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Editorial

Gut Microbiome Bridges Over Troubled Joints

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Osteoarthritis (OA) is the most prevalent joint condition causing chronic pain and disability. OA has generally been considered as a degenerative joint disease characterized by structural damage in the articular cartilage; however, OA is, in fact, more complex and heterogeneous involving cartilage, bone, and synovium further affected by multiple biomechanical and biochemical factors. With regard to these numerous factors, there is growing evidence that obesity and metabolic syndromes are associated with OA [1,2]. Reports of increased OA risk in non-weight bearing joints of obese patients suggest that metabolic factors can cause the perpetuation of OA [3,4]. Furthermore, it is speculated that adipokines and pro-inflammatory cytokines released from fat tissues might contribute to the development and progression of OA [5]. However, the exact mechanistic role of obesity on OA is yet to be fully understood.

Gut microbiome has gained much interest as a player in the pathogenesis of various diseases including OA. Physiologically, balanced community of microbial organisms resides in the gut and interacts with the human host by regulating the metabolism and immune responses of the host. However, disrupted gut microbial community could trigger dysregulated metabolic and immune responses. For instance, a study with gut microbiota from twin mice showed that "obese microbiota" transplantation transmitted obesity-associated metabolic phenotype, supporting the causal role of gut microbiota in obesity-related metabolic disorder [6]. Gut dysbiosis can also contribute to autoimmune and autoinflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, spondyloarthritis, and systemic lupus erythematosus by increasing gut permeability, bacterial translocation, and immune system activation [7].

It is not clear whether gut microbiome has a direct causal relationship with OA or altered gut microbiome is a consequence of OA-related change. However, there are several preclinical studies which might support the direct connection between gut microbiome and OA. For instance, a study by Ulici et al. [8] observed less severe meniscus injury-induced OA in germ-free mice compared to specific pathogen free mice. Moreover, OA severity was enhanced in mice transplanted with fecal microbiota of OA patients with metabolic syndrome [9]. Another study has also seen reduced synovial inflammation and cartilage loss in obese OA mouse model after the modulation of gut microbiota by oligofructose (prebiotics) administration and the restoration of gut microbial composition (toward increased abundance of beneficial gut bacteria) [10]. These results suggest that gut microbiome might be linked to obesity and metabolic syndrome that could aggravate OA severity. In addition, gut microbiome could have a direct influence in cartilage, chondrocyte, and subchondral bone marrow damage [11]. Gut microbiome was recently found in human and mouse OA cartilage samples showing distinct composition and function compared to control cartilage samples, although this finding needs to be confirmed in further studies [12].

A recent study by Lee and Song [13] published in *Journal of Rheumatic Diseases* investigated a causal relationship between the gut microbiome and OA risk using a publicly accessible summary statistics datasets of gut microbiome, including the genome-wide association studies (GWAS) data of 3,326 individuals of European descent

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(as an exposure), summary GWAS data from 3,498 UK patients with knee and/or hip OA, and 11,009 controls of European descent (as an outcome). Because there is a lack of studies regarding the role of gut microbiome in human OA, this study has value in terms of examining the causal relationship between gut microbiome and OA using Mendelian Randomization design. Here, no causal relationship between gut microbiome and OA risk was found. However, we need to consider some crucial points while interpreting the results. First, there was no data regarding the outcomes of OA, such as pain and inflammatory markers. A recent microbiome cohort study revealed that the abundance of certain gut microbe species was associated with more severe knee joint pain and inflammation in patients with OA [14]. Second, several metabolites and endotoxins released from gut microbes can also contribute to the pathogenesis of OA. For instance, lipopolysaccharide, a bacterial component playing as an endotoxin, was associated with OA severity and pain in patients with knee OA [15]. Third, the complexity of OA pathogenesis involving multiple factors (mechanic stress, metabolic, aging, hormonal, and genetic factors) makes it difficult to unravel the direct relationship between gut microbiome and OA [16].

In summary, gut microbiome may be involved in OA pathogenesis and affect OA outcomes by promoting local and systemic inflammation. This relationship may mean that "good" microbiome could reverse this pathogenic process. However, more data is needed to confirm this role of gut microbiome in the highly complex OA pathogenesis

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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