of 14 taxonomic features [52]. It should be noted that neomycin in particular is a common choice in animal models of antibiotic-induced dysbiosis, as it has a profound effect on intestinal flora and poor oral bioavailability, which largely limits the effects to the enteric system [49]. Taken together, this evidence strongly suggests that changes in the gut microbiome have major influences on bone formation, remodeling, and healing. The differences in bone strength based on various microbiome models further highlight the complexity of this relationship [52].

These effects have also been demonstrated in the setting of implant osseointegration. The mouse study by Zhao et al. discussed in the previous section also included a group receiving an intramedullary implant with and without antibiotic-induced dysbiosis. The dysbiosis group demonstrated delayed osseointegration of the implant, lower bone mineral density, deficient endochondral ossification and bone formation, reduced osteoblastogenesis, and enhanced osteoclastogenesis. This suggests that gut microbial dysregulation, particularly in the setting of oral antibiotic use, may interfere with successful orthopedic instrumentation [50].

It has thus been demonstrated that the microbiome has an effect on bone healing and health, but there is also

evidence to suggest the reciprocal relationship—how bone healing impacts the gut microbiome. A 2023 study utilized a mouse model to examine the role of yδ and Th17 cells, both of which are producers of IL-17A which plays a major role in inflammation during fracture repair. As Th17 cells are induced by gut segmented filamentous bacteria (SFB), the study utilized two groups: one lacking gut segmented filamentous bacteria (SFB−) and one containing gut segmented filamentous bacteria (SFB+). After confirming higher Th17 levels in the SFB+ group, a subset of both groups received antibiotics to induce dysbiosis and subjects then underwent bone fracture. SFB+ mice that did not receive antibiotics were found to have significantly greater increases in IL-17A, TNF, IL-1B, and IL-6 levels in the gut as well as the fracture callus when compared to the dysbiosis group. The SFB− mice demonstrated only small increases in TNF and IL-1B, regardless of antibiotic-induced dysbiosis [53]. This study demonstrates that fracture activates yδ T cells in the callus; these cells increase systemic inflammation causing increases in gut permeability. The study delineated that this both increases Th17 dependence on the microbiome and increases migration of Th17 T cells to the callus to contribute to cytokine production and fracture healing [53].

Largely, studies have built microbiome models and explored bone changes at the immunologic level. Moran et al. further examined how the phenomenon of orthopedic implant loosening affects the gut microbiome. This study utilized a rat model injected with sterile particles or cobalt-chrome particles after placement of bilateral titanium femoral intramedullary rods to simulate the particulate model of aseptic loosening. In rats that demonstrated loosening of the implant, the gut microbiome was also altered: For both types of particles, the *Firmicutes*-to-*Bacteroidetes* (F/B) ratio was significantly increased compared to naïve rats [54]. This supports the concept that implant loosening affects the gut microbiome, demonstrating a bidirectional interplay in the gut-bone axis.

Regarding bone formation and healing, animal models have largely been examined to understand the impact of dysbiosis on skeletal maturation along with growth and repair with fewer studies studying the reciprocal relationship—the impact of fracture repair on animal models simulating dysbiosis.

Degenerative Disc Disease

The existence of a gut-disc axis has also been described in recent literature. Yao et al. studied a rat model who underwent a disc injury and then received FMT from healthy rats. Their results showed reduced cartilage tissue damage and a greater degree of order and regularity in cellular arrangement on histopathological analysis of intervertebral disc tissue in the FMT group compared to the no-FMT group. Immunohistochemical analysis of both serum and intervertebral disc tissue revealed reduced markers of inflammation (TNF-a, IL-1B, and IL-6), extracellular matrix catabolism (MMP-3 and MMP-13), and inflammation-regulated cell death (NLRP3 and Caspase-1) in the animals with disc damage who had received FMT compared to those who did not [55]. This indicates that the gut microbiome has a significant effect on inflammatory damage to the intervertebral disc following trauma.

In humans, there is evidence for various mechanisms by which dysbiosis affects disc health [56]. Rajasekaran et al. challenged the notion of sterility in healthy discs by demonstrating a unique microbiome in both healthy and diseased intervertebral discs. By comparing 16SrRNA sequencing from disc specimens to established human gut and skin microbiomes, they found 58 bacteria in common between disc and gut, and 29 between disc and skin. Furthermore, gut bacteria known to be beneficial (e.g., *Lactobacillus*) were significantly more abundant in healthy discs ($P = 0.022$), indicating a correlation between gut health and disc health [57].

Other mechanisms in the gut-disc axis have been proposed, but are largely speculative due to the lack of available literature examining these effects directly. However, it is known that the presence of bacteria in intervertebral discs results in immune system and blood vessel infiltration into normally anaerobic tissue [56]. In addition to accelerating disc degeneration, inflammation within the disc has been shown to upregulate neurogenic factors such as brain-derived neurotrophic factor and nerve growth factor, resulting in the generation of nociceptive nerve fibers and pain-associated cation channels that contribute to perceived low back pain [58]. Thus, an altered gut microbiome resulting in increased microbial presence in the systemic circulation may aggravate intervertebral disc disease and result in more dramatic symptoms.

Nerve and Spinal Cord Injury

Spinal cord injury (SCI) is associated with disrupted innervation to organs and systems below the level of injury, and this can impact the gut flora [21]. Imbalances in autonomic tone after loss of sympathetic input from the brainstem and spinal cord can affect gut motility, secretions, vascular tone, and immune function, which all contribute to gut microbiome dysregulation. Since sympathetic spinal nerves innervate gastrointestinal-associated lymphoid tissue (GALT), SCI leads to impaired immune function [59].

It has been demonstrated that the superior cervical ganglion, an important component of the sympathetic nervous

system, plays a particularly important role in the gut microbiome. Zhang et al. examined the effects on the gut microbiome in the setting of bilateral superior cervical ganglionectomy (SCGx) in a rat model to mimic SCI. Fecal samples were taken at 7 and 14 days, and there were significant differences across 11 gut bacteria in the SCGx group compared to the control group [60]. This illustrates the complex relationship between the sympathetic nervous system and the gut microbiome.

Valido et al. examined changes in the microbiome and its relation to spinal cord injury (SCI) in both animal and human models in a review of 19 studies. Across these studies, they observed a consistent and statistically significant difference in the gut microbiome for those with SCI compared to those without. In animals and people with SCI, there was a notable decrease in butyrate-producing bacteria such as *Roseburia*, *Faecalibacterium*, and *Megamonas*. Additionally, they noted an increase in *Anaerotruncus*, *Lachnoclostridium*, and *Alistipes* in SCI groups [21]. These bacteria have a close association with obesity and metabolic disorders, likely due to limited physical activity in those with SCI, and are associated with systemic inflammation. A similar pattern of gut changes is also associated with mood symptoms, anxiety, and greater infection susceptibility [21–31, 32••, 33–38, 39••, 40••, 41•, 42–59]—Schmidt et al. demonstrated significant reduction in anxiety-like behavior in rats with SCI who received FMT [61].

It has also been demonstrated that these changes in gut microbiota are temporal in nature following SCI. Doelman et al. examined changes in gut microbiota after SCI both acutely (0–14 days) and subacutely (> 14 days) in a porcine model. When comparing the two time periods, there was a significant difference across four of the 10 phyla including *Firmicutes*, *Spirochaetes*, *Tenericutes*, and *Fibrobacteres*. Among those groups, *Spirochaetes* demonstrated an increase in abundance that was significant between the two timepoints and also significantly greater than the control group without SCI [62]. This illustrates the complexity of the effects of SCI on gut microbiome with continued changes longitudinally after injury.

In addition to the direct effect of SCI on gut microbiota, there is also evidence that improving gut health can affect outcomes after neuronal injury. Rodenhouse et al. studied the relationship between probiotic use and traumatic peripheral nerve injury (TPNI) recovery in a mouse model of antibiotic-induced dysbiosis, and found that subjects without probiotics had poorer functional recovery after TPNI. Conversely, the administration of butyrate-rich probiotics prior to injury greatly improved functional recovery, independent of induced dysbiosis. Additionally, the administration of pre-injury or post-injury probiotics was shown to mitigate the effects of pre-injury antibiotic-induced dysbiosis [63]. These findings demonstrate the importance of the gut microbiome when it comes to nerve injury recovery and the detrimental effects antibiotics can have if administered without preserving the gut microbiome. As this study did not explore these effects longitudinally, there may be an avenue for this research in the future.

He et al. sought to determine whether the gut microbiome could be restored in SCI patients, with the hope of improving prognosis. The study utilized a mouse model and resveratrol, a suppressor of microglial activation known to have anti-oxidative, anti-inflammatory, anti-bacterial, and anti-neurodegenerative properties. The results indicated that while untreated mice displayed a greater abundance of *Clostridiales* and a decrease in *Erysipelotrichales* in the gut following SCI, these effects were reversed after the administration of resveratrol. This corresponded with an increase in butyrate-producing bacteria, indicating that the medication affected gut microbiome composition in addition to other neurological benefits. Furthermore, to confirm the relationship between microbiome and improved neurological function, a fecal transplant test was performed that demonstrated improved function in the recipient rats [64].

These studies indicate that gut microbiome composition is strongly associated with neurological recovery, and is a viable target for interventions to improve outcomes in patients with SCI.

Conclusion

This review demonstrates the potential effect of the gut microbiome on musculoskeletal disease. There is substantial evidence for feedback and feedforward mechanisms between the gut microbiome and the bones, joints, tendons, nerves, and muscles, largely involving the interplay of intestinal barrier permeability and systemic inflammation. A number of microbes in particular have been implicated in the literature, although these findings are not consistent across individuals and populations owing to a high degree of variability by individual and geographic region. There is evidence that interventions targeting the gut microbiome, such as probiotic supplementation and FMT, can slow the progression or ameliorate the effects of some orthopedic problems.

This review has a number of limitations: Many of the results are limited to animal studies, which may not translate clinically to humans. Many studies describe associations and may not indicate causal relationships between the microbiome and orthopedic outcomes in all cases. Additionally, interactions between the gut ecosystem and host health are highly multifactorial, and unknown confounding variables may have influenced our conclusions. Further research is needed to explore the potential benefits of gut microbiome interventions and to more fully characterize the role of gut

flora in the pathogenesis and progression of disease in the spine and extremities.

Author Contributions DH, AG, JI, and MP did the manuscript research and writing. DH, AE, and WH edited the manuscript. SK and WH generated the idea for the manuscript. MP and DH prepared the manuscript for submission. All authors reviewed the manuscript.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Competing Interests Dr. Wellington Hsu is an advisory board member of Stryker, Medtronic, Asahi, and Bioventus. Dr. Adam Edelstein is a consultant for Depuy and Corin; he is also on the Editorial Board of Arthroplasty Today and serves on the AAHKS Publications Committee.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kong G, Zhang W, Zhang S, et al. The gut microbiota and metabolite profiles are altered in patients with spinal cord injury. Mol Brain 2023;16(1):26. https://doi.org/10.1186/s13041-023-01014-0 [published Online First: 20230220].
2. Singh V, Lee G, Son H, et al. Butyrate producers, "the sentinel of gut": their intestinal significance with and beyond butyrate, and prospective use as microbial therapeutics. Front Microbiol. 2022;13:1103836. https://doi.org/10.3389/fmicb.2022.1103836[publishedOnlineFirst:20230112].
3. Abdelhamid AG, El-Masry SS, El-Dougdoug NK. Probiotic Lactobacillus and Bifidobacterium strains possess safety characteristics, antiviral activities and host adherence factors revealed by genome mining. Epma j 2019;10(4):337-50. https://doi.org/10.1007/s13167-019-00184-z [published Online First: 20190905].
4. Nowak A, Paliwoda A, Błasiak J. Anti-proliferative, pro-apoptotic and anti-oxidative activity of Lactobacillus and Bifidobacterium strains: a review of mechanisms and therapeutic perspectives. Crit Rev Food Sci Nutr 2019;59(21):3456-67. https://doi.org/10.1080/10408398.2018.1494539 [published Online First: 20181016].
5. Sampaio-Maia B, Simões-Silva L, Pestana M, Araujo R, Soares-Silva IJ. The role of the gut microbiome on chronic kidney disease. Adv Appl Microbiol 2016;96:65-94. https://doi.org/10.1016/bs.aambs.2016.06.002 [published Online First: 20160718].
6. Paun A, Danska JS. Modulation of type 1 and type 2 diabetes risk by the intestinal microbiome. Pediatr Diabetes 2016;17(7):469-77. https://doi.org/10.1111/pedi.12424 [published Online First: 20160803].
7. Burcelin R. Gut microbiota and immune crosstalk in metabolic disease. Mol Metab 2016;5(9):771-81. https://doi.org/10.1016/j.molmet.2016.05.016 [published Online First: 20160606].
8. Jostins L, Ripke S, Weersma RK, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012;491(7422):119–24. https://doi.org/10.1038/nature11582.
9. Ponziani FR, Picca A, Marzetti E, et al. Characterization of the gut-liver-muscle axis in cirrhotic patients with sarcopenia. Liver Int 2021;41(6):1320-34. https://doi.org/10.1111/liv.14876 [published Online First: 20210325].
10. Guan Z, Luo L, Liu S, et al. The role of depletion of gut microbiota in osteoporosis and osteoarthritis: a narrative review. Front Endocrinol (Lausanne) 2022;13:847401. https://doi.org/10.3389/fendo.2022.847401 [published Online First: 20220328].
11. Picca A, Fanelli F, Calvani R, et al. Gut dysbiosis and muscle aging: searching for novel targets against sarcopenia. Mediators Inflamm 2018;2018:7026198. https://doi.org/10.1155/2018/7026198 [published Online First: 20180130].
12. Wei Y, Zhu W, Gong J, et al. Fecal microbiota transplantation improves the quality of life in patients with inflammatory bowel disease. Gastroenterol Res Pract 2015;2015:517597. https://doi.org/10.1155/2015/517597 [published Online First: 20150604].
13. Vaughn BP, Vatanen T, Allegretti JR, et al. Increased intestinal microbial diversity following fecal microbiota transplant for active Crohn's disease. Inflamm Bowel Dis. 2016;22(9):2182–90. https://doi.org/10.1097/mib.0000000000000893.
14. Huang Z, Chen J, Li B, et al. Faecal microbiota transplantation from metabolically compromised human donors accelerates osteoarthritis in mice. Ann Rheum Dis 2020;79(5):646-56. https://doi.org/10.1136/annrheumdis-2019-216471 [published Online First: 20200323].
15. Collins KH, Schwartz DJ, Lenz KL, Harris CA, Guilak F. Taxonomic changes in the gut microbiota are associated with cartilage damage independent of adiposity, high fat diet, and joint injury. Sci Rep. 2021;11(1):14560. https://doi.org/10.1038/s41598-021-94125-4.
16. Holub MN, Wahhab A, Rouse JR, et al. Peptidoglycan in osteoarthritis synovial tissue is associated with joint inflammation. Res Sq 2023. https://doi.org/10.21203/rs.3.rs-2842385/v1 [published Online First: 20230428].
17. Wei J, Zhang C, Zhang Y, et al. Association between gut microbiota and symptomatic hand osteoarthritis: data from the Xiangya Osteoarthritis Study. Arthritis Rheumatol 2021;73(9):1656-62. https://doi.org/10.1002/art.41729 [published Online First: 20210806].
18. Bonato A, Zenobi-Wong M, Barreto G, Huang Z. A systematic review of microbiome composition in osteoarthritis subjects. Osteoarthritis Cartilage 2022;30(6):786-801. https://doi.org/10.1016/j.joca.2021.12.006 [published Online First: 20211225]
19. • Liu S, Li G, Xu H, et al. "Cross-talk" between gut microbiome dysbiosis and osteoarthritis progression: a systematic review. Front Immunol 2023;14:1150572. https://doi.org/10.3389/fimmu.2023.1150572 [published Online First: 20230425]. **This paper is of importance because it establishes that gut microbiome composition may not be generalizable across population.**
20. Das M, Cronin O, Keohane DM, et al. Gut microbiota alterations associated with reduced bone mineral density in older adults. Rheumatology (Oxford). 2019;58(12):2295–304. https://doi.org/10.1093/rheumatology/kez302.
21. Valido E, Bertolo A, Fränkl GP, et al. Systematic review of the changes in the microbiome following spinal cord injury: animal and human evidence. Spinal Cord. 2022;60(4):288–300. https://doi.org/10.1038/s41393-021-00737-y.

22. Cho KH, Na HS, Jhun J, et al. Lactobacillus (LA-1) and butyrate inhibit osteoarthritis by controlling autophagy and inflammatory cell death of chondrocytes. Front Immunol 2022;13:930511. https://doi.org/10.3389/fimmu.2022.930511 [published Online First: 20221017].
23. He J, Xu S, Zhang B, et al. Gut microbiota and metabolite alterations associated with reduced bone mineral density or bone metabolic indexes in postmenopausal osteoporosis. Aging (Albany NY) 2020;12(9):8583-604. https://doi.org/10.18632/aging.103168 [published Online First: 20200511].
24. Li C, Huang Q, Yang R, et al. Gut microbiota composition and bone mineral loss-epidemiologic evidence from individuals in Wuhan, China. Osteoporos Int 2019;30(5):1003-13. https://doi.org/10.1007/s00198-019-04855-5 [published Online First: 20190121].
25. Wang J, Wang Y, Gao W, et al. Diversity analysis of gut microbiota in osteoporosis and osteopenia patients. PeerJ 2017;5:e3450. https://doi.org/10.7717/peerj.3450 [published Online First: 20170615].
26. Ma S, Qin J, Hao Y, Shi Y, Fu L. Structural and functional changes of gut microbiota in ovariectomized rats and their correlations with altered bone mass. Aging (Albany NY) 2020;12(11):10736-53. https://doi.org/10.18632/aging.103290 [published Online First: 20200602].
27. Ma S, Qin J, Hao Y, Fu L. Association of gut microbiota composition and function with an aged rat model of senile osteoporosis using 16S rRNA and metagenomic sequencing analysis. Aging (Albany NY) 2020;12(11):10795-808. https://doi.org/10.18632/aging.103293 [published Online First: 20200602].
28. Yuan Y, Yang J, Zhuge A, Li L, Ni S. Gut microbiota modulates osteoclast glutathione synthesis and mitochondrial biogenesis in mice subjected to ovariectomy. Cell Prolif 2022;55(3):e13194. https://doi.org/10.1111/cpr.13194 [published Online First: 20220126].
29. Ozaki D, Kubota R, Maeno T, Abdelhakim M, Hitosugi N. Association between gut microbiota, bone metabolism, and fracture risk in postmenopausal Japanese women. Osteoporos Int 2021;32(1):145-56. https://doi.org/10.1007/s00198-020-05728-y [published Online First: 20201125].
30. Zhou J, Wang R, Zhao R, et al. Intermittent parathyroid hormone alters gut microbiota in ovariectomized osteoporotic rats. Orthop Surg 2022;14(9):2330-38. https://doi.org/10.1111/os.13419 [published Online First: 20220810].
31. Ma S, Wang N, Zhang P, Wu W, Fu L. Fecal microbiota transplantation mitigates bone loss by improving gut microbiome composition and gut barrier function in aged rats. PeerJ 2021;9:e12293. https://doi.org/10.7717/peerj.12293 [published Online First: 20211021].
32.•• Yu J, Cao G, Yuan S, Luo C, Yu J, Cai M. Probiotic supplements and bone health in postmenopausal women: a meta-analysis of randomised controlled trials. BMJ Open 2021;11(3):e041393. https://doi.org/10.1136/bmjopen-2020-041393 [published Online First: 20210302]. **This paper is of major importance because the meta-analysis of randomized controlled trials provides very high-quality evidence in line with the goals of this review.**
33. Morales MG, Olguín H, Di Capua G, Brandan E, Simon F, Cabello-Verrugio C. Endotoxin-induced skeletal muscle wasting is prevented by angiotensin-(1-7) through a p38 MAPK-dependent mechanism. Clin Sci (Lond) 2015;129(6):461-76. https://doi.org/10.1042/cs20140840 [published Online First: 20150519].
34. Zhou J, Liu B, Liang C, Li Y, Song YH. Cytokine signaling in skeletal muscle wasting. Trends Endocrinol Metab 2016;27(5):335-47. https://doi.org/10.1016/j.tem.2016.03.002 [published Online First: 20160326].
35. van Tongeren SP, Slaets JP, Harmsen HJ, Welling GW. Fecal microbiota composition and frailty. Appl Environ Microbiol. 2005;71(10):6438–42. https://doi.org/10.1128/aem.71.10.6438-6442.2005.
36. Petersen LM, Bautista EJ, Nguyen H, et al. Community characteristics of the gut microbiomes of competitive cyclists. Microbiome 2017;5(1):98. https://doi.org/10.1186/s40168-017-0320-4 [published Online First: 20170810].
37. Jackson MA, Jeffery IB, Beaumont M, et al. Signatures of early frailty in the gut microbiota. Genome Med 2016;8(1):8. https://doi.org/10.1186/s13073-016-0262-7 [published Online First: 20160129].
38. Dasarathy J, McCullough AJ, Dasarathy S. Sarcopenia in alcoholic liver disease: clinical and molecular advances. Alcohol Clin Exp Res 2017;41(8):1419-31. https://doi.org/10.1111/acer.13425 [published Online First: 20170711].
39.•• Huang WC, Lee MC, Lee CC, et al. Effect of Lactobacillus plantarum TWK10 on exercise physiological adaptation, performance, and body composition in healthy humans. Nutrients 2019;11(11). https://doi.org/10.3390/nu11112836 [published Online First: 20191119]. **This paper is of major importance because randomized controlled trials provide high-quality evidence in line with the goals of this review.**
40.•• Theou O, Jayanama K, Fernández-Garrido J, et al. Can a prebiotic formulation reduce frailty levels in older people? J Frailty Aging 2019;8(1):48-52. https://doi.org/10.14283/jfa.2018.39. **This paper is of major importance because randomized controlled trials provide high-quality evidence in line with the goals of this review.**
41.• Picca A, Ponziani FR, Calvani R, et al. Gut microbial, inflammatory and metabolic signatures in older people with physical frailty and sarcopenia: results from the BIOSPHERE study. Nutrients 2019;12(1). https://doi.org/10.3390/nu12010065 [published Online First: 20191226]. **This paper is of importance because it is a large study investigating the associations between the gut microbiome and frailty, with broad implications for the geriatric population.**
42. Khosravi A, Mazmanian SK. Disruption of the gut microbiome as a risk factor for microbial infections. Curr Opin Microbiol 2013;16(2):221-7. https://doi.org/10.1016/j.mib.2013.03.009 [published Online First: 20130415].
43. Khosravi A, Yáñez A, Price JG, et al. Gut microbiota promote hematopoiesis to control bacterial infection. Cell Host Microbe. 2014;15(3):374–81. https://doi.org/10.1016/j.chom.2014.02.006.
44. Chassaing B, Aitken JD, Gewirtz AT, Vijay-Kumar M. Gut microbiota drives metabolic disease in immunologically altered mice. Adv Immunol. 2012;116:93–112. https://doi.org/10.1016/b978-0-12-394300-2.00003-x.
45. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature. 2006;444(7122):1027–31. https://doi.org/10.1038/nature05414.
46. Scher JU, Littman DR, Abramson SB. Microbiome in inflammatory arthritis and human rheumatic diseases. Arthritis Rheumatol. 2016;68(1):35–45. https://doi.org/10.1002/art.39259.
47. Kane AV, Dinh DM, Ward HD. Childhood malnutrition and the intestinal microbiome. Pediatr Res 2015;77(1-2):256-62. https://doi.org/10.1038/pr.2014.179 [published Online First: 20141030].
48. Chisari E, Cho J, Wouthuyzen-Bakker M, Parvizi J. Periprosthetic joint infection and the Trojan Horse theory: examining the role of gut dysbiosis and epithelial integrity. J Arthroplasty 2022;37(7):1369-74. https://doi.org/10.1016/j.arth.2022.03.030 [published Online First: 20220314].
49. Hernandez CJ, Yang X, Ji G, et al. Disruption of the gut microbiome increases the risk of periprosthetic joint infection in mice.

Clin Orthop Relat Res. 2019;477(11):2588–98. https://doi.org/10.1097/corr.0000000000000851.
50. Zhao X, Zhang Z, Wang Y, et al. Association of antibiotic alterations in gut microbiota with decreased osseointegration of an intramedullary nail in mice with and without osteomyelitis. Front Endocrinol (Lausanne) 2021;12:774257. https://doi.org/10.3389/fendo.2021.774257 [published Online First: 20211209].
51. Carson MD, Warner AJ, Hathaway-Schrader JD, et al. Minocycline-induced disruption of the intestinal FXR/FGF15 axis impairs osteogenesis in mice. JCI Insight 2023;8(1). https://doi.org/10.1172/jci.insight.160578 [published Online First: 20230110].
52. Luna M, Guss JD, Vasquez-Bolanos LS, et al. Components of the gut microbiome that influence bone tissue-level strength. J Bone Miner Res 2021;36(9):1823-34. https://doi.org/10.1002/jbmr.4341 [published Online First: 20210604].
53. Dar HY, Perrien DS, Pal S, et al. Callus γδ T cells and microbe-induced intestinal Th17 cells improve fracture healing in mice. J Clin Invest 2023;133(8). https://doi.org/10.1172/jci166577 [published Online First: 20230417].
54. Moran MM, Wilson BM, Li J, et al. The gut microbiota may be a novel pathogenic mechanism in loosening of orthopedic implants in rats. Faseb j 2020;34(11):14302-17. https://doi.org/10.1096/fj.202001364R [published Online First: 20200915].
55. Yao B, Cai Y, Wang W, et al. The effect of gut microbiota on the progression of intervertebral disc degeneration. Orthop Surg 2023;15(3):858-67. https://doi.org/10.1111/os.13626 [published Online First: 20230104].
56. Li W, Lai K, Chopra N, Zheng Z, Das A, Diwan AD. Gut-disc axis: a cause of intervertebral disc degeneration and low back pain? Eur Spine J. 2022;31(4):917–25. https://doi.org/10.1007/s00586-022-07152-8.
57. Rajasekaran S, Soundararajan DCR, Tangavel C, et al. Human intervertebral discs harbour a unique microbiome and dysbiosis determines health and disease. Eur Spine J 2020;29(7):1621-40. https://doi.org/10.1007/s00586-020-06446-z [published Online First: 20200514].
58. Risbud MV, Shapiro IM. Role of cytokines in intervertebral disc degeneration: pain and disc content. Nat Rev Rheumatol 2014;10(1):44-56. https://doi.org/10.1038/nrrheum.2013.160 [published Online First: 20131029].
59. Kigerl KA, Zane K, Adams K, Sullivan MB, Popovich PG. The spinal cord-gut-immune axis as a master regulator of health and neurological function after spinal cord injury. Exp Neurol 2020;323:113085. https://doi.org/10.1016/j.expneurol.2019.113085 [published Online First: 20191022].
60. Zhang W, Li Y, Sun T, et al. Superior cervical ganglionectomy alters gut microbiota in rats. Am J Transl Res 2022;14(3):2037–50 [published Online First: 20220315].
61. Schmidt EKA, Torres-Espin A, Raposo PJF, et al. Fecal transplant prevents gut dysbiosis and anxiety-like behaviour after spinal cord injury in rats. PLoS One 2020;15(1):e0226128. https://doi.org/10.1371/journal.pone.0226128 [published Online First: 20200115].
62. Doelman A, Tigchelaar S, McConeghy B, et al. Characterization of the gut microbiome in a porcine model of thoracic spinal cord injury. BMC Genomics 2021;22(1):775. https://doi.org/10.1186/s12864-021-07979-3 [published Online First: 20211030].
63. Rodenhouse A, Talukder MAH, Lee JI, et al. Altered gut microbiota composition with antibiotic treatment impairs functional recovery after traumatic peripheral nerve crush injury in mice: effects of probiotics with butyrate producing bacteria. BMC Res Notes 2022;15(1):80. https://doi.org/10.1186/s13104-022-05967-8 [published Online First: 20220223].
64. He N, Shen G, Jin X, et al. Resveratrol suppresses microglial activation and promotes functional recovery of traumatic spinal cord via improving intestinal microbiota. Pharmacol Res 2022;183:106377. https://doi.org/10.1016/j.phrs.2022.106377 [published Online First: 20220801].