



An unexpected connection: A narrative review of the associations between Gut Microbiome and Musculoskeletal Pain

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Abstract

Purpose Multiple diverse factors contribute to musculoskeletal pain, a major cause of physical dysfunction and health-related costs worldwide. Rapidly growing evidence demonstrates that the gut microbiome has overarching influences on human health and the body's homeostasis and resilience to internal and external perturbations. This broad role of the gut microbiome is potentially relevant and connected to musculoskeletal pain, though the literature on the topic is limited. Thus, the literature on the topic of musculoskeletal pain and gut microbiome was explored.

Methods This narrative review explores the vast array of reported metabolites associated with inflammation and immune-metabolic response, which are known contributors to musculoskeletal pain. Moreover, it covers known modifiable (e.g., diet, lifestyle choices, exposure to prescription drugs, pollutants, and chemicals) and non-modifiable factors (e.g., gut architecture, genetics, age, birth history, and early feeding patterns) that are known to contribute to changes to the gut microbiome. Particular attention is devoted to modifiable factors, as the ultimate goal of researching this topic is to implement gut microbiome health interventions into clinical practice.

Results Overall, numerous associations exist in the literature that could converge on the gut microbiome's pivotal role in musculoskeletal health. Particularly, a variety of metabolites that are either directly produced or indirectly modulated by the gut microbiome have been highlighted.

Conclusion The review highlights noticeable connections between the gut and musculoskeletal health, thus warranting future research to focus on the gut microbiome's role in musculoskeletal conditions.

Keywords Gut microbiome · Musculoskeletal pain · Inflammation · Homeostasis · Pain modulation

Introduction

The complex and multi-dimensional experience of pain involves various mechanisms, which are only partially understood. The relationship between gut microbiome (GM) and painful conditions has received increasing research attention. Growing evidence shows that GM is a crucial modulator of human physiological homeostasis, playing a not-fully-understood but undoubtedly significant role in systemic inflammation, immunity, circadian rhythm, and regulation of hormone levels; all these aspects of homeostasis have been linked to pain. GM has been associated with visceral pain [1], inflammatory pain, headache, neuropathic pain, chronic pain, and opioid tolerance [2]. With contributions from multiple types of pain, musculoskeletal (MSK) pain is highly prevalent [3], a significant source of disability [4], and a frequent reason for medical care [5]. There is initial evidence linking GM and MSK pain, though the

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mechanisms are not clarified yet. This review covers the current literature on the common mechanisms of GM and pain modulation, focusing on potential connections between GM and MSK pain mechanisms to help direct further research on the topic.

The composition of the GM is complex and spans three kingdoms (bacteria, archaea, fungi), and it has recently been expanded to include viruses [6]. In 2012, a paper pointed at the number of known species composing the GM to be over 1000 [7], while a more recent effort (2019) to study the composition raised that number to almost 2000 species [8].

The overall genomic material from intestinal microbes has been estimated to be greater than 100 times the size of the human genome [9]. While more than 99% of the GM bacteria are from only four phyla (Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria), most bacteria in healthy adults come from Firmicutes or Bacteroidetes [10]. It is currently postulated that the microbiome population is shaped through adaptation that likely involves factors on multiple levels [11] (personal, interpersonal, environmental, and geographical).

GM samples for analysis are collected from stool, and microbiome profiling is conducted using, in most cases, culture-independent methods to sequence 16S rRNA gene amplicons or shotgun sequencing of whole microbial communities (metagenomics). Other methods for studying the GM population exist, such as whole microbial community RNA sequencing (metatranscriptomics), while proteomics and metabolomics can be used to obtain simultaneous information about the host and microbiome [12]. The choice of method to use is often dictated by funding and technology, as higher costs and more complex methodologies accompany more thorough analyses.

Gut microbiome and pain

Gut microbiome homeostasis and disruption

In healthy individuals, GM is characterized by a state of dynamic homeostasis defined by the richness and diversity of the GM population [13] and by its stability and resilience through perturbations of various types [14]. Numerous modifiable and non-modifiable factors play a role in determining the GM composition and its alterations (Table 1). In physiological homeostasis, the GM has been hypothesized to play a role in properly maintaining the permeability of the intestinal wall [15]. Such permeability is fundamental in how numerous antigens (from foods, pathogens, and gut microbes) are treated in the gut and how they affect the immune response [16].

Perturbations to a healthy GM ecosystem can result in dysbiosis, a distinct ecological state of the microbial

community [59]. Dysbiosis could involve changes to critical bacterial species, leading to altered permeability, physiological and metabolic functions, and ultimately predisposing diseases. An example of dysbiosis is the so-called “leaky gut syndrome”, a condition characterized by altered permeability of the intestinal walls to antigens [60], leading to systemic inflammation and aberrant immune response [61]. Other examples of diseases characterized by altered and specific gut microbiome blueprints include neurodegenerative diseases [62], metabolic syndrome [63], and inflammatory bowel disease [10].

In the case of painful conditions, a handful of specific species correlates with disease status. One example includes *Faecalibacterium Prausnitzii* (FP), whose lower concentrations correlate with osteoarthritis severity in older female adults [64], and Crohn’s disease (a condition for which pain is the most common symptom) [65]. In line with these findings, higher concentrations of FP correlate with antinociceptive effects in a rat model of Irritable Bowel Disease [66]. Other species relevant to painful conditions are the *Streptococcus* species, with an increase associated with knee osteoarthritis pain [67], or the *Coprococcus* species, the depletion of which has been associated with chronic widespread pain [68].

While individual species have been implicated in many conditions, overall evidence highlights that interactions among different species are complex and more likely to explain the pathophysiology of various diseases (including painful ones) than any single species alone. For example, a recently published study found that a combination of species correctly predicted the diagnosis of 88% of fibromyalgia patients [69].

Gut microbiome, inflammation, immune response, and impact on host physiology

The current evidence converges on the crucial role of GM in mediating systemic inflammation. In a state of inflammation (both local and systemic), the body can change how stimuli are perceived and processed. For example, in an inflammatory state, noxious stimuli can produce an increased response to pain, known as hyperalgesia, while non-noxious stimuli can be perceived as painful, known as allodynia [70]. The state of low-grade chronic systemic inflammation has been theorized to predispose to chronic pain and other chronic diseases [71].

Converging evidence highlights that GM can impact the inflammatory state by producing various metabolites (explained in the next section) and modulating systemic inflammatory cytokines production. For example, a study on healthy subjects linked the GM composition to the capacity to produce inflammatory cytokines (IL-1b, IL-6, TNF α , IFN γ , IL-17, and IL-22) [72]. A recent study on cytokine

Table 1 Known contributing factors to GM composition and alteration

	Examples	References
<i>Non-modifiable factors</i>		
Gut architecture	Microphysical gut structure	[17]
	Macrophysical gut structure	[17]
Human genetics	FUT2	[18]
	NOD2	[19]
	LCT	[20]
Birthing history	Vaginal delivery	[21]
	C-section	[22]
Early feeding patterns	Breastfeeding	[23]
	Formula	[24]
Age (or life stages)	Children,	[25]
	Adults,	[26]
	Elderly	[27]
Geographic location	Climate,	[28]
	Lifestyles,	[29]
	Genetic background,	[30, 31]
	Dwelling location,	[32]
	Food access,	[33]
Members of minorities	Employment	[34]
	Ethnicity	[35, 36]
	Self-identified race	[33]
	Sexual identity	[33]
	Gender status	[33]
<i>Modifiable factors</i>		
Diet	Dietary patterns	
	Western	[37]
	Mediterranean	[38]
	Pro- or anti-inflammatory dietary tendencies	[39]
Lifestyle choices	Smoking,	[40]
	Alcohol consumption,	[41]
	Exercise	[42]
Traumatic events	Traumatic brain injury,	[43, 44]
	Spinal cord injury,	[45, 46]
	Chronic stress	[47, 48]
Interventions	Probiotic,	[49]
	Prebiotic,	[50]
	Fecal microbiota transplant (FMT)	[51]
Prescription Drugs	Antibiotics,	[52]
	Proton pump inhibitors,	[53]
	Laxatives,	[54]
	Metformin	[55]
Exposure to chemicals pollutants, or drugs	Cadmium chloride,	[56]
	Arsenite,	[57]
	glyphosate	[58]

levels in SARS-CoV-2 patients highlighted that cytokine levels mediated by the GM composition were associated with the magnitude of the COVID-19 severity [73]. Another study on mice suggested GM modulating specific cytokines by affecting T cells [74].

Several reviews also emphasized the proven link between GM and immune-mediated inflammatory response. The modulatory changes that the GM has on the immune response are mediated by changes to the function of B and T cells, which also influences the host's resistance to pathogens

[75]. These immune function changes also impact the various GM-mediated cytokines and chemokines levels' (e.g., IL-1, IL-6, IL-10, TGF β , TNF α , IFN γ , IL-17, and IL-22). Such changes have been related to a variety of alterations of physiological homeostasis, including metabolic function (insulin resistance and obesity [76], exercise-induced stress behavior and its impact on the gut-microbiota-brain axis [77], and cancer [78]), modulation of nerve function (blood–brain barrier integrity and brain health [79]), and autoimmunity [80].

Gut microbiome metabolites as possible contributors to pain

The GM produces a broad spectrum of metabolites that impact the human body on multiple levels (Table 2), from a local impact on the GI tract to organ-specific distal from the GI tract to systemic [81]. The GM's multiple metabolites that correlate with pain will be addressed in this section to highlight the possible involvement of specific pathways and mechanisms that should be investigated in future studies and could become relevant for potential therapies.

Table 2 GM metabolites as possible contributing mechanisms of pain

Hormones (or compounds acting as hormones)		References
<i>Direct effect from GM</i>	Short chain fatty acids	Butyrate [69, 82]
		Propionate [69, 82]
	Neurotransmitters	Serotonin [83]
		Dopamine [84, 85]
		Noradrenaline [86]
		Glutamate [87, 88]
<i>Indirect effect from GM</i>	Hypothalamic–pituitary–adrenal axis (HPA)	GABA [87, 88]
		Cortisol [89]
	GI hormones	Leptin [90–92]
		Ghrelin [93]
Vitamins and nutrients		References
D		[94, 95]
B1-Thiamine		[96]
B2-Riboflavin		
B3-Nicotinic acid		
B5-Pantothenic acid		
B6-Pyridoxine		
B7-Biotin		
B9-Folic acid		
B12-Cyanocobalamin		[96, 97]
para-aminobenzoic acid		[96]
Inositol choline		

GM in humans produces various hormones (or compounds acting as such), so GM can be considered an endocrine organ functionally [98]. This definition relies on the fact that GM produces numerous chemicals that act via the bloodstream to distal sites in the human body. These hormones can be classified as being directly produced by the GM or indirectly regulated by the GM.

Hormones (and compounds acting as hormones) directly produced by the gut microbiome

The first group includes chemicals that mediate pain, including short-term fatty acids (SCFAs) and neurotransmitters (including some precursors). SCFAs are produced in the large intestine by the GM through anaerobic fermentation of dietary fibers [99]; bacteria from the Bacteroidetes phylum mainly produce propionate, while bacteria from the Firmicutes phylum mainly produce butyrate [82]. SCFAs play a critical role in modulating intestinal inflammation and epithelial barrier function [82]; dysfunction at the epithelial barrier level is one of the leading causes of “leaky gut syndrome” that plays a vital role in various painful conditions. Moreover, SCFAs produced in the gut can enter the bloodstream [82], further contributing to the modulation of systemic inflammation [81]. For example, butyrate and propionate serum levels were significantly altered in a group of subjects affected by fibromyalgia compared to healthy controls [69].

Serotonin, dopamine, noradrenaline, glutamate, and GABA are directly produced by the GM or indirectly regulated by it. Dopamine, long considered a key modulator of reward-seeking behavior, is produced in large quantities in the gut [100]; it also participates in the immune response [101], thus being important in the modulation of systemic inflammation. Interestingly, at least 50% of dopamine is synthesized in the gut, with GM likely playing a significant part in the production process [102]. Its complex role in the human body includes a modulatory function for chronic pain through the nigrostriatal and mesolimbic pathways [103]. Also, growing evidence has been mounting on the implications of dopamine dysregulation in the brain as a pivotal player in chronic pain's sensory and affective aspects [84]. A review of mice studies strongly suggested that alterations in the GM significantly compromise dopaminergic neurotransmission in the brain [85].

Serotonin, a complex neuromodulator that regulates various processes [104], including mood regulation [105], learning and memory skills [106], and various other physiological processes, is estimated to be produced 90% in the gut [107]. Of specific importance for pain, serotonin plays a crucial role in the gut-brain axis [108], connecting the central nervous system and the gastrointestinal tract bidirectionally [109]. The decades-old concept of the gut-brain axis has

recently been broadened to include the GM in the so-called gut-brain-microbiome axis [110] (or the microbiota-gut axis [111]); this more inclusive concept owes to the growing evidence of the GM's role in modulating the gut-brain pathway [112]. For example, GM (through various species, including Clostridia, Bacteroides, and Escherichia [113]) can alter serotonin levels by affecting the production of tryptophan, serotonin's precursor [114]. Moreover, the brain-gut microbiome axis modulates other different physiological functions associated with pain, such as modulation of the systemic inflammation in various mice models [115], alteration of the GI tract function [116] and directly impacting different kinds of painful syndromes [83] in humans.

The production of noradrenaline has been associated with both specific species (Escherichia, Saccharomyces, and Bacillus [117]) and alpha diversity levels in different studies [118]. This key neurotransmitter plays a role in pain modulation [86] and analgesia [119]. Moreover, noradrenaline plays a definite role in the mediation of inflammation [120], participating in both the acute and the chronic regulation of the immune response [121] through its effect on the autonomic nervous system [122] and regulation of the circadian rhythm [123].

Glutamate and GABA, functioning respectively as the primary excitatory [124] and inhibitory [125] neurometabolites in the central nervous system, play various key physiological roles (e.g., inflammation [126]), including the processing and modulation of pain [87]. Alterations in the metabolism of both molecules have been associated with chronic pain [88]. Various gut microbes participate in the production of both these metabolites. For example, certain species have been found to directly produce glutamate (Lactobacillus and Bifidobacterium [127]), whereas Bacteroides have been associated with GABA production and related specific brain signatures typical of depression [128].

Hormones indirectly produced by the gut microbiome

The second group of indirect regulation of hormones by the GM includes cortisol (chief stress hormone in the hypothalamic–pituitary–adrenal axis (HPA) [129]) and the GI hormones ghrelin and leptin, which are also relevant mediators and modulators of pain. Cortisol is the principal stress hormone in humans [130]. While it does not directly affect pain [131], a chronic cortisol dysfunction can negatively impact the body's ability to cope with prolonged stress. Maladaptive responses to stress can perpetuate widespread inflammation and pain, potentially sustaining mechanisms predisposing to chronic pain [89]. In mice models, specific pathogens in the GM (e.g., E. Coli infection) can heighten the HPA activity levels, thus driving the stress response higher than in cases where the GM is free of such pathogens [132].

The GI hormone ghrelin has an anti-inflammatory effect by increasing the level of anti-inflammatory cytokines in the serum. Rat-model studies exploring the role of ghrelin on pain showed its anti-nociceptive effects on acute pain [133], neuropathic pain [134], and inflammatory pain [135]. In humans, evidence points to a modulatory effect of GM on the serum levels of ghrelin [93]. Though this evidence is not conclusive, it also points to a participating role of ghrelin on the gut-brain axis when dealing with stress [136], furthering its potential role in mediating pain.

Leptin participates in the pathogenesis of neuropathic pain [90], but it also has a role in immunometabolic inflammation, characteristic of many chronic pain conditions [91]. Moreover, a study suggests that serum concentration of leptin may be a promising biomarker for predicting acute pain transition to chronic [92]. The effect of leptin on inflammation and immunometabolism makes it a potential candidate for the therapeutic development of novel interventions for treating autoimmunity [137] and metabolic diseases [138]. In rat models, the number of specific gut microbial species populations correlates with the modulation of serum levels of leptin [139]. In humans, the GM indirect modulation of leptin appears to be regulated through the production of other metabolites, such as SCFAs [140].

Vitamins and nutrients produced by the gut microbiome

A healthy GM contributes to the production of various vitamins and nutrients [141], the lack of many of which have been associated with pain (e.g., Vitamins of the B group and Vitamin D).

There is a well-established body of evidence that many microbes that reside in the gut produce vitamins of the B group [142]. Among the group B vitamins, the largest body of literature focuses on the positive effects of vitamin B12 in painful conditions, particularly for decreased low back pain and neuralgia [97]. The evidence for the other vitamins that are part of the B group is weak and unable to differentiate between individual vitamins' effects because these vitamins are most often administered together in available studies. For example, a Cochrane review from 2008 [96] highlighted that the vitamin B group positively affects neuropathic pain and patients' functional level. Overall, the analgesic effect of the group B vitamins could be explained by anti-inflammatory, anti-nociceptive, and neuroprotective effects widely described in the literature.

For vitamin D, the evidence is less strong. While there is evidence that vitamin D levels in the plasma affect the gut microbiome [143], no evidence could be found of the

reverse association. Significant literature points to the association between vitamin D and pain severity. A systematic review and meta-analysis of observational studies pointed at a significant association between vitamin D and low back pain [144], though it did not find an association between this vitamin and pain intensity. Moreover, two other reviews found that vitamin D supplementation has a meaningful, beneficial effect of reducing pain in patients experiencing chronic pain [94] and chronic widespread pain [95] while being safe. While the mechanisms behind this pain-decreasing effect are currently unclear, it has been postulated that they may have to do with the anti-inflammatory effect of vitamin D [94].

Other metabolites produced by the gut microbiome with a potential indirect effect on pain

A growing body of evidence suggests that epigenetics and mRNA expression are altered in pain subjects [97]. Various metabolites produced by the GM have an active role in epigenetics, for example, acetyl-CoA [145], lactate [146], glycine [147], serine [148], and methionine [149]. Moreover, preliminary evidence points to a potential role for Acetyl-CoA and lactate in the immune and inflammatory responses [150, 151]. Interestingly, specific B vitamins (including B2, B3, B5, B6, B9, and B12) also participate in regulating genetic responses to environmental factors (epigenetics) through the modulation of chromatin-modulating enzymes [152]. Overall, the presence of these currently poorly understood mechanisms points to the overarching complexity and involvement of multiple systems in the painful experience.

Gut microbiome and specific pain syndromes

Inflammatory and neuropathic pain

A study on inflammatory pain [153] found that nociceptive pain signal is decreased in germ-free mice compared to conventional mice. The authors concluded that the interactions between microbiome and host are essential in modulating inflammatory pain. Another study [154] highlighted that pernicious changes in the GM of mice correlate with temporomandibular joint (TMJ) inflammatory pain. Subsequent improvement of GM through fecal transplantation caused a reduction in such pain, strongly suggesting that careful manipulation of the GM has the potential to be used as a therapeutic approach.

Neuropathic pain, caused by a lesion to a nerve of the somatosensory nervous system, has also been impacted by

GM-mediated alterations of inflammatory metabolites in rats [155]. Another study [156] used a chronic constriction injury model of neuropathic pain on mice and found that GM modulates neuropathic pain by affecting T cell-mediated immune and inflammatory responses. This finding underlines the relevance of the GM to the modulation of pain even when pain is mechanically induced. Another study on adults affected by HIV experiencing neuropathic pain found that gut dysbiosis-driven loss of alpha diversity in GM was significantly associated with peripheral neuropathic pain [157]. The authors described that increased pro-inflammatory and decreased anti-inflammatory GM metabolites could explain these results.

Pain perception and generalized pain

Chronic pain and Fibromyalgia

Chronic widespread pain (CWP) has been characterized by decreased alpha diversity of the GM. In a study on a chronic widespread pain population, *Coprococcus comes* was the most significantly reduced species in the GM [68]. A study also found that the alpha diversity of GM is reduced in fibromyalgia patients [158]. This study's participants significantly reduced the population of bacteria from the Bifidobacterium and Eubacterium genera. This finding is interesting because both of these genera participate in the metabolism of neurotransmitters in the host. Further analysis of the serum metabolome discovered significant changes in the levels of glutamate and serine. The authors concluded that the changes in the GM were associated with changes in neurotransmitter metabolism, which contributed to fibromyalgia's clinical presentation.

Pain perception

Based on the framework that correlates the gut-brain axis to various diseases, a recent study showed that acute pain perception and anxiety state were associated with specific species within the GM of young, healthy males [159]. Specifically, pain sensitivity showed a positive association with bacteria from the Firmicutes phylum and a negative association with bacteria from the Bacteroidetes phylum. Moreover, a correlation was observed between anxiety state and the Bifidobacterium genus. Nonetheless, acute pain perception and anxiety were not directly correlated.

Another study that looked at stool classification to ascertain GM's status found that stool consistency was a significant predictor of pain perception in healthy subjects [160]. This study used the Bristol Stool Form Scale (a widely used diagnostic medical tool designed to classify human stool into seven categories) and found a significant and positive

association with pain and anxiety. Even though this study did not look directly at the correlation between GM and Bristol Stool Form Scale, other studies did [161], finding the associations significant and worthy of inclusion in future studies on GM.

Opioid tolerance

The opioid epidemic affecting the US has severe repercussions on individuals and society. On the one hand, the long-term use of opioids for various pain conditions has been associated with adverse changes in the GM; on the other hand, the GM may predispose and even mediate the opioid tolerance that results from chronic exposure to opioids [162]. From an individual's health perspective, opioid use and gut microbiome health interaction seem reciprocally interactive.

The mechanisms involved have been postulated to vary from opioid use, possibly inducing gut dysbiosis, disrupting the gut barrier (resulting in the "leaky gut syndrome" mentioned above), and facilitating the translocation of pernicious bacteria. Other hypothesized mechanisms include initiating Toll-Like Receptors (TLRs)-mediating gut inflammation (with concurrent releasing of pro-inflammatory cytokine), and regulating neuronal excitability in the peripheral nervous system [2].

GM and musculoskeletal pain

OA pain

Though various reviews could be found on GM and OA [163, 164], only one considered the impact of GM composition on pain symptoms [165]. Sánchez Romero et al., who reviewed GM and OA pain, found only three studies on the subject. Overall, the review highlighted weak evidence for the link between GM and OA pain, mainly due to the lack of high-quality research.

A Dutch study highlighted significant correlations between GM composition and knee OA [166]. The results were significant after adjusting for smoking, alcohol intake, and BMI. A more prominent presence of *Streptococcus* species in the subjects' stool samples was associated with more severe knee osteoarthritis (assessed through joint effusion) and increased OA knee pain. The results were replicated using a different Dutch cohort; *Streptococcus* species were also significantly associated with OA pain in this case. The authors were able to determine that the inflammation localized at the knee joint was driving the link between GM and pain; thus, they concluded that GM could be a potential way to treat OA-driven knee pain,

Another study compared symptomatic vs. asymptomatic hand OA in a large cohort ($n = 1388$) [167]. It found differences in the relative abundance of specific species, such as a low relative abundance of the genus *Roseburia* and a high relative abundance of the genera *Biophila* and *Desulfovibrio* in the symptomatic hand pain group. The study also found alterations in functional pathways relative to amino acids, carbohydrates, and lipid metabolism. Overall, the authors concluded that GM-related metabolic dysfunction might play a part in how systemic inflammation links to OA's pain symptoms.

A prior study examined GM after a 12-week supplementation of Green-lipped mussel extract or glucosamine sulfate [168]. The consumption of either compound did not significantly correlate with changes in the GM; however, it showed decreases in various species associated with higher inflammatory status (e.g., *Clostridia* and *Staphylococcus*) and an increase in species associated with decreased inflammatory status (e.g., *Lactobacillus* and *Eubacterium*). The authors concluded that GM should be considered when studying the pathogenesis and treatment of musculoskeletal conditions.

LBP obese subjects

Only one study explored the association between back pain and GM composition [169]. The study looked at a cohort of 36 obese subjects with ($n = 14$) or without ($n = 22$) LBP, a subset of a larger trial on Vitamin D supplementation. The study found significant differences in specific bacterial genera between groups; *Adlercreutzia*, *Roseburia*, and *Uncl. Christensenellaceae* were significantly more abundant in LBP participants, while *Dialister* and *Lactobacillus* were more abundant among those without LBP. The authors also concluded that increased inflammation could have been the cause for such association, thus suggesting an underlying mechanism found elsewhere in scientific literature.

Conclusion

No single gut species or combination of gut species has been consistently associated with health conditions across different host populations. This inconsistency may be due to multiple causes, the foremost of which is that the literature on the topic is relatively recent and lacks comprehensive and systematic studies to understand this complex area of research fully. For example, it could be that the changes in microbiome species across different populations, ages, genetic backgrounds, and lifestyles converge into different patterns of pathological microbiota populations. These complex interactions would require large longitudinal studies to be addressed and are challenging to run for multiple reasons, including costs, time demands, and participant attrition.

Furthermore, it could be that some subsets of affected host populations may be more prone than others to changes in microbiota composition leading to pathological outcomes; this possibility could be mediated by a variety of mechanisms, including genetic predispositions and overall health status. If this is the case, the complexity of researching the topic will require access to large datasets and, potentially, broad cooperation among research groups to power studies large enough to address the complexity of the subject related to health and disease. Last, it could be that the intricacy of the interaction is due to a bidirectional, self-feeding pattern. In this case, an initial perturbation of the GM could lead to obesity and changes in diet, leading to pain and intolerance to physical activity, thus further exacerbating GM alterations.

In conclusion, research is still nascent on the potential role of GM in MSK pain, as evidenced by the scarcity of literature on this topic; nonetheless, a good amount of scientific research highlights numerous possible mechanistic contributors to this association, thus justifying further investigation. This combination of scarce literature and multiple plausible mechanisms raises several questions and strongly encourages more research in the area. Such research should answer questions on the association between GM and musculoskeletal pain and if this relationship is causal. Moreover, it should assess the specific GM changes that drive MSK pain and what mechanisms and therapeutic targets could be identified for clinical interventions. Ideally, a combination of larger systematic cohort studies and clinical trials could help determine these associations and their feasibility for implementation in clinical practice.

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Authors contributions VTE conceptualized and designed the study, performed the literature review and collected data from it, analyzed and synthesized the content from the literature review, critically revised the manuscript for important intellectual content. GS conceptualized and designed the study, interpreted and synthesized the content from the literature review, critically revised the manuscript for important intellectual content. NV interpreted and synthesized the content from the literature review, critically revised the manuscript for important intellectual content. BM interpreted and synthesized the content from the literature review, critically revised the manuscript for important intellectual content. AM interpreted and synthesized the content from the literature review, critically revised the manuscript for important intellectual content. All authors gave final approval for publication and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations

Conflict of interest All other authors have no competing interests to declare that are relevant to the content of this article.

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