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Editorial

The Human Gut Microbiome and Its Relationship with Osteoarthritis Pain

Silvia Turroni, PhD,* Paolo Pedersini, MSc,† and Jorge Hugo Villafañe, PhD†

*University of Bologna, Bologna, Italy; †IRCCS Fondazione Don Carlo Gnocchi, Milan, Italy

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Editorial

The gut microbiome constitutes the largest reservoir of the human microbiome and probably the one most capable of influencing the health of the whole body through multiple system-level interactions. Composed mainly of bacteria but also fungi and viruses, this microbial ecosystem is highly diverse and complex, functionally redundant, individual specific, plastic, and resilient. An alteration of its structure, i.e., dysbiosis, has been shown to participate in the onset and progression of various metabolic and inflammatory diseases. This is mainly due to the increase of opportunistic pathogens or pathobionts and/or the depletion of health-associated taxa, such as short-chain fatty acid producers, with impaired intestinal permeability (i.e., leaky gut) and altered immune signaling [1]. It is therefore not surprising that the gut microbiome can also be a crucial factor in the management of osteoarthritis (OA). Exposure to stress and pain may lead to alterations in the interactions between the brain and the intestine (i.e., the gut–brain axis) by changing gastrointestinal secretion, gut motility and permeability, and microbial gene expression and quorum-sensing signals, thus contributing to dysbiosis and increasing the rate of translocation of bacterial products or even bacteria, thereby eliciting systemic inflammation [2] (Figure 1). It has been hypothesized that patients with OA-related pain will exhibit an imbalance of the gut microbiota associated with pain intensity [3].

Pain in OA cannot be attributed only to peripheral nociception, and modulation by nociceptive processing contributes to the pain experience. The discrepancies between pain in OA and the severity of radiographic findings are usually associated with the propensity of some patients to show a sensitization phenotype and are supported by recent theories that OA involves complex mechanisms of altered pain transmission [4]. Pain in OA is related to innumerable internal and external factors, including environmental changes, diet, exercise, disease, stress, and genetics. A growing body of literature supports the importance of the brain–gut interaction in pain perception and points to the gut microbiota as a possible key factor in pain processing [5]. The microbiota may interfere with nociceptive signaling via various routes, including enteric and vagus neural communication and the endocrine and immune systems. In particular, the integrity of the intestinal barrier has been identified as an important checkpoint, which can allow the passage of microbial metabolites or vesicles presenting immunogenic epitopes, which can prime local and systemic macrophages, exacerbating joint inflammation and damage, thus leading to increased pain [6]. However, the current evidence is still limited, which emphasizes the need for large longitudinal cohort studies and mechanistic experiments in model systems. This will ideally lead to the identification of microbiome targets for the development of new microbiome-based precision strategies aimed at modulating pain pathways, thus optimizing peripheral manual and physical therapies for conservative nonpharmacological pain management in patients with OA.

In recent decades, the burden of OA has increased because of longer life expectancy but also because of the modern lifestyle, in particular physical inactivity and inadequate diets, which promote chronic low-grade inflammation and obesity. There is currently no gold standard

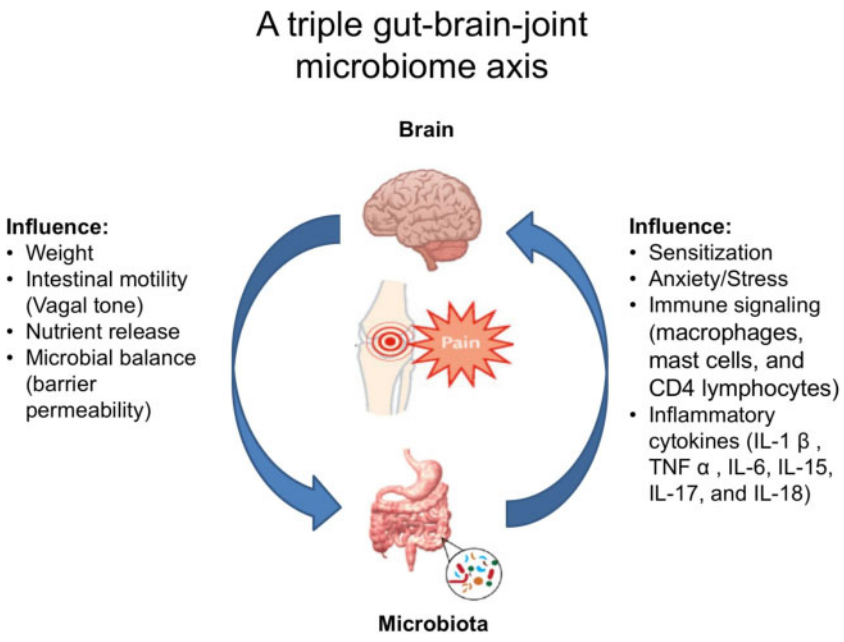

Figure 1. A triple gut–brain–joint microbiome axis. IL = interleukin; TNF = tumor necrosis factor.

method for treating patients with OA. Conservative non-pharmacological treatment has been shown to relieve symptoms in patients in early-stage OA disease and can stave off surgical interventions either temporarily or in the long term [7]. Applying a multimodal treatment that includes targeting of gut microbiota is a relatively new therapeutic strategy that can be easily applied by physicians in different clinical settings worldwide. Our hypothesis of gut microbiota involvement opens the way for future research on the modulation of pain pathways through the manipulation of microbial communities (e.g., by diet, pre- or probiotics, and physical activity), ultimately leading to practical targets to optimize pain management in OA. Emerging evidence suggests that alterations in nociceptive processing within the peripheral and/or central nervous system may be a key factor in accounting for variations in clinical presentations of pain associated with OA. Understanding the associations between OA and gut microbiota could lead to improved treatment approaches, greater therapeutic efficacy, and improved patient health.

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PERSPECTIVE & COMMENTARY

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Commentary

Optimizing Acetaminophen Use in Patients with Risk Factors for Hepatotoxicity: Reviewing Dosing Recommendations in Adults

Deanna K. Bauerlein, PharmD, BCPS*,‡ Allison P. Williams† and Preeti R. John, MD, MPH, FACS, CPE, HEC-C†,‡

*Veterans Affairs New Jersey Health Care System, East Orange, New Jersey; †University of Maryland School of Medicine, Baltimore, Maryland; ‡Veterans Affairs Maryland Health Care System, Baltimore, Maryland, USA

Introduction

Acetaminophen is the most commonly used analgesic and antipyretic in the United States, with more than 60 million Americans using the drug on a weekly basis [1]. In contrast to nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen is associated with fewer gastrointestinal, cardiovascular, and renal adverse drug events and drug interactions. The clearance of acetaminophen also does not change in relation to age, and thus acetaminophen is recommended by the American Geriatrics Society for chronic pain [2]. Following the opioid crisis and heightened awareness by the medical community of the need for multimodal analgesia, adjuncts to opioids such as acetaminophen are being used more commonly to treat acute and chronic pain. Unfortunately, acetaminophen-induced hepatotoxicity resulting from unintentional overdose is the most common cause of acute liver failure in the United States, resulting in 30,000 hospital admissions per year [1]. It accounts for more than 50% of overdose-related acute liver failure and 20% of liver transplant cases [1]. Although adverse effects caused by acetaminophen represent a significant public health concern, the Food and Drug Administration's (FDA's) recommendations for maximum daily adult dosing have remained unchanged for decades, with no formal