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The Microbiome and Bone and Joint Disease

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Abstract

Purpose of Review—Changes in the constituents and activity of the microbiome have been associated with a number of conditions linked to bone and joint disease. This review concentrates on ways in which the microbiome is known to influence osteoarthritis and osteoporosis.

Recent Findings—Animal studies have demonstrated that changes in the microbiome can mediate the effects of obesity on cartilage degeneration. Additionally, the microbiome influences the amount of bone (bone quantity), as well as bone tissue material properties (bone quality). Early clinical findings support the effects of the microbiome on osteoporosis and osteoarthritis.

Summary—Although animal studies implicate the microbiome in the development of bone and joint disease, available results are limited and can be conflicting. Further investigation of the mechanisms leading from changes in the microbiome to alterations in bones and joints are necessary.

Keywords

microbiome; osteoarthritis; osteoporosis; bone; inflammation

Introduction

The human body is populated by trillions of microbial organisms, a population that is similar in size to that of human cells in the body [1]. The microbial organisms populating the human body together with the molecular products of those organisms constitute the human microbiome. Organisms within the microbiome include bacteria, archaea, and single-celled eukaryotes, which together are referred to as the microbiota. The human body hosts microbial species at all interfaces with the environment, including skin, oral cavity, vaginal space, urethra, and gastrointestinal tract. In humans, the vast majority of the microbiome is present in the gastrointestinal tract, which consists of over 1000 distinct species of microbes in most humans [2]. Recent investigations have associated alterations in the microbiome with a number of chronic clinical conditions including obesity and diabetes, heart disease,

and Alzheimer's disease [3]. Here I review recent findings linking the microbiome to chronic diseases of bones and joints.

The presence and physiologic importance of the microbiome have been recognized since the large-scale use of antibiotics began over 70 years ago. An early indication of the effects of the microbiome on the musculoskeletal system was the increased growth rates in farm animals fed low doses of antibiotics. In farm animals, oral antibiotics alter the composition of the microbial species in the gut, leading to more efficient caloric absorption that enables more rapid growth [4–6]. Early investigations into the impact of the microbiome on host physiology were limited by the fact that the vast majority of organisms within the microbiome could not be grown under laboratory conditions, making it impossible to identify or even characterize most of the constituents of the gut flora. In the past 10 years advancements in high-throughput sequencing and associated computational approaches have made it possible to identify the constituents and functional capacity of the components of the gut microbiota, thereby leading to rapid advances in our understanding of the role of the microbiome on physiology and disease processes.

There are three key concepts to understand regarding the function of the microbiome. First, the microbiome is a network of interacting microbial species. The microbial network within the gut involves interdependencies, competition for resources, and the secretion of antibiotics to limit the growth of competing species. The constituents of the microbiota are in a dynamic equilibrium that fluctuates with daily variations in diet. Hence, the microbiome is not a collection of microbial species, but a dynamic network of interacting microbes. Because most species in the gut interact with one another, it can be difficult to prove that a single microbial species is the cause of a condition in the host, and in most cases one must consider the possibility that the true causative microbe is from a species that interacts closely with one that has been identified [7]. Second, because species within a mature microbiome are interdependent, the gut microbial community is resistant to change. Following an acute interruption such as a short-term change in diet or a short course of oral antibiotics, the composition of the gut flora mostly returns to its initial condition in composition (although some long-term changes can occur) [8, 9, 3]. The robust nature of the gut microbiota makes it difficult to colonize a microbial community with a new species, since a newly introduced species must compete with species that are already well integrated into the community. Long-term colonization requires an environmental niche for the newly introduced species. Fecal transplant, used as a treatment for *Clostridium difficile* infections, is effective because it transfers an entire gut flora community, rather than a single species [10]. Lastly, many of the microbes within the gut are poorly characterized. As few as 10% of the species within the gut flora are readily grown in laboratory conditions, thereby limiting characterization of fundamental phenotypes (shape, metabolic activity, etc.) in 80–90% of the species within the human microbiome. Hence, many of the species common in the gut flora are recognized only by DNA sequence. Rapid advances in the field are increasingly leading to identification of new species and it is not unusual for a study correlating the microbiome with a clinical condition to identify an uncharacterized microbial species.

Mechanisms Behind the Role of the Microbiome in Bone and Joint Health

There are relatively few mechanistic descriptions of how changes in the microbial community in the gut lead to alterations in distant organs such as bones and joints. Studies of host-microbe interactions have identified many ways in which changes in the microbiome may influence distant organs, which I classify in three ways: regulation of nutritional absorption, regulation of the immune system at the gut endothelium, and translocation of microbes and molecular products of bacteria across the endothelial barrier and into the systemic circulation (Fig 1) [11].

Nutritional absorption in the gut is regulated to some degree by the gut microbiota. As mentioned previously, the contents of the gut microbiome can alter caloric intake at the gut endothelium, thereby changing the ratio of calories absorbed to the amount of food eaten [4–6]. Alterations in caloric absorption are one way in which the gut flora can influence the development of obesity [12]. Alterations in the gut flora may also cause excessive inflammatory responses at the gut lining, which can impair the absorption of key nutrients. Additionally, the gut flora are the source of a number of key vitamins used by the body including cobalamin (B12), biotin (B7), folate, thiamine (B1), pyridoxal phosphate, pantothenic acid (B5), niacin (B3), vitamin K, and tetrahydrofolate [13]. Vitamins produced by commensal organisms influence organs throughout the body and may therefore influence the function of the cardiovascular system, the central nervous system, and potentially the musculoskeletal system.

Immune cells at the gut endothelium are in constant contact with the gut microbiota. Dendritic cell processes extending through the gut endothelium respond to the presence of the gut flora through secretion of factors that lead to changes in gut microbial populations and other immune cells [14]. Additionally, microbes within the gut secrete factors such as short chain fatty acids that can mediate the activity of T cells thereby reducing local inflammation. Immune cell response to the gut flora may lead to secretion of pro- or anti-inflammatory factors and/or the migration of activated immune cells to the systemic circulation and eventually to the bone and the synovium.

Translocation of microbes and microbial molecules across the gut endothelium is another process in which the microbiota may influence bone and joint disease. While the gut lining forms a barrier that limits transport across the endothelium, microbial associated molecular patterns (MAMPs) often penetrate the gut endothelium and enter the systemic circulation. MAMPs include factors such as lipopolysaccharide (LPS), peptidoglycan, flagellin, and bacterial cell-free DNA. MAMPs that translocate across the endothelial barrier can initiate pro-inflammatory responses in resident immune cells. In addition, MAMPs in the systemic circulation are transported to the joint where they can stimulate innate immune receptors in bone, cartilage, and the synovium. Although circulating LPS is best understood in terms of its effect on bone and joint health [15], there is evidence that peptidoglycan [16], flagellin, and bacterial cell-free DNA originating in the gut flora are present in the systemic circulation. Additionally, the translocation of live microbes across the gut endothelium remains a possibility. Live bacteria transported to bone and joint can then directly stimulate innate immune receptors in local cell populations (even if a local infection is never

established). While the ability of live bacteria to cross the endothelial barrier and be transported through the systemic inflammation to distant organs is controversial, hematogenous seeding of bacteria is a well-recognized cause of periprosthetic joint infection, suggesting that the process is possible.

Inflammatory Arthritis

Alterations in the microbiome are associated with a number of inflammatory processes at the gut endothelium with the potential to alter systemic inflammation. The ability of the microbiome to regulate gut inflammation and immune responses initiating at the gut boundary suggests, therefore, a potential role in regulating inflammatory arthritis. The role of the microbiome on inflammatory arthritis has been discussed in prior reviews [17, 18], which highlight an increasing collection of clinical and preclinical studies linking the gut microbiota to rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. A recent study closely links *Prevotella copri* in the gut to rheumatoid arthritis [19]. The current review will concentrate on what is known about the effects of microbiome on osteoarthritis and bone.

Osteoarthritis

While there are considerable data supporting the idea that the microbiome contributes to inflammatory arthritis, less is known about the effects of the microbiome on osteoarthritis. Osteoarthritis is viewed traditionally as a mechanically induced condition and the role of inflammatory factors, such as those derived from the microbiota, have been considered minor. Recent findings, however, suggest that systemic inflammation can contribute to the development of osteoarthritis. For example, patients with obesity have increased risk of osteoarthritis in non-weightbearing joints in the upper extremities [20, 21]. Furthermore, animals in a state of low-grade chronic systemic inflammation due to a high-fat diet develop osteoarthritis from loads that are too small to initiate osteoarthritis in lean controls [22, 23]. Additionally, animals with increased body weight due to diet show reduced progression of osteoarthritis in response to increased loading during exercise, the opposite of the expected response if mechanical loading were the only cause [24].

A recent report suggests that interactions between systemic inflammation and osteoarthritis may be regulated by the microbiome. Using destabilization of the medial meniscus (DMM) to induce osteoarthritis in mice, Schott and colleagues reported that animals with systemic inflammation caused by diet-induced obesity developed more intense joint degradation than lean mice (as measured by histology) [25]. Furthermore, they showed that the effect of a high fat diet on the development of osteoarthritis could be prevented through prolonged dosing of prebiotics that altered the composition of the gut microbiota (prebiotics are nutrients that promote the growth of beneficial organisms). This study is exciting in that it is the first to demonstrate an effect of the microbiota on osteoarthritis. However, the effect of the prebiotics was limited to obese mice (no effect of prebiotic treatment was observed in the joints of lean mice following DMM surgery). Additionally, while the study showed changes in the microbiota associated with prebiotic treatment, how the modifications to the gut microbiome lead to changes in the joint remains to be determined. Another study examined cartilage in rats with diet-induced obesity and found obese animals to have alterations in the

composition of articular cartilage (increased Mankin score) as compared to lean animals and that the change in Mankin score was correlated with alterations in the constituents of the gut flora [26]. Although this study did not include frank osteoarthritis, the increase in Mankin score is indicative of changes in cartilage that are present prior to cartilage degradation and, together with the study by Schott and colleagues, suggests that the microbiome may influence osteoarthritis, particularly under conditions of obesity.

The translocation of microbiota-derived molecules into the systemic circulation is one way in which the microbiome may mediate osteoarthritis. A recent clinical study (n=25 patients) reported that systemic and synovial concentrations of bacterial LPS were positively correlated with the joint inflammatory response and the severity of joint degradation (measured as osteophyte score, joint space narrowing, and pain) [15]. As the microbiota are the primary source of circulating LPS, these findings suggest a correlation between the microbiota and the severity of established osteoarthritis [27]. The specific process that causes the increase in systemic LPS remains to be determined. However, LPS is readily measured in blood serum and may be useful as a biomarker of osteoarthritis severity [27].

These three studies raise the possibility that the microbiome may mediate the effects of mechanical load in causing the development of osteoarthritis. With the increasing number of studies examining the effects of the microbiome on osteoarthritis, it is expected that our understanding of the topic will greatly increase over the next few years.

Bone

The primary clinical concern for bone is osteoporosis and fragility fracture. Fragility fractures are clinical fractures that result from low energy loads (falls from a standing height or less severe) that are often associated with low bone mass characteristic of osteoporosis. Whether or not a fracture occurs is determined by the load (magnitude and direction), as well as by the bone's ability resist the load. The ability of a bone to resist fracture is related to the amount of bone present (bone quantity), as well as the material properties of the bone tissue (bone quality). Alterations in the microbiome that are relevant to fracture risk may occur through changes in bone quantity, bone quality or both.

Many clinical conditions that are associated with or contribute to the development of osteoporosis are also associated with changes in the gut microbiota [11]. However, to date there is only one report linking the microbiome to osteoporosis in humans: the gut flora in patients with osteoporosis (defined using bone mineral density (BMD)) was recently reported to be different from that of normal controls (microbiota assessed by analysis of fecal 16S rRNA) [28]. While the report is clearly limited by a small sample size (n=6/group), it does support the idea that osteoporosis is associated with changes in the gut microbiota.

A series of preclinical studies reported over the last five years suggests that the microbiome may influence bone quantity (morphology and density). Three primary methods have been used to demonstrate an effect of the microbiome on bone: examination of germ-free mice, chronic treatment with oral antibiotics to manipulate the gut flora, and treatment with

probiotics [11]. Germ free mice are raised in sterile incubators and are never exposed to live microbes in their life (MAMPs and dead bacteria may be present in the sterilized food and water provided to the animals). Changes in bone phenotype in germ-free mice therefore represent a condition without a live microbiota. There are mixed findings regarding the bone phenotype of germ-free mice. Germ free mice may have increased bone mass/density or reduced bone mass/density compared to conventionally raised animals [29, 30, 11, 31]. A major challenge in interpreting differences among studies of germ free mice is that the studies are not consistent in terms of mouse strain, sex or age. Yan and colleagues recently showed that, in growing germ-free mice (8 weeks of age), exposure to bacteria caused an acute increase in bone remodeling leading to a reduction in bone mass, but that long-term exposure has negligible effects on trabecular bone volume and can even increase long bone growth [32]. Additionally, they showed that short chain fatty acids (a product of bacterial metabolism) may mediate the effect of the microbiome in bone by modifying circulating insulin-like growth factor 1 (IGF-1). In addition to regulating overall bone mass, the gut microbiota may also influence the rates of bone loss; germ-free mice do not lose as much bone mass as conventionally raised mice following estrogen depletion [33].

Chronic antibiotic treatment has also been used to study the effects of alterations in the gut microbiota on bone morphology and density. Oral antibiotics are a standard method of manipulating the gut microbiota in animal studies. Most often the antibiotics used are poorly absorbed at the gut endothelium, thereby ensuring that the treatment only influences the gut flora. Additionally, selection of antibiotics/antibiotic doses that do not, by themselves, cause gut inflammation, provides a useful means for studying the effects of changes in the gut microbiota without the alterations in the immune system observed in germ-free mice. Although cocktails of multiple antibiotics in drinking water can greatly reduce the bacterial load within the gut, oral antibiotics do not remove all microbes. The gut flora in treated mice may change over time as organisms that are resistant to the dosed antibiotics replace species that are susceptible. Alterations in the gut microbiota caused by antibiotics influence bone mass and density in a manner related to duration of dosing and animal age and appear to mirror the conditions of germ free mice [34, 35, 32].

Probiotics have also been shown to regulate bone mass [36]. Probiotics are bacterial species that can have beneficial effects in the gut by regulating immune responses at the gut endothelium and/or by competing for resources/interacting with resident species that have a negative effect on the host. Probiotics rarely colonize the gut flora and must therefore be dosed frequently to maintain their beneficial effects. Probiotics including *Lactobacillus spp.* have anti-inflammatory effects at the gut endothelium that can lead to beneficial changes in bone mass and/or density. In mice, treatment with probiotics reduces bone loss associated with ovariectomy [37, 33] and can regulate gut inflammation [38].

So far I have described the effects of the microbiome on bone morphology and density but have not discussed bone mechanical properties. A recent report shows that changes in the microbiome can influence bone mechanical performance. Guss and colleagues examined the bone biomechanical phenotype in mice with an alteration in gut flora caused by either an immune deficiency (deficient in Toll-like Receptor 5) or through chronic treatment with oral antibiotics [39]. Mice submitted to chronic antibiotic treatment showed reductions in whole

bone strength that were greater than expected from the associated changes in bone morphology. A similar but smaller in magnitude effect on bone strength was observed in mice with altered gut microbiota due to Toll-like receptor 5 deficiency. These findings suggest that alterations in the gut flora can result in changes in bone tissue material properties that lead to reduced whole bone strength. Hence, in addition to altering bone quantity, the gut microbiota may also alter bone quality. Traditional diagnostic assays such as bone mineral density are sensitive to changes in bone quantity but are not sensitive to changes in bone tissue material properties, suggesting that alterations in the gut microbiome have the potential to alter risk of fragility fracture in ways that are not apparent using clinical imaging.

Conclusion

The few studies that have been performed relating the microbiome to osteoarthritis suggest that the microbiome can influence joint degeneration, most likely by influencing the contribution of systemic inflammation to osteoarthritis. That being said, experimental findings so far have only evaluated osteoarthritis associated with obesity. The increasingly popular view of osteoarthritis is that it is a heterogeneous disease with multiple subtypes [40], but it is not known if the microbiome is influential in all subtypes. Additionally, to date, the effects of the microbiota on osteoarthritis have been examined only in situations with established disease (the DMM model or patients) and it is unclear if the microbiota influences the early and potentially reversible steps toward cartilage degradation. Understanding the contribution of the microbiome to early disease development is key for using the microbiome as a biomarker of disease progress or even as a target for intervention.

Our understanding of the effects of the microbiome on bone is more advanced than that of osteoarthritis but many questions still remain. First, since a majority of the preclinical studies are performed in growing animals, there is concern that effects on longitudinal growth may be different from the effects observed after skeletal maturity. Indeed, the studies on duration of exposure to the microbiota [32] were performed in growing animals suggesting that the changes could be regulating rates of bone growth. Additionally, the finding that the microbiota influences bone quality in addition to bone quantity raises the possibility that a poor microbiota may increase bone fragility in ways that are not apparent from clinical measures of bone mineral density (a key indicator of fracture risk) and, therefore, go undetected in clinical screening. While there are many stimuli that can alter bone remodeling and modeling in ways that change bone quantity, there are few known mechanisms of altering bone tissue quality (to date only genetic abnormalities and tissue age are recognized causes) and the potential that the microbiome may influence bone tissue material properties suggests that there may be other ways of regulating bone tissue quality.

Lastly, as the field of the microbiome is still in its early stages, most studies examining the role of the microbiome report correlations with disease or disease processes but little attention has been paid to causative mechanisms [3]. Only through strong collaborations among microbiologists, ecologists, and musculoskeletal researchers will it be possible to understand the role of the microbiome in bones and joints.

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Figure 1.

A cartoon illustrating host-microbe interactions at the gut endothelial barrier is shown. Three primary ways of influencing the systemic circulation are shown: alterations in nutritional absorption, stimulation of resident immune cells and translocation of microbial associated molecular patterns (MAMPs) across the endothelial barrier. Factors are distributed to the bone and joint through the systemic circulation. Abbreviations: DC – Dendritic Cell, EC – Endothelial Cell, MAMPs – Microbial Associated Molecular Patterns. From [11] used with permission.