Review

Diffusion Idiopathic Skeletal Hyperostosis (DISH), a Link between Gut Microbiota and Spinal Degenerative Diseases

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Review

Diffusion Idiopathic Skeletal Hyperostosis (DISH), a Link between Gut Microbiota and Spinal Degenerative Diseases

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Abstract: The interplay between Diffuse Idiopathic Skeletal Hyperostosis (DISH) and the gut microbiota represents a compelling area of research, offering insights into the relationship between spinal degenerative diseases and the gut's microbial inhabitants. This comprehensive review seeks to unravel the complex connection, shedding light on its implications for human health and potential therapeutic avenues. A crucial section dives into the world of gut microbiota (GM), exploring its impact on human health, featuring its defining characteristics, and highlighting its role in metabolism, immunomodulation, host interaction, and how its composition changes over time. The subsequent portion delves into the relationship between microbiome composition and pathological bone development, including the link between Intervertebral Disc Degeneration (IDD) and gut inflammation, emphasizing how gut inflammation and GM dysbiosis play pivotal roles. Further dissecting the interconnections, various axes of influence, including the gut-spine axis, gut-bone axis, gut-joint axis, gut-disc axis (specific to DISH), gut-ligament axis, and gut-muscle axis, are discussed. Of particular interest is the section on the impact of GM on DISH-derived pain, addressing a critical aspect of the condition's manifestation. The review discusses the potential of GM modulation as a treatment for DISH, providing hope for therapeutic advancements. Additionally, it highlights the positive impact of lifestyle interventions, such as dietary modifications, sleep optimization, and exercise regimens, in mitigating GM dysbiosis and potentially improving DISH outcomes. Lastly, the intriguing prospect of fecal microbiome transplant and its implications for DISH management is examined, opening new avenues for research and therapeutic interventions. In conclusion, this comprehensive review underscores the intricate interplay between DISH and the gut microbiota, offering a fresh perspective on the impact of GM on spinal degenerative diseases. It emphasizes the potential for innovative treatments, such as GM modulation and lifestyle interventions, and presents fecal microbiome transplant as an exciting area for future exploration.

Keywords: DISH; gut microbiota; skeletal hyperostosis; spondylitis; irritable bowel syndrome; inflammatory bowel disease; intervertebral disc degeneration

Introduction

Hyperostosis is a medical condition characterized by the excessive growth and thickening of bone tissue in various parts of the body. This abnormal bone growth can affect different bones, leading to a range of clinical manifestations and symptoms [1,2]. Hyperostosis can occur as a primary condition or as a secondary response to other underlying diseases or factors. Understanding hyperostosis requires an exploration of its types, causes, clinical implications, and management. Craniofacial, Frontal, Hyperostosis Frontalis Interna (HFI), and Diffuse Idiopathic Skeletal Hyperostosis (DISH) are the major forms of hyperostosis. The underlying causes of hyperostosis can vary depending on the specific type. In some cases, genetic factors may contribute to an individual's

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susceptibility to hyperostosis. However, secondary hyperostosis is often associated with other factors, such as: Inflammatory Diseases, Metabolic Disorders, Trauma and Aging. Hyperostosis can have significant clinical implications depending on its location and extent. Some common effects and complications associated with hyperostosis are Reduced Range of Motion, Pains, Altered Appearance, Functional Impairment, and Comorbidities. The Treatment of hyperostosis is largely based on managing its associated symptoms and complications. While there is no cure for hyperostosis, management strategies may include: Pain Management, Surgical Interventions, Management of Underlying Conditions and Lifestyle Modifications [3,4].

Diffuse Idiopathic Skeletal Hyperostosis (DISH), also known as Forestier's disease, is a systemic skeletal disorder characterized by the calcification and ossification of ligaments and entheses, primarily affecting the spine and peripheral joints [5,6]. DISH is characterized by Abnormal Bone Growth, Spinal Involvement, Peripheral Joint Involvement, and Symptoms. The exact cause of DISH is not well understood, and it is often classified as an idiopathic condition, meaning the underlying cause is unknown. However, some factors such as aging, genetics, and metabolic factors may contribute to its development and progression. DISH may have several clinical implications such as stiffness and reduced mobility, pain, and increased fracture risk. Diagnosing DISH typically involves clinical evaluation and imaging studies, such as X-rays and CT scans, which can reveal characteristic findings like flowing candle wax appearance along the spine. Pain management, maintaining mobility, monitoring, and preventing complications and surgical interventions are some generally focused areas in the management and treatment of DISH [7–9].

Diffuse Idiopathic Skeletal Hyperostosis (DISH) has several economic implications, both for individuals affected by the condition and for healthcare systems. Individuals with DISH may require frequent medical consultations, diagnostic imaging, and various treatments to manage their symptoms and complications. These costs can include the expenses related to X-rays, CT scans, and MRI scans for diagnosis and monitoring. DISH can cause pain, stiffness, and reduced mobility, which may impact an individual's ability to work, particularly in physically demanding occupations resulting in absenteeism and reduced work productivity. In severe cases, DISH can lead to significant disability, requiring social support services and disability benefits. Individuals with DISH may need assistance with daily activities and may require home modifications or medical equipment, which can result in financial burdens. In the healthcare sector, research into the causes, diagnosis, and management of DISH may require funding and resources. This includes studies focused on developing more effective treatments and interventions. On a broader scale, the economic impact of DISH extends to society. As the condition affects primarily older adults, the economic burden may increase with an aging population, particularly in countries with a higher prevalence of DISH [10,11]. Health insurance providers may incur higher costs due to the diagnosis and management of DISH, including covering expenses related to medications, surgeries, and rehabilitation services. Beyond direct healthcare costs, the economic impact includes the intangible costs related to reduced quality of life and productivity loss for individuals with DISH and their families [12,13]. It's imperative to note that the economic impact of DISH can vary widely, vividly among individuals, depending on the severity of their condition, their access to healthcare services, and the level of support they receive. Furthermore, the economic consequences of DISH are intertwined with broader healthcare and socioeconomic factors. Researchers and policymakers may continue to investigate these economic aspects to better understand and address the challenges posed by this condition [14].

Diffuse Idiopathic Skeletal Hyperostosis (DISH) presents several challenges for both individuals affected by the condition and healthcare providers. DISH can be challenging to diagnose accurately, especially in its early stages, as it may mimic other musculoskeletal conditions, such as ankylosing spondylitis or osteoarthritis. Lack of awareness among healthcare providers can lead to underdiagnoses or misdiagnosis, delaying appropriate treatment and management. DISH can also manifest with varying symptoms and severity among individuals [15]. While some may experience mild stiffness and discomfort, others may suffer from severe pain and reduced mobility. The heterogeneity of symptoms makes it difficult to establish standardized treatment approaches. There are no well-established, universally accepted treatment guidelines for DISH due to its rarity and the

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absence of a cure. Treatment decisions often rely on individual symptom management rather than standardized protocols. Pain management can be particularly challenging in individuals with DISH, as chronic pain may not always respond adequately to standard medications and balancing pain relief with potential side effects of pain medications, especially in the long term, can be complex [16]. DISH remains a relatively understudied condition, resulting in limited scientific research and clinical trials. Lack of awareness among healthcare professionals and the general public can further hinder early diagnosis and intervention. Therefore, DISH can significantly affect an individual's quality of life due to pain, stiffness, and reduced mobility. The condition may limit an individual's ability to perform daily activities and engage in physical and social activities. Furthermore, Surgical interventions, while effective in some cases, pose risks and complications, particularly in older individuals with DISH. Decisions regarding surgery must carefully weigh potential benefits against surgical risks [5]. DISH is a chronic condition, and long-term management is essential to address evolving symptoms and potential complications. Individuals with DISH may require ongoing medical care and lifestyle modifications to maintain their quality of life. Disparities in access to healthcare services and specialists may exist, affecting the ability of some individuals to receive timely and appropriate care for DISH. Finally, there is a need for more comprehensive research into the causes, pathophysiology, and treatment strategies for DISH. - Expanding research efforts can help improve our understanding of the condition and lead to better management approaches. The challenges associated with DISH are the motive of this review as we intend to contribute to the wider understanding of DISH, its link with the gut microbiota and spinal degenerative diseases.

Our objective is to embark on a journey of exploration, delving into the intricate connections between Diffuse Idiopathic Skeletal Hyperostosis (DISH) and the gut microbiota in the context of spinal degenerative diseases. This involves highlighting the noteworthy contributions of other researchers in our collective pursuit of understanding the broader significance of the gut microbiota in relation to health.

Gut microbiota (GM)

The gut microbiota, often referred to as the gut microbiome, constitutes a complex and diverse community of microorganisms, primarily consisting of bacteria, residing within the digestive system of humans and various animal species. These microorganisms serve as fundamental actors in a multitude of facets related to health and illness. The gut microbiota is a remarkably intricate ecosystem, housing trillions of microorganisms representing a wide array of species. While bacteria are the predominant constituents, other microorganisms, encompassing viruses, fungi, and archaea, also make significant contributions to the intricate tapestry of the gut microbiome [17,18].

The functions carried out by the gut microbiota are indispensable for the human body's overall well-being (Figure 1). Specific strains of bacteria in the gut play a vital role in the digestion of complex carbohydrates and dietary fiber, substances that the human body would struggle to break down unaided. Furthermore, these microorganisms are essential in facilitating the absorption of essential nutrients and minerals, thereby ensuring that the body receives the sustenance it requires. Their involvement extends to the development and orchestration of the immune system, and they act as sentinels preventing the unchecked proliferation of harmful pathogens by competing for essential resources. Additionally, these microorganisms are integral to the metabolic processes responsible for breaking down dietary compounds and synthesizing essential vitamins and beneficial short-chain fatty acids. The gut microbiota also contributes to the safeguarding of the gut barrier, serving as a protective shield to prevent harmful substances from permeating into the bloodstream [19,20].

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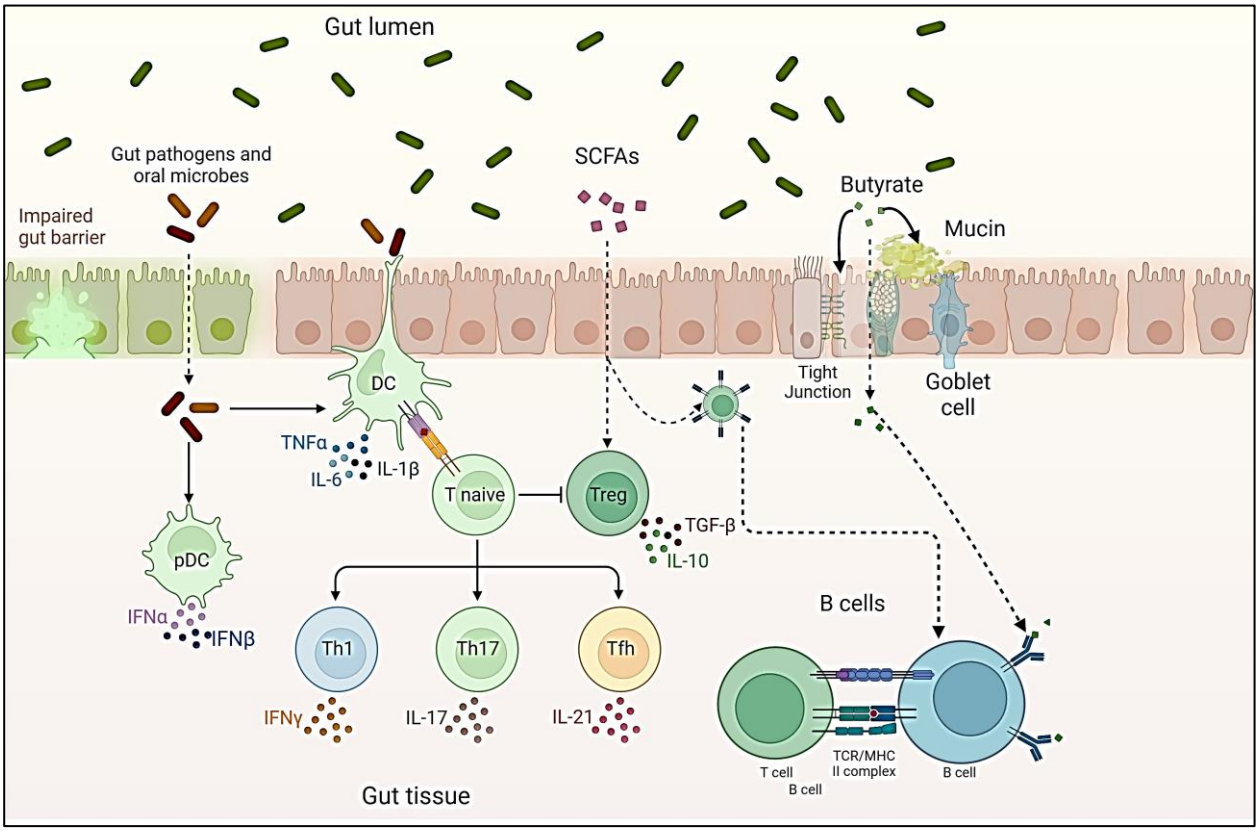

Figure 1. Role of the Gut Microbiota in autoimmune diseases. Dendritic cells are tolerogenic, and they play a role in the induction of anti-antigen tolerance. Various factors, such as SCFAs (e.g., Butyrate, propionate, Butanoic acid), non-degradable oligosaccharides, vitamin D3, and retinoic acid, can trigger a tolerogenic effect of DCs. Butyrate is also known to affect tight junction formation and thus critical in keeping the integrity of the gut lining. Immunologically, the various features of this process include the ability of DCs to resist maturation and the reduction in levels of costimulatory markers. In addition to this, the activation of membrane-bound TNF receptor and the induction of various anti-inflammatory cytokines (TGF-β, IL-27 and IL-10, IL-6, IL-2, and IL-12) are also important factors in the development of healthy gut system. When pathogenic bacteria disrupt this process, it leads to the activation of tDCs, and when activated by pulsed DCs, these tDCs can generate autoantigens that can be delivered to effector T cells. Even though, the development of the regulatory T cells is dependent on cell contact, DCs can also interact with tissue-resident T cells to form an innate tolerance mechanism, which contributes to the development of tolerogenic phenotypes. SCFAs from GM such as butyrate can directly bind to B-cells antibodies thus disrupting the ability of B-cells to interact with T-cells to activate them.

The composition and equilibrium of the gut microbiota exert a profound impact on an individual's health. Any disruption in this balance, often referred to as dysbiosis, has been closely associated with a wide spectrum of health conditions. These encompass gastrointestinal disorders, autoimmune diseases, metabolic disorders, and intriguingly, mental health concerns [21].

Diet wields a substantial influence over the composition of the gut microbiota. Diets rich in dietary fiber, for instance, promote the flourishing of beneficial bacteria, whereas diets abundant in sugars and heavily processed foods can encourage the proliferation of less advantageous microorganisms. Furthermore, the administration of antibiotics can significantly disrupt the equilibrium of the gut microbiota by indiscriminately eradicating both harmful and beneficial bacteria. Some medications can also exert an influence on the composition of the gut microbiome. In recent years, emerging research has shed light on the existence of a bidirectional communication system known as the gut-brain axis, which facilitates intricate interactions between the gut and the

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brain. Changes in the gut microbiota have been demonstrated to potentially influence mental health and behavior [22,23].

Efforts to manipulate the gut microbiota through various interventions, including probiotics (live beneficial bacteria), prebiotics (substances that promote the growth of beneficial bacteria), and fecal microbiota transplantation (FMT), are areas of active research with promising therapeutic potential [24]. (FMT, in particular, involves the transfer of fecal matter from a healthy donor into the gastrointestinal tract of a recipient to address specific medical conditions. The analysis of an individual's gut microbiota profile, achieved through the practice of gut microbiome sequencing, holds tremendous promise for the field of personalized medicine. It has the potential to revolutionize the diagnosis and treatment of a wide spectrum of diseases, tailored to the unique composition of an individual's microbiota [25].

The gut microbiota exerts a substantial influence on metabolism and the delicate balance of energy within the body. Imbalances in this microbial community have been closely associated with significant global health challenges such as obesity, type 2 diabetes, and metabolic syndrome. These health concerns transcend borders and affect populations worldwide. Additionally, an unhealthy gut microbiota can play a contributing role in the development of gastrointestinal disorders like irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), conditions that impact millions of individuals across the globe. The intricate gut-brain axis, facilitating bidirectional communication between the digestive system and the brain, has emerged as a critical link. Alterations in the gut microbiota, capable of affecting mental health, have been linked to conditions like depression and anxiety [17].

In the United States, dietary choices wield considerable influence over the composition of the gut microbiota. High consumption of processed foods and the addition of sugars to diets can significantly disturb the balance of gut bacteria, potentially contributing to metabolic and digestive problems. The prevalent issues of obesity and type 2 diabetes have taken center stage as major health challenges in the U.S. The gut microbiota's role in regulating metabolism and influencing body weight places it at the forefront of addressing these health concerns. Within the spectrum of inflammatory bowel diseases (IBD), including conditions like Crohn's disease and ulcerative colitis, the impact on the health of Americans is undeniable [26]. Research into the gut microbiota's role in these diseases remains an active area of investigation. In the United States, probiotics, live beneficial bacteria, and prebiotics, substances that foster the growth of beneficial bacteria, are commonly consumed with the hope of reaping potential gut health benefits. The U.S. stands as a hub for pioneering research institutions and esteemed medical centers dedicated to studying the impact of the gut microbiota on a wide array of health conditions. The knowledge gleaned from this research informs clinical practices and dietary recommendations, significantly influencing health care approaches [27,28].

The gut microbiota's influence on human health is a topic that commands global interest and extensive research efforts. It holds implications for areas as diverse as public health, nutrition, and clinical medicine. As the understanding of the gut microbiota's multifaceted role in health and disease continues to evolve, the potential for manipulation through interventions like probiotics, prebiotics, and dietary modifications emerges as a promising avenue for enhancing health outcomes [29]. Both on a global scale and within the United States, promoting a balanced and diverse gut microbiota through a wholesome diet, regular physical activity, and the judicious use of antibiotics remains a central focus for the maintenance of overall health. Additionally, the concept of personalized medicine, which takes into account an individual's unique gut microbiota profile, is steadily emerging as a potential strategy for improving health and preventing disease [30,31].

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Gut Microbiota and nutrition

Bresser et al. [32], substantially explored the link between gut microbiota and nutrition and emphasized it as a foundational element of human health. The gut microbiota, an intricate assembly of microorganisms inhabiting the gastrointestinal tract, fulfills a crucial function in the digestion and utilization of nutrients derived from our diets.

Fiber-rich foods, such as fruits, vegetables, and whole grains, are essential for maintaining a healthy gut microbiota. Gut bacteria ferment dietary fiber, producing short-chain fatty acids like butyrate, which are known to have various health benefits [33]. Prebiotics are non-digestible compounds found in certain foods that serve as nourishment for beneficial gut bacteria. Examples include inulin, found in chicory root, and oligofructose, found in onions. Consuming prebiotic-rich foods can promote the growth of these beneficial bacteria. [34], in their 2023 review explored in details prebiotics and probiotics and their influence on the gut microbiota. They state that probiotics are live beneficial bacteria that can be consumed through foods like yogurt or in supplement form. They can introduce specific strains of beneficial bacteria into the gut, potentially improving its composition. Similarly, [35] linked fermented foods and their benefits in nutrition. They explained that fermented foods like yogurt, kefir, sauerkraut, and kimchi contain live beneficial bacteria. These foods can help maintain a balanced gut microbiota and provide probiotic benefits.

A diverse and balanced diet with a variety of nutrients and food groups is crucial for supporting a diverse gut microbiota. A lack of dietary diversity may lead to a less diverse gut microbial community. Diets high in processed foods and added sugars can negatively impact the gut microbiota. These diets can encourage the growth of less beneficial microorganisms and are associated with various health issues. The gut microbiota can influence weight regulation and metabolism [36]. Imbalances in the gut microbiota have been linked to obesity and metabolic disorders. Hence, understanding an individual's unique gut microbiota composition through microbiome sequencing can lead to personalized dietary recommendations that optimize health. Certain medical conditions, such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), are influenced by the gut microbiota. Nutrition can be used as a therapeutic tool to manage these conditions [20].

In this discussion, we will explore various facets of the gut microbiota and their intricate relationships with nutrition, including metabolism, immunomodulation, host interaction, alterations in gut microbiota composition, the effects of aging, nutritional modifications, drug metabolism, and the influence of lifestyle. It's important to emphasize that maintaining a well-rounded and diverse diet rich in fiber, prebiotics, and probiotics is indispensable for nurturing a healthy gut microbiota. Nutrition not only shapes the composition of the gut microbiota but also extends its impact to encompass overarching aspects of health, spanning metabolism, immune functionality, and digestive well-being. Thus, making informed dietary decisions that foster a flourishing gut microbiota stands as a cornerstone of overall well-being.

Gut Microbiota and metabolism

The connection between gut microbiota and metabolism is intricate and ever-changing, holding significant implications for human well-being. Below, we will delve into several noteworthy ways through which the gut microbiota collaborates with metabolism.

Energy accumulation: Energy accumulation, a fundamental aspect of human health and vitality, is intricately connected to the symbiotic relationship between the gut microbiota and dietary components. The human digestive system has its limitations in breaking down complex carbohydrates and fibers effectively. However, the gut microbiota steps in as a crucial partner in this metabolic process. Within the intricate ecosystem of the gastrointestinal tract, the gut microbiota thrives on dietary fiber, particularly from sources like fruits, vegetables, and whole grains. These indigestible fibers are, in fact, the microbiota's preferred food source [37]. Through a process known as microbial fermentation, these fibers are transformed into short-chain fatty acids (SCFAs), with butyrate, acetate, and propionate being the most prominent among them. The significance of these SCFAs is profound. Not only do they play an essential role in maintaining gut health, but they also

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serve as an additional energy reservoir for the human body. Upon their production, SCFAs are absorbed through the intestinal lining, allowing the body to harness the energy contained within them. Butyrate, in particular, is renowned for its role in upholding the integrity of the gut barrier, which is vital in preventing harmful substances from infiltrating the bloodstream. Furthermore, these SCFAs contribute to a balanced microbial community in the gut, promoting overall well-being [38].

However, the efficiency of this energy accumulation process depends on the composition of the gut microbiota. A diverse and balanced microbial community is more adept at breaking down dietary fibers and producing SCFAs. In contrast, an imbalanced microbiota, often resulting from dietary choices that favor processed foods over fiber-rich options, can hinder this process. By appreciating the link between gut microbiota and energy accumulation, individuals can make informed dietary decisions. Emphasizing fiber-rich foods, prebiotics, and probiotics in one's diet can support a diverse and balanced gut microbiota. This, in turn, ensures that the microbial partners in our gastrointestinal tract effectively contribute to energy accumulation, which is not only vital for health but also for sustaining the vigor required for our daily lives [39,40].

Metabolic Efficiency: Metabolic efficiency, a critical aspect of overall health and well-being, is intricately linked to the composition of the gut microbiota. The gut microbiota, a complex community of microorganisms residing in the gastrointestinal tract, plays a pivotal role in energy metabolism. Its role in extracting and storing energy from the diet is of particular significance. An altered gut microbiota composition can have far-reaching consequences for how efficiently the body harnesses energy from the foods we consume. The gut microbiota's composition is a dynamic and diverse ecosystem, consisting of numerous bacterial species, and this diversity contributes to its influence on metabolic processes [41].

[42], explored prebiotics and the human gut microbiota: From breakdown mechanisms to the impact on metabolic health, and reckon that, the key mechanisms through which the gut microbiota affects metabolic efficiency is by breaking down complex carbohydrates and dietary fibers that the human body cannot digest on its own. This microbial fermentation process yields short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate. These SCFAs are not only crucial for gut health but also serve as an additional energy source for the body. They can be absorbed through the intestinal lining and utilized as an energy reservoir. However, when the balance of the gut microbiota is disrupted, for instance, due to poor dietary choices or environmental factors, it can lead to imbalances in the production of SCFAs. These imbalances can influence energy metabolism and storage. In cases where certain bacterial strains dominate, they may be more efficient in extracting calories from the same amount of food, potentially contributing to excess calorie intake and, ultimately, weight gain. Weight gain and obesity have been strongly associated with an imbalanced gut microbiota composition. Some microbial strains may indeed extract more calories from identical food quantities, which can tip the energy balance towards surplus. Over time, this imbalance can lead to excessive calorie storage in the form of body fat, contributing to weight gain and obesity [43].

Dietary choices that support a healthy gut microbiota, such as consuming fiber-rich foods, prebiotics, and probiotics, can contribute to optimal metabolic function and overall health. By recognizing the link between gut microbiota and metabolic efficiency, individuals can make informed dietary decisions that promote a thriving gut microbiota and long-term well-being [43].

Appetite modulation: Appetite regulation is a multifaceted process influenced by various factors, and the gut microbiota has emerged as a significant player in this intricate interplay. It exerts its influence by modulating the secretion of hormones that signal hunger and satiety, ultimately shaping our dietary choices and meal patterns [44].

One such hormone is leptin, often referred to as the "satiety hormone." Leptin is produced by adipose tissue and plays a central role in regulating food intake. When leptin levels rise, it sends signals to the brain, indicating that the body has sufficient energy stores, and consequently, it's time to stop eating. On the flip side, when leptin levels are low, it signals hunger and the need to consume more food. The gut microbiota has been shown to influence leptin production and sensitivity. An imbalance in the gut microbiota can disrupt these hormonal signals, potentially leading to a decreased sensitivity to leptin. This can result in individuals feeling less full after eating, which may

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contribute to overeating and, ultimately, weight gain. This is confirmed in a review published by [45] on "*the Leptin signaling in obesity and colorectal cancer*". Another hormone impacted by the gut microbiota is ghrelin, often referred to as the "hunger hormone." Ghrelin is produced in the stomach and stimulates appetite, signaling to the brain that it's time to eat. When the gut microbiota is imbalanced, it can affect ghrelin levels, potentially leading to heightened feelings of hunger and increased food intake. In addition to these hormonal effects, the gut microbiota can also influence food preferences. Specific microbial strains may have preference for particular nutrients, leading to cravings for certain types of foods. This can contribute to dietary patterns that are less healthy, as the gut microbiota's influence drives the consumption of foods that may not align with an individual's nutritional goals [46].

Glucose and Lipid Metabolism: Glucose and lipid metabolism are critical components of the body's energy regulation and overall health, and the gut microbiota wields a significant influence over both processes.

In the realm of lipid metabolism, the gut microbiota plays a pivotal role in the breakdown and absorption of dietary fats. A well-balanced microbiota contributes to the efficient processing of fats, aiding in the digestion and assimilation of these essential nutrients. However, an imbalanced gut microbiota, known as dysbiosis, can disrupt this harmonious relationship. Dysbiosis can lead to alterations in lipid profiles, which may result in conditions like dyslipidemia. Dyslipidemia involves abnormal levels of lipids, including high levels of cholesterol and triglycerides in the bloodstream, which are known risk factors for heart disease. This illustrates the profound impact that the gut microbiota can have on lipid metabolism and, consequently, on cardiovascular health [47].

Furthermore, the gut microbiota is intricately involved in glucose metabolism, a critical aspect of energy regulation. The ability to efficiently utilize glucose for energy is closely tied to insulin sensitivity. Insulin, a hormone produced by the pancreas, allows cells to absorb glucose from the bloodstream, facilitating its use as an energy source. However, when the gut microbiota is imbalanced, it can influence insulin sensitivity, potentially leading to insulin resistance. Insulin resistance is a key factor in the development of type 2 diabetes. In individuals with insulin resistance, the body's cells do not respond effectively to insulin, leading to elevated blood sugar levels [48]. Over time, this can result in the onset of diabetes, a chronic condition with serious health implications. The gut microbiota's involvement in glucose and lipid metabolism is far-reaching and intricate. It underscores the importance of maintaining a healthy and balanced gut microbiota to support proper energy regulation and metabolic health. Disruptions in this delicate balance can contribute to conditions like dyslipidemia and type 2 diabetes, highlighting the critical role of the gut microbiota in overall well-being [20].

Metabolism and Inflammation: Metabolism and inflammation are intricately connected, and an unbalanced gut microbiota can set the stage for a cascade of health issues. One of the most significant consequences is the potential for chronic inflammation, which has profound implications for metabolic health. Chronic inflammation, often stemming from an altered gut microbiota composition, is closely associated with metabolic disorders, such as metabolic syndrome. This cluster of conditions, including high blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels, can significantly increase the risk of heart disease, stroke, and type 2 diabetes [49]. The interplay between the gut microbiota and inflammation is complex. An imbalanced microbial community can lead to the release of pro-inflammatory molecules and hinder the production of anti-inflammatory compounds. As a result, the body's finely tuned metabolic processes can be disrupted. One of the key manifestations of this disruption is insulin resistance, a hallmark of metabolic syndrome and a precursor to type 2 diabetes. Insulin is a hormone that helps regulate blood sugar levels by allowing cells to take in glucose for energy. When the body becomes resistant to insulin, as is often the case in chronic inflammation, it struggles to use glucose effectively. This can lead to elevated blood sugar levels, which, if left uncontrolled, can result in diabetes [50].

Short-Chain Fatty Acids (SCFA): Short-chain fatty acids (SCFAs), the metabolic byproducts of microbial activity in the gut, wield a significant influence over various aspects of human health. Among these SCFAs, butyrate takes the spotlight as a remarkable and versatile compound, celebrated

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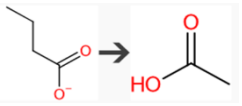
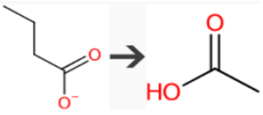
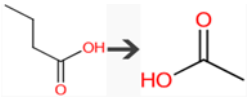
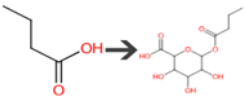
for its multifaceted role in preserving the integrity of the gut barrier and mitigating inflammatory responses. Butyrate plays a pivotal role in maintaining the integrity of the gut barrier, a critical defense mechanism that separates the gut's contents from the body's internal environment. The gut barrier is lined with epithelial cells held together by tight junctions. Butyrate reinforces these tight junctions, enhancing the barrier's strength and impermeability [51]. Some common SCFAa and their biotranfromations are shown in Table 1. A robust gut barrier prevents the unwanted passage of harmful substances, such as toxins and pathogens, into the bloodstream, reducing the risk of systemic inflammation and immune responses. Also, butyrate is a potent anti-inflammatory agent as it exerts its anti-inflammatory effects by inhibiting the activity of pro-inflammatory molecules and promoting the production of anti-inflammatory compounds. This duality of action helps balance the immune response in the gut and reduces the risk of chronic, low-grade inflammation, which is associated with various diseases, including inflammatory bowel diseases (IBD) and metabolic disorders. The cells lining the colon, known as colonocytes, primarily rely on butyrate as their primary energy source. This metabolic preference ensures the health and functionality of the colonic epithelium. A deficiency of butyrate can lead to colonocyte dysfunction and compromise the gut's overall performance [52].

Biotransformation of common Short Chain Fatty Acids

The main source of carbon for the host's microbiome is SCFAs, which are known to be formed by the fermentation of dietary fibers. The ratio of SCFAs to the number of microorganisms in the colon is influenced by the composition of the gut microbiome and the type of dietary fibers that are used by the microorganisms as substrates. There yet remains a link between further biotransformation of SCFAs and metabolite's effect on human health. Among the most common types of SCFAs found in the human colon are propionic acid, butyric acid, and acetic acid. These substances make up about 90% to 95% of the SCFAs found in the colon. GM has the potential to not only produce these SCFAs but also modify them into completely different forms. Table 1, summarizes the most predominant SCFAs in the gut and their modification by human GM.

Table 1. Biotransformation of common Short Chain Fatty Acids. USGBE, Uspecified Gut Bacterial Enzyme. Biotransformation data were derived from Biotransformer 3.0 by submitting the SMILES of the SCFAs to this online biotransformation prediction server (available at https://biotransformer.ca/queries).

Name	Enzymes	Reaction type	Biotransformation reaction
Methanoic acid	USGBE	beta-Oxidation of carboxylic acid	
Ethanoic acid	USGBE	beta-Oxidation of carboxylic acid	
Propanoic acid	ND	ND	ND
Butanoic acid	USGBE	beta-Oxidation of carboxylic acid	
Butanoic acid	Bacterial UDP-glucuronosyltransferase	O-Glucuronidation of aliphatic acid	

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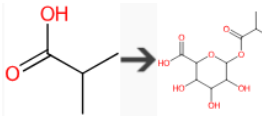
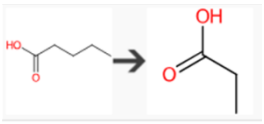
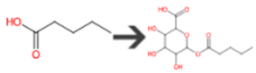
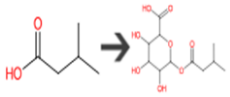
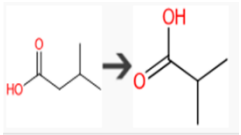
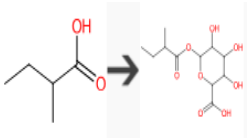
2-Methylpropanoic acid	SULFOTRANSFERASE	alpha-Amino acid to aldoxime	
Pentanoic acid	Unspecified gut bacterial enzyme	beta-Oxidation of carboxylic acid	
Pentanoic acid	Bacterial UDP-glucuronosyltransferase	O-Glucuronidation of aliphatic acid	
3-Methylbutanoic acid	Unspecified gut bacterial enzyme	alpha-Oxidation of carboxylic acid	
3-Methylbutanoic acid	Bacterial UDP-glucuronosyltransferase	O-Glucuronidation of aliphatic acid	
2-Methylbutanoic acid	Bacterial UDP-glucuronosyltransferase	O-Glucuronidation of aliphatic acid	

Furthermore, butyrate plays a role in regulating the expression of genes involved in diverse cellular processes. This gene regulation affects various aspects of gut health, including cell proliferation, differentiation, and apoptosis (programmed cell death). In this way, butyrate helps maintain a balanced and healthy gut lining. It is associated with potential anti-cancer properties. It can inhibit the growth of cancer cells, induce apoptosis in abnormal cells, and regulate cell cycle progression. These effects highlight its role in the protection against colorectal cancer. Emerging research suggests that butyrate may have implications for neurological health. The gut-brain connection, often referred to as the "gut-brain axis," implies that substances produced in the gut can influence brain function. Butyrate, through its anti-inflammatory and neuroprotective properties, may play a role in supporting cognitive function and potentially impact conditions like depression and anxiety [53]. The multifaceted significance of butyrate in gut health and beyond underscores the intricate interplay between the gut microbiota and the overall well-being of the human body. Recognizing the pivotal role of butyrate in preserving gut barrier integrity and quelling inflammation emphasizes the importance of maintaining a balanced gut microbiota through dietary choices rich in fiber, prebiotics, and probiotics. This proactive approach to gut health contributes to the promotion

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of a flourishing, resilient, and harmonious gut environment, with far-reaching implications for overall health and vitality [54–56].

Bile Acid Metabolism: The impact of the gut microbiota extends far beyond the confines of the gastrointestinal tract and reaches into various critical aspects of human physiology. One such fundamental influence is on bile acid metabolism, a process that plays a pivotal role in the digestion and absorption of dietary fats. Bile acids are synthesized in the liver and secreted into the small intestine, where they emulsify dietary fats, enabling their breakdown and absorption [57]. However, the intricate interplay between gut microbes and bile acids has revealed a profound connection with significant implications for metabolism and the overall balance of energy within the body. Within the gut, some members of the microbiota possess enzymes that can chemically modify primary bile acids produced by the liver. These modifications lead to the generation of secondary bile acids with distinct properties. The composition of bile acids, including the ratio of primary to secondary bile acids, can be influenced by the gut microbiota [58].

Bile acids are essential for the digestion and absorption of dietary fats. They emulsify fat molecules, breaking them into smaller droplets that can be more readily acted upon by digestive enzymes. This process is crucial for the efficient uptake of dietary lipids and fat-soluble vitamins, such as vitamins A, D, E, and K. Changes in bile acid profiles can have profound consequences on metabolism and the balance of energy within the body. Alterations in the composition and ratio of bile acids can influence fat absorption, energy expenditure, and fat storage. This, in turn, may have implications for body weight and the development of metabolic disorders like obesity and non-alcoholic fatty liver disease (NAFLD) [59]. Bile acids also play a role in hormone signaling. They can interact with receptors in the gut, such as the farnesoid X receptor (FXR) and the Takeda G-protein receptor 5 (TGR5), which have downstream effects on metabolism and energy utilization. The composition of bile acids in the gut can influence the structure and function of the gut microbiota. Some bile acids have antimicrobial properties and can impact the relative abundance of different microbial species in the gut [60].

It is exciting to see researchers making collaborative efforts explore bile acid profiles and the gut microbiota through dietary interventions, medications, and probiotics to address conditions associated with metabolic disturbances.

Body Weight and Composition: The delicate association between the composition of the gut microbiota and obesity has become a focal point of research in the field of human health. An imbalance or dysbiosis in the gut microbiota, marked by an alteration in the relative abundance of various microbial species, has been closely associated with disruptions in the body's overall physique, most notably obesity [61]. One of the pivotal mechanisms through which the gut microbiota contributes to obesity revolves around the extraction and utilization of calories from the diet. It has been observed that specific microbial strains, when dominant in the gut, can exhibit an enhanced capacity to extract additional calories from identical food quantities. This heightened caloric extraction can lead to an imbalance in energy homeostasis and contribute to weight gain over time [62].

Certain gut microbes have evolved to be highly efficient at breaking down complex carbohydrates, fiber, and other dietary components that are normally indigestible by the human host. This ability allows them to access additional calories that would otherwise pass through the gut undigested. Microbial fermentation of undigested dietary components in the colon produces short-chain fatty acids (SCFAs), which can serve as an additional energy source [63]. These SCFAs are absorbed and utilized by the body, contributing to the overall calorie load. Dysbiosis in the gut microbiota can also trigger low-grade inflammation and metabolic disturbances. Chronic inflammation can disrupt the body's hormonal signaling related to appetite, metabolism, and fat storage. Furthermore, the gut microbiota influences the production of certain hormones, including those involved in appetite regulation and energy expenditure. Imbalances in these hormones can lead to overeating and a reduction in energy expenditure, further promoting weight gain [45].

Drug Metabolism: The gut microbiota's role in drug metabolism primarily centers around the biotransformation of drugs, a process that can lead to either enhanced or diminished drug

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effectiveness. Several factors contribute to this phenomenon: Gut bacteria can produce enzymes that can activate or inactivate drugs. For example, certain drugs may be transformed into more potent or less active forms by these microbial enzymes, affecting their therapeutic effects, some drugs are metabolized by the gut microbiota into less toxic byproducts, reducing their potential side effects. This microbial detoxification process can enhance drug safety, changes in the gut microbiota composition can affect drug absorption in the intestines [64]. An imbalanced microbiota might hinder the absorption of certain drugs, diminishing their efficacy, the gut microbiota can also modulate drug transporters in the intestines, which regulate the movement of drugs from the gut into the bloodstream. Altered transporter activity can impact drug bioavailability. By competing for nutrients and space in the gut, gut bacteria can affect the overall bioavailability of drugs. This competition can either increase or decrease a drug's concentration in the body [65].

The variability in gut microbiota composition among individuals underscores the personalized nature of drug responses. As a result, two people taking the same medication may experience different therapeutic outcomes and side effects based on their unique gut microbiota profiles. This interplay between gut bacteria and drugs has profound implications for medicine. Researchers are actively exploring the potential of harnessing the gut microbiota to optimize drug therapies. Customized drug treatments that consider an individual's microbiome could lead to more effective, safer, and better-tolerated medications [66].

Metabolic Health Interventions: Metabolic health is a critical aspect of overall well-being, and emerging research suggests that manipulating the gut microbiota through various interventions holds promise in this regard. Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are some of the innovative approaches that are being explored as potential tools for enhancing metabolic health. Probiotics and prebiotics are already discussed in earlier sections. Fecal microbiota transplantation (FMT) is a more advanced and specialized intervention [67]. It involves transferring the fecal matter from a healthy donor into the intestines of a recipient to restore a healthier microbial balance. FMT has been primarily used to treat conditions like recurrent Clostridium difficile infections, but ongoing research explores its potential applications for metabolic disorders. By replenishing the gut with a diverse and balanced microbiota, FMT may address microbial imbalances associated with metabolic health issues. These interventions hold great promise, but it's important to note that the field of manipulating the gut microbiota for metabolic health is still in its early stages. More research is needed to understand the specific strains, doses, and duration of interventions required for optimal results. Furthermore, individual responses to these interventions can vary, highlighting the need for personalized approaches in the future [68,69].

The gut microbiota significantly influences various aspects of metabolism, including energy harvest, appetite regulation, lipid and glucose metabolism, and inflammation. Maintaining a balanced and diverse gut microbiota through a healthy diet, regular exercise, and avoidance of unnecessary antibiotic use is a key focus for supporting metabolic health [69].

Gut Microbiota and immunomodulation

Immune System Development: The gut microbiota plays a fundamental role in the development and maturation of the immune system, particularly in early life. Exposure to a diverse range of microbes helps train the immune system to distinguish between harmful pathogens and beneficial microorganisms. The role of the gut microbiota in immune system development is a pivotal aspect of human health, especially during early life. The human body, upon birth, is a relatively sterile environment, and the infant's gut is gradually colonized by microorganisms acquired from the mother, environment, and nutrition [70]. This colonization process is crucial for the development and maturation of the immune system. The gut microbiota serves as an essential educator for the immune system, particularly in infants and young children. Exposure to a diverse range of microbes during this critical period helps to train the immune system to distinguish between harmful pathogens and beneficial microorganisms. This is a fundamental process that ensures the immune system responds appropriately to threats while maintaining tolerance to harmless substances. The gut microbiota provides an essential education to the developing immune system. It exposes the immune cells to a

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wide array of microorganisms, allowing the immune system to "learn" and recognize what is safe and what is a potential threat. This education helps in the proper development of immune responses [71].

The gut microbiota plays a role in regulating the immune system's inflammatory responses. It helps prevent excessive or unnecessary inflammation that can lead to autoimmune conditions or allergies. Properly balanced gut microbiota can promote the immune system's ability to respond effectively when needed while maintaining a state of tolerance and non-reactivity to beneficial microbes and harmless substances. A diverse and healthy gut microbiota can serve as a barrier against harmful pathogens. Beneficial microorganisms occupy ecological niches in the gut, making it challenging for pathogenic invaders to establish themselves [72]. This helps to enhance the innate defense mechanisms of the immune system. The gut microbiota is closely linked to the integrity of the gut barrier. A healthy gut lining with tight junctions between cells prevents the entry of harmful microbes and substances into the bloodstream. By maintaining this barrier, the gut microbiota contributes to overall immune system health. Disruptions in the early colonization of the gut microbiota, such as through the use of antibiotics or a lack of exposure to diverse microorganisms, can have lasting effects on immune system development. These disruptions may be associated with an increased risk of immune-related conditions like allergies, asthma, and autoimmune diseases [73].

Immune Tolerance: The concept of immune tolerance is fundamental to the proper functioning of the immune system. Immune tolerance refers to the ability of the immune system to recognize and tolerate harmless substances, such as allergens or the body's own tissues, without mounting an unnecessary or harmful immune response. This state of balance is crucial for preventing immune overreactions, allergies, and autoimmune conditions, where the immune system mistakenly attacks the body's own cells and tissues [74,75]. The presence of diverse gut microbes helps educate immune cells, teaching them to differentiate between beneficial microorganisms and potentially harmful invaders. This education enables immune cells to avoid attacking beneficial microbes and remain tolerant to them. A well-balanced gut microbiota helps regulate inflammation within the gut and the body as a whole. Inflammation is a fundamental immune response, but when it is excessive or chronic, it can lead to tissue damage and autoimmune conditions. The gut microbiota helps maintain the appropriate balance of inflammation, preventing unnecessary immune responses against harmless substances. Healthy and diverse gut microbiota acts as a protective barrier against harmful pathogens, preventing them from establishing themselves in the gut. By inhibiting the growth of pathogens, the gut microbiota reduces the need for a heightened immune response [76,77].

Some gut microbes can produce substances that have an immunomodulatory effect. These molecules can help dampen immune reactions and promote immune tolerance. Conversely, when there is an imbalance in the composition of the gut microbiota, known as dysbiosis, the risk of immune tolerance disruption increases. Dysbiosis can lead to an inappropriate immune response against harmless substances and an increased risk of allergic reactions or autoimmune diseases. In the case of allergies, an imbalanced gut microbiota can cause the immune system to overreact to allergens, such as pollen, dust mites, or certain foods. This overreaction can result in allergic symptoms like sneezing, itching, or gastrointestinal distress. [78] in their descriptive review explains that, in autoimmune conditions, dysbiosis can contribute to the immune system mistakenly targeting the body's own cells and tissues. For example, in diseases like rheumatoid arthritis, inflammatory bowel disease, or multiple sclerosis, the immune system attacks healthy tissues, leading to chronic inflammation and tissue damage. Gut microbiota influences both the innate and adaptive arms of the immune system. They interact with immune cells, such as macrophages and dendritic cells, and affect the production of cytokines and antibodies, Table 2 indicates some major cytokines and their roles [79].

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Table 2. Major cytokines are involved in intestinal health and pathology, along with their specific functions. These cytokines play crucial roles in maintaining intestinal health, but imbalances or dysregulation can lead to intestinal pathologies, including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis. Understanding the functions of these cytokines is essential for developing treatments for gastrointestinal condition.

No.	Cytokine	Cell(s) Targeted	Diseases	Function in Intestinal Health and Pathology	References
1.	Interleukin-10 (IL-10)	Mφ, T cells, B cells, Dendritic cells, NK cells	Inflammatory bowel diseases, Cancer, Autoimmune diseases, Asthma, Transplant rejection	1. Anti-inflammatory cytokine 2. Regulates immune responses. 3. Maintains intestinal homeostasis by suppressing excessive immune activation. 4. Protective role against colitis and other inflammatory bowel diseases	[81]
2.	Vascular Endothelial Growth Factor (VEGF)	Nerve Cells, Myocardial Cells, Cancer Cells, Fibroblasts, Mφ	Psoriasis, Cancer, Age-Related Macular Degeneration (AMD), Diabetic Retinopathy, Macular Edema	1. VEGF is a signaling protein that primarily stimulates the formation of blood vessels.	[59]
3.	Tumor Necrosis Factor-alpha (TNF-α)	Mφ, Endothelial cells, Neutrophils, T cells, B cells, Fibroblast.	Rheumatoid Arthritis, Inflammatory Bowel Disease (IBD), Psoriasis, Ankylosing Spondylitis, Sarcoidosis	1. Induces inflammation and cell death. 2. Implicated in Crohn's disease and ulcerative colitis. 3. Target of anti-TNF therapies in IBD	[82]
4.	Amphiregulin (Areg)	Ovarian Cells, Mucosal Cells, Cancer Cells, I mmune cells, Smooth Muscle Cells	Inflammatory Bowel Disease (IBD), Cancer, Lung Diseases, Renal Disease, Arthritis	1. Areg is an epidermal growth factor involved in cell growth, proliferation, differentiation, and tissue repair.	[83]
5.	Interleukin-6 (IL-6)	T Cells, B cells, Mφ, Neutrophils, CNS cells, Muscle cells, Hepatocytes.	Covid-19, Sepsis, Chronic Obstructive Pulmonary Disease (COPD), Metabolic Disorders, Cardiovascular Disease	1. Pro-inflammatory cytokine 2. Regulates the acute phase response. 3. Involved in IBD pathogenesis. 4. Promotes inflammatory signaling	[84]
6.	Oncostatin M (OSM)	Hepatocytes, Fibroblasts, Endothelial Cells, Immune Cells, Cartilage Cells, Neurons	Respiratory Diseases, Musculoskeletal Disorders, Cardiovascular Disease, Neurological Diseases, Liver Diseases	1. OSM is primarily involved in immune regulation, inflammation, and tissue repair.	[85]
7.	Interleukin-15 (IL-15)	NK cells, Memory CD8+ T Cells, Tissue-Resident Lymphocytes, Adipocytes, B cells.	HIV/AIDS, Type 1 Diabetes, Celiac Disease, Neurological Disorders, Celiac Disease	1. IL-15 is primarily involved in the proliferation, activation, and survival of various immune cells, particularly natural killer (NK) cells and memory CD8+ T cells.	[56]
8.	Interleukin-17 (IL-17)	Neutrophils, Mφ, T cells, B cells,	Multiple Sclerosis (MS), Rheumatoid Arthritis, Asthma, Spondyloarthritis,	1. Pro-inflammatory cytokine. 2. Drives inflammation and neutrophil recruitment.	[87]

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		Fibroblast, Epithelial cells.	Cytokine Release Syndrome	3. Linked to autoimmune diseases like Crohn's disease. 4. Promotes barrier defense mechanisms	
9.	Interleukin-11 (IL-11)	Epithelial cells, Hematopoietic stem cells, Cardiomyocytes, Osteoblasts, Placental Cells.	Multiple Myeloma, Breast Cancer, Ovarian Cancer, Thrombocytosis, Osteolytic Bone Diseases	1. IL-11 is primarily involved in the regulation of immune responses, inflammation, and hematopoiesis (the formation of blood cellular components).	[88]
10.	Interferon-gamma (IFN-γ)	Mφ, T cells, NK cells, B cells, Dendritic cells, Endothelial cells, Fibroblast	Tuberculosis (TB), Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Chronic Inflammatory Conditions, Cancer	1. Pro-inflammatory cytokines - Enhances immune responses. 2. Linked to pathogenesis of inflammatory bowel diseases (IBD). 3. Regulates inflammation and tissue injury	[89]
11.	Interleukin-10 (IL-10)	Mφ, T cells, B cells, certain epithelial cells, fibroblasts, and endothelial cells.	Multiple Sclerosis (MS), Asthma, HIV/AIDS, Rheumatoid Arthritis (RA), Crohn's Disease	1. IL-10 is primarily involved in regulating immune responses and has anti-inflammatory properties.	[90]
12.	Interleukin-22 (IL-22)	Epithelial cells, Keratinocytes, Intestinal epithelial cells, pancreatic islet cells, Respiratory epithelial cells.	Obesity, Psoriasis, Liver Inflammation and Fibrosis, Fungal Infections, Crohn's Disease	1. Regulates tissue repair and epithelial barrier integrity. 2. Promotes mucosal wound healing. 3. Implicated in defense against infections and IBD - Supports homeostasis in the intestine	[83]
13.	Interleukin-2 (IL-2)	Tregs, T cells, NK cells, B cells, Dendritic cells, Activated Monocytes and Mφ	Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), Type 1 Diabetes, Graft-versus-Host Disease (GVHD), Cytokine Release Syndrome (CRS)	1. IL-2 is primarily involved in the activation and proliferation of T cells, a type of white blood cell central to immune responses.	[84]
14.	Interleukin-23 (IL-23)	Th17, Mφ, NK cells, Dendritic cells	Cancer, Psoriatic Arthritis, Ankylosing Spondylitis, Psoriasis, ulcerative colitis	1. Pro-inflammatory cytokine - Drives Th17 cell differentiation. 2. Involved in pathogenesis of Crohn's diseases. 3. Enhances pro-inflammatory responses	[85]
15.	Granulocyte - Macrophage Colony-Stimulating Factor (GM-CSF)	Granulocytes, T cells, Hematopoietic stem cells, Endothelial cells, Mφ	Lung Diseases, Chronic Obstructive Pulmonary Disease (COPD, Asthma, Multiple Sclerosis, Rheumatoid Arthritis	1. GM-CSF is primarily involved in stimulating the production, maturation, and activation of white blood cells, including granulocytes and macrophages.	[86]
16.	Transforming Growth Factor-beta (TGF-β)	T cells, B cells, Hematopoietic stem cell, Cancer cells, Fibroblast,	Kidney Diseases, Ocular Diseases, Rheumatic Diseases, Cardiovascular Diseases, Fibrosis	1. Has both pro-inflammatory and anti-inflammatory functions. 2. Regulates immune cell differentiation.	[87]

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		Stromal cells, Endothelial cells		3. Involved in immune tolerance and tissue repair. 4. Balances inflammatory responses	
17.	Interleukin-7 (IL-7)	T cells, B cells, NK cells, Common lymphoid progenitors.	Graft-Versus-Host Disease (GVHD), Bone Marrow Disorders, Lymphopenia, HIV/AIDS, Cancer	1. IL-7 is primarily involved in the development, maintenance, and regulation of immune cells, particularly T cells.	[44]
18.	Interleukin-1 (IL-1)	B cells, T cells, Mφ, Monocytes, Nervous system cells, Bone cells, Keratinocytes.	Fever Syndromes, Gout, Osteoarthritis, Rheumatoid Arthritis, Crohn's disease and ulcerative colitis	1. Pro-inflammatory cytokine. 2. Induces inflammation and fever. 3. Plays a role in gut inflammation and mucosal responses. 4. Implicated in IBD and other gut disorders	[88]
19.	Interleukin-33 (IL-33)	Mast cells, Th2 cells, ILC2s, Tregs, NK cells, Epithelial cells.	Fibrotic Diseases, Chronic Obstructive Pulmonary Disease (COPD), Neurological Diseases, Rheumatoid Arthritis	1. IL-33 is primarily involved in regulating immune responses, inflammation, and tissue repair.	[91]
20.	Interleukin-4 (IL-4)	Th2 cells, B cells, Mφ, Mast cells, Skin cells, Hematopoietic stem cells, Fibroblast	Allergic Diseases, Asthma, Eosinophilic Disorders, Atopic Dermatitis, IgG4-Related Disease	1. IL-4 is primarily an anti-inflammatory cytokine. It suppresses pro-inflammatory immune responses, helping to prevent excessive inflammation in the intestinal mucosa	[92]
21.	Interleukin-5 (IL-5)	Eosinophils, B cells, IECs	Eosinophilic Esophagitis (EoE), Asthma, Eosinophilic Bronchitis, Hypereosinophilic Syndrome (HES), Atopic Dermatitis (Eczema)	1. IL-5 is primarily associated with the regulation and activation of eosinophils, a type of white blood cell involved in the immune response to parasitic infections and allergic reactions.	[93]
22.	Interleukin-9 (IL-9)	Th9 cells, Mast cells, T cells, B cells, Epithelial cells.	Allergic Rhinitis, Parasitic Infections, Inflammatory Bowel Disease (IBD), Atopic Dermatitis, Asthma	1. IL-9 is primarily involved in modulating immune responses, particularly in the context of allergies, inflammation, and autoimmune reactions.	[94]
23.	Interleukin-13 (IL-13)	B cells, T cells, Mφ, Airway epithelial cells, Smooth muscle cells, Eosinophils	Asthma, Atopic Dermatitis, Allergic Rhinitis, Eosinophilic Esophagitis, Fibrosis	1. IL-13 is primarily involved in regulating immune responses, particularly in the context of allergies, inflammation, and immune homeostasis.	[92]
24.	Interleukin-25 (IL-25)	Th2 cells, Mast cells, Dendritic cells, Eosinophils, ILC2 cells.	Type 2 Inflammatory Responses, Inflammatory Bowel Disease (IBD), Eosinophilic Esophagitis, Atopic Dermatitis, Allergic Rhinitis	1. IL-25 is primarily involved in regulating immune responses, particularly in promoting type 2 immune responses, which are associated with allergies and immunity against parasitic infections.	[95]

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25.	Thymic Stromal Lymphopoietin (TSLP)	Dendritic cells, B cells, Epithelial cells, Mast cells, ILCs, T cells	Allergic Conjunctivitis, Psoriasis, Chronic Obstructive Pulmonary Disease (COPD), Eosinophilic Esophagitis, Allergic Rhinitis	1. TSLP is a cytokine that is primarily involved in regulating immune responses, particularly in the context of allergies and inflammatory conditions.	[96]

Anti-Inflammatory consequences: Anti-Inflammatory Effects of Gut Bacteria: The relationship between gut bacteria and inflammation is a critical aspect of human health. Inflammation is a natural and necessary response of the immune system to injury or infection. However, chronic, or excessive inflammation can lead to various health problems, including autoimmune diseases, allergies, and inflammatory bowel diseases [80].Gut bacteria play a crucial role in modulating inflammation, primarily through the production of bioactive molecules, such as short-chain fatty acids (SCFAs). A healthy gut barrier prevents harmful substances, such as bacteria or toxins, from leaking into the bloodstream and triggering an immune response. When the gut barrier is compromised, it can lead to increased inflammation. Chronic inflammation in the gut is a hallmark of conditions like inflammatory bowel disease (IBD) [97]. By reducing inflammation in the gut, SCFAs produced by gut bacteria can help manage and prevent these diseases. In addition to their local effects in the gut, SCFAs can also impact inflammation throughout the body. They can help reduce systemic inflammation, which is associated with various chronic diseases, including cardiovascular disease and metabolic disorders. A healthy gut microbiota contributes to the integrity of the intestinal barrier, preventing the passage of harmful substances and pathogens from the gut into the bloodstream. An imbalanced microbiota can lead to "leaky gut," which may contribute to systemic inflammation and immune activation [51].

Protection Against Pathogens: The dynamic environment of the gut microbiota is shaped by intricate interactions, and one crucial role of beneficial gut bacteria is to provide protection against invading pathogens. Beneficial gut bacteria and pathogens vie for the same resources and niche spaces within the gut [98]. This competition can help prevent harmful pathogens from gaining a foothold and proliferating. Essentially, the presence of beneficial bacteria can make it challenging for pathogenic invaders to establish themselves. Beneficial gut bacteria aren't just passive competitors; they are actively engaged in producing substances that inhibit the growth of pathogenic microbes. These antimicrobial substances can directly kill or suppress the proliferation of harmful pathogens [99].

A healthy gut barrier is essential in preventing pathogens from breaching the intestinal lining and entering the bloodstream. Beneficial gut bacteria contribute to maintaining the integrity of the gut barrier. They help ensure that it functions effectively as a protective shield against invading pathogens [100]. The presence of beneficial bacteria in the gut also plays a crucial role in supporting the immune system's response to pathogens. They help train the immune system to distinguish between harmful invaders and beneficial microorganisms, thus preventing unnecessary immune responses. Some beneficial gut bacteria can neutralize or detoxify the toxins produced by pathogenic microbes. This can mitigate the harmful effects of these toxins on the body. When populations of beneficial bacteria are robust and diverse, they can help keep the numbers of potentially harmful bacteria in check. This balanced microbial community is less conducive to the overgrowth of pathogens [101].

Immune Memory: Beyond its immediate interactions with pathogens, the gut microbiota plays a fascinating role in establishing immune memory, a fundamental aspect of the body's defense mechanisms. Immune memory enables the immune system to recognize and respond more effectively to pathogens it has previously encountered. Exposure to the diverse array of microorganisms residing in the gut provides valuable training for the immune system [102]. This is particularly important during early life when the immune system is still developing. The immune cells become familiar with the various microbial patterns and antigens. In essence, the gut microbiota acts as a kind of immune boot camp, teaching the immune system to distinguish between harmless

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microorganisms and harmful pathogens. Within the immune system, a group of specialized cells known as memory T cells plays a pivotal role in immune memory [103]. These cells "remember" previous encounters with pathogens, allowing for faster and more effective responses upon reinfection. The exposure to the gut microbiota results in the generation of specific memory T cells that recognize and respond to microbial antigens. When a pathogen that the immune system has previously encountered tries to infect the body again, the memory T cells specific to that pathogen can rapidly mount a defense. This swifter response can often prevent the pathogen from causing severe illness or even go unnoticed, as the immune system efficiently neutralizes it. The concept of immune memory bears similarity to the principles of vaccination. In both cases, the immune system learns to recognize and respond to a pathogen without causing the disease [104] The gut microbiota essentially acts as a continuous "vaccination" process, priming the immune system to maintain readiness against known microbial foes.it has been explained that the greater the diversity of microbes encountered in the gut, the more versatile and robust the immune memory becomes. A diverse and balanced gut microbiota, fostered by a diet rich in fiber, prebiotics, and probiotics, is instrumental in enhancing this protective function. These concepts were succinctly explored by several researchers and most particularly [105].

Gut Microbiota and host interaction

The interaction between gut microbiota and the host is a complex and dynamic relationship that significantly influences human health. The gut microbiota assists in the breakdown and fermentation of dietary components that are otherwise indigestible by the human host. This process results in the production of short-chain fatty acids (SCFAs) and other metabolites that can be absorbed and used by the host as an additional energy source. SCFAs like butyrate play a crucial role in maintaining the health of the host's intestinal cells [51]. Gut microbes are involved in the digestion of complex carbohydrates and fiber, releasing essential nutrients that may not be accessible to the host otherwise. This interaction helps improve nutrient absorption. The gut microbiota contributes to the integrity of the intestinal barrier. A balanced microbiota prevents harmful substances, pathogens, and undigested food particles from crossing the gut lining and entering the bloodstream. This barrier function is vital for maintaining overall health. An equilibrium between the host and gut microbiota promotes a symbiotic relationship [47]. The host provides a habitat and nutrients for the microbiota, while the microbiota, in turn, contributes to host health by aiding in digestion, metabolism, and protecting against pathogens. The gut microbiota interacts with the host's immune system and plays a role in training the immune system, promoting immune tolerance, and protecting against harmful pathogens. Dysbiosis or an imbalanced gut microbiota can disrupt this interaction and potentially lead to autoimmune diseases or allergies. Additionally, gut microbiota produces metabolites and signaling molecules that can influence the host's physiological processes [21]. These molecules can affect metabolism, inflammation, and even mood. Bidirectional communication occurs between the host and gut microbiota through signaling pathways and molecules. The gut-brain axis is one example of this crosstalk, where the gut communicates with the brain and can influence mental health. Gut microbes can influence the host's hormonal balance, including hormones related to appetite and energy balance. This can have implications for conditions like obesity and metabolic syndrome. Some beneficial microbes have been linked to specific health benefits, such as the promotion of cardiovascular health, reduced inflammation, and improved metabolic function. Dysbiosis can disrupt the host-microbiota interaction and contribute to a range of health problems, including gastrointestinal disorders, autoimmune diseases, and metabolic disorders. Study of an individual's gut microbiota profile holds promise for personalized medicine, where health treatments and dietary recommendations can be tailored to a person's unique microbial composition [23].

The interaction between the gut microbiota and the host is a multifaceted and mutually beneficial relationship. Maintaining a balanced and diverse gut microbiota is essential for overall health, and disruptions in this interaction can lead to various health issues. Research in this field is ongoing, with the aim of developing interventions to support host-microbiota interactions and promote better health outcomes [106].

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Changes in Gut Microbiota composition.

Changes in the composition of the gut microbiota, also known as dysbiosis, can have significant impacts on human health. One of the most influential factors in altering gut microbiota composition is diet. A diet rich in fiber and plant-based foods can promote the growth of beneficial bacteria, while a diet high in sugars and processed foods can lead to an overgrowth of less beneficial microbes [107]. These dietary shifts can happen relatively quickly, impacting the composition of the gut microbiota. Antibiotics are designed to kill or inhibit bacteria, but they can't distinguish between harmful and beneficial microbes. As a result, antibiotic use can lead to significant changes in gut microbiota composition. This disruption can have short-term and long-term consequences for health. Infections or illnesses that affect the gastrointestinal tract can also result in shifts in gut microbiota composition. Pathogens can displace beneficial bacteria, leading to an imbalance. High levels of chronic stress can impact gut microbiota composition. The gut-brain axis plays a role in this relationship [108], with stress-related changes in gut function influencing the microbiota and vice versa. As people age, there can be alterations in gut microbiota composition. These changes may be linked to shifts in dietary habits, medications, and overall health. Maintaining a diverse and balanced gut microbiota becomes increasingly important with age. Travelling and lifestyle choices are other associated factors; travelling to different regions or exposure to new environments can introduce the gut to new microbes and disrupt the existing balance, and lifestyle choices, including exercise and sleep patterns, can affect gut microbiota composition. Regular exercise has been associated with a more diverse and balanced microbiota [109]. Furthermore, an individual's genetic makeup can influence their gut microbiota. As well as emotional and psychological factors can influence gut microbiota composition through the gut-brain axis. Stress, anxiety, and depression can affect gut health and, in turn, impact mental health. All these can have far-reaching effects on health. Dysbiosis has been associated with conditions such as obesity, type 2 diabetes, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and even mental health issues like depression and anxiety. In some cases, it's possible to restore a healthy gut microbiota through dietary changes, probiotics, prebiotics, and other interventions. Fecal microbiota transplantation (FMT) is a more extreme but effective method for addressing dysbiosis [25].

Aging and Gut Microbiota composition

Aging is associated with changes in gut microbiota composition, and these changes can have important implications for the health of older individuals. Generally, the gut microbiota of older individuals tends to have lower diversity compared to younger individuals. This means that there are fewer different types of microorganisms present in the gut. With age, there is often a decrease in beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*. These bacteria play important roles in digestion and the production of essential vitamins and short-chain fatty acids [110]. Conversely, some potentially harmful bacteria may become more prevalent in the gut of older individuals. These changes can potentially contribute to digestive issues and inflammation. Dietary habits can play a significant role in the changes observed in the gut microbiota of older adults. Dietary patterns, including lower fiber intake and reduced consumption of fresh fruits and vegetables, can contribute to these shifts. Older individuals often take more medications, and some drugs, particularly antibiotics and proton pump inhibitors, can alter the gut microbiota [107]. Antibiotics, for example, can indiscriminately kill both harmful and beneficial bacteria. Changes in gut microbiota composition in older adults can affect various aspects of health. These include digestive problems, increased susceptibility to infections, and potentially contributing to conditions like irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). The gut microbiota plays a crucial role in immune function. Alterations in the microbiota composition can affect the aging immune system, potentially leading to increased susceptibility to infections and decreased response to vaccines [111]. It has been reported that a less diverse and balanced gut microbiota can affect the absorption of essential nutrients, such as certain vitamins and minerals, which can be a concern for older adults who may already be at risk of nutritional deficiencies. Some studies also associate changes in the gut microbiota can contribute to chronic low-level inflammation, which is associated with a range of age-related

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conditions, including cardiovascular disease, diabetes, and cognitive decline [112]. Hence, maintaining a healthy gut microbiota in older age is important. Strategies to support gut health include consuming a diet rich in fiber, prebiotics, and probiotics, staying hydrated, and minimizing the use of unnecessary antibiotics. Prebiotics, which are non-digestible fibers that promote the growth of beneficial bacteria, and probiotics, which are live beneficial bacteria, can be beneficial in promoting a healthy gut microbiota in older adults. As each person's gut microbiota is unique, personalized approaches to diet and interventions may be more effective in promoting gut health in older individuals [113].

Nutritional alteration and Gut Microbiota composition

Nutritional alterations can significantly impact the composition of the gut microbiota. The gut microbiota refers to the diverse community of microorganisms residing in the gastrointestinal tract, primarily the colon, and their composition can be influenced by changes in dietary patterns and nutrient intake. several studies have attributed Diets rich in fiber, particularly soluble fiber found in fruits, vegetables, and whole grains, to the promotion of the growth of beneficial gut bacteria [114]. These bacteria, like *Bifidobacterium* and *Lactobacillus*, ferment dietary fiber to produce short-chain fatty acids (SCFAs), which are important for gut health. Recent reports on the nutritional aspect of the gut microbiota have also linked dietary alterations that increase protein and carbohydrates intake, especially animal-based proteins, can affect the gut microbiota. High-protein diets can lead to an increase in certain bacteria that metabolize proteins, potentially generating harmful byproducts like ammonia and sulfides [115]. The type of carbohydrates consumed can also influence gut microbiota composition. A diet high in simple sugars and refined carbohydrates may favor the growth of bacteria associated with inflammation, while complex carbohydrates may support the growth of beneficial bacteria. Dietary fats, particularly saturated and trans fats, have also been associated with shifts in gut microbiota composition. A diet high in unhealthy fats may contribute to an unfavorable microbial profile. Some studies suggest that artificial sweeteners can alter the gut microbiota and may be linked to metabolic disturbances [116]. Food additives and preservatives and alcohol may also influence the gut microbiota. For example, emulsifiers used in processed foods have been studied for their potential impact on gut health. Excessive alcohol consumption can affect gut microbiota diversity and lead to imbalances. Chronic alcohol intake is associated with negative changes in microbial composition [117].

Microbiome composition and pathological bone development and involution

The composition of the microbiome, particularly in the gut, has increasingly been recognized as playing a role in pathological bone development and involution. Pathological bone development refers to conditions where bones grow abnormally or in a manner that is detrimental to overall health. Conversely, involution signifies the natural reduction in bone density and mass that occurs as people age. The gut microbiome has been linked to systemic inflammation [39]. Chronic inflammation is a key factor in pathological bone development. It can stimulate bone resorption, a process where bone tissue is broken down and released into the bloodstream. This can lead to conditions like osteoporosis. Gut bacteria can also significantly influence the host's immune system. Similarly, the gut microbiome is involved in nutrient absorption, including the uptake of minerals like calcium, which is crucial for bone health. An imbalanced microbiome might impair the absorption of these vital nutrients, potentially leading to weak or brittle bones [118]. (SCFAs as previously discussed have been associated with bone health These SCFAs can have both anti-inflammatory and immunomodulatory effects. Butyrate, in particular, is known for its potential role in preserving bone density. Another notable influence of the gut microbiota is hormonal balance. Hormones like estrogen and testosterone play a significant role in maintaining bone health. Furthermore, crosstalk with other tissues has impacted the rate of bone development and involution [119].

Intervertebral disc (IVD) degeneration (IDD) and gut inflammation

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Intervertebral disc (IVD) degeneration (IDD) and gut inflammation are two seemingly unrelated health conditions, but emerging research suggests potential connections between them. IDD refers to the gradual deterioration of the intervertebral discs in the spine, which can lead to back pain and other spinal issues. Gut inflammation typically refers to inflammatory conditions in the gastrointestinal tract, such as inflammatory bowel diseases (IBD) [39,119]. We attempt a deeper discussion of the relationship between these two in connection with the gut microbiota in this section.

Inflammatory mediators and cytokines produced during gut inflammation can enter the bloodstream and circulate throughout the body. These molecules can potentially reach the intervertebral discs in the spine and trigger or exacerbate inflammation in the discs. This inflammation is believed to be a key driver of IDD. The gut is a crucial site for immune system activity. When the gut becomes inflamed, it can trigger an immune response that affects other parts of the body. This immune response could potentially contribute to the development of inflammatory conditions in the intervertebral discs. The gut microbiome, composed of trillions of microorganisms, plays a pivotal role in gut health. An imbalance in the gut microbiome, referred to as dysbiosis, has been associated with gut inflammation. Some studies suggest that gut dysbiosis might be linked to systemic inflammation that could impact IDD [120]. Inflammation in the gut can impair nutrient absorption. The intervertebral discs, like other tissues, require specific nutrients for maintenance and repair. Reduced nutrient availability due to gut inflammation might affect the health of these discs. Chronic gut inflammation can lead to generalized inflammation and heightened pain perception throughout the body. This heightened pain perception may intensify the discomfort experienced by individuals with IDD. The medications commonly used to manage gut inflammation, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may have side effects affecting bone health, which could potentially impact the spinal discs. Gut inflammation can result in systemic inflammation, which affects various parts of the body. Systemic inflammation has been linked to a range of chronic health conditions, including those related to spinal health [121].

It's important to note that research into the connections between IDD and gut inflammation is underway and complex. The exact mechanisms through which these conditions may be linked are not fully understood. However, there is a growing recognition that systemic inflammation, gut health, and spinal health are interconnected in ways that warrant further investigation. It is recommended that individuals with IDD or gut inflammation should work closely with healthcare professionals to manage their conditions. Furthermore, promoting a balanced gut microbiome through dietary and lifestyle choices may contribute to overall health and could potentially benefit both spinal and gut health [122].

The Gut-spine axis

The gut-spine axis is an emerging concept in medical research that explores the potential bidirectional communication and influence between the gut (specifically, the gut microbiome) and the spine (particularly the intervertebral discs and spinal health). This concept is part of a broader understanding of how different parts of the body are interconnected, and it highlights the potential impact of gut health on spinal health and vice versa. Inflammatory processes in the gut can lead to systemic inflammation, which may affect various tissues and organs, including the spine [123]. This systemic inflammation can contribute to or exacerbate spinal conditions, such as intervertebral disc degeneration. The gut is a major site for immune system activity. When gut health is compromised, it can lead to immune responses that impact other areas of the body. Immune crosstalk between the gut and spine could potentially influence spinal health. The gut microbiome, consisting of trillions of microorganisms, plays a crucial role in overall health. Imbalances in the gut microbiome (dysbiosis) have been linked to inflammatory conditions. The gut microbiome might have a role in modulating systemic inflammation, which could influence spinal health. Gut health is also essential for proper nutrient absorption [124]. The intervertebral discs, like other tissues, require specific nutrients for maintenance and repair. Gut-related nutrient absorption issues could potentially affect the health of the spinal discs.

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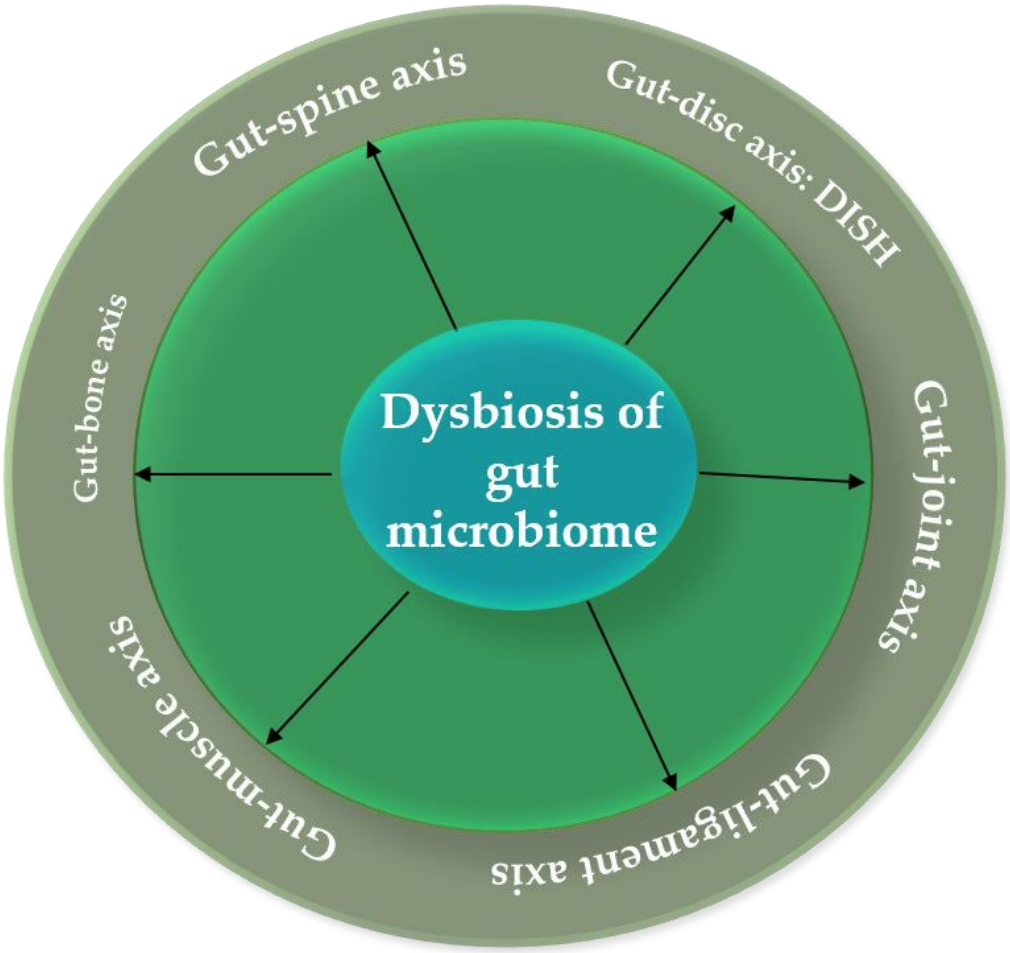

Figure 2. Dysbiosis of Gut Microbiota and its associated diseases.

Chronic gut inflammation can lead to heightened pain perception throughout the body. This heightened pain perception may intensify the discomfort experienced by individuals with spinal conditions. Medications used to manage gut inflammation, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may have side effects affecting bone health, which could impact the spine. While research into the gut-spine axis is ongoing and complex, the concept has implications for the comprehensive understanding and management of spinal disorders. It suggests that addressing gut health and systemic inflammation might be relevant in the prevention and treatment of spine-related issues [125].

Gut-bone axis: osteoporosis and hyperostotic diseases

The gut-bone axis is a realm of scientific investigation delving into the intricate interplay between the gut, notably the gut microbiome, and the well-being of bones. This axis is pivotal in comprehending how gut-related factors can impact ailments like osteoporosis, marked by diminished bone density, and hyperostotic diseases, characterized by inordinate bone growth [126]. The gut serves as the primary site for absorbing vital nutrients, including essential minerals like calcium and vitamin D, which are indispensable for robust bone health. Any disturbances within the gut that impede nutrient absorption hold the potential to result in fragile bones (osteoporosis) or aberrant bone proliferation (hyperostotic diseases) [127]. An imbalanced gut microbiome can incite gut inflammation, which, subsequently, may spark systemic inflammation. Chronic inflammation is intricately connected to bone loss, as it upsets the intricate equilibrium between the creation and absorption of bone, thus contributing to osteoporosis. The bacteria in the gut generate short-chain fatty acids (SCFAs) as byproducts of their metabolism. SCFAs have been correlated with sound bone

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health. For instance, butyrate, a specific SCFA, is believed to contribute to the promotion of robust bone density. The gut microbiome can exert influence over hormonal equilibrium. Hormones such as estrogen and testosterone are crucial for sustaining the density of bones. An imbalance in these hormones can contribute to the onset of either osteoporosis or hyperostotic diseases [17].

Certain medications, such as proton pump inhibitors (PPIs), which are employed to reduce stomach acid, can interfere with the absorption of calcium, thereby potentially affecting bone health. Moreover, specific medications may manifest side effects linked to bone density. The gut-bone axis exemplifies the intricate interconnectedness of diverse bodily organs and systems. The gut communicates with bone tissues through signaling molecules and byproducts of metabolism, thus casting an impact on the remodeling of bone. Although a substantial portion of research concerning the gut-bone axis centers on osteoporosis, hyperostotic diseases characterized by excessive bone growth might also be subject to the influences of gut-related factors. The precise mechanisms governing these conditions continue to be a subject of ongoing exploration [128,129].

Gut-joint axis: Osteoarthritis (OA) and facet joint syndrome

The gut-joint axis is a field of study that investigates the intricate relationship between the gut, particularly the gut microbiome, and joint health. This axis plays a crucial role in understanding how gut-related factors can influence conditions such as osteoarthritis (OA), characterized by the degeneration of joint cartilage, and facet joint syndrome, a source of spinal pain [130]. The gut is the primary site for nutrient absorption, including essential vitamins and minerals. Nutrients absorbed in the gut are vital for joint health, as they play a role in maintaining the integrity of cartilage and joint tissues. Any disruptions in the gut that affect nutrient absorption can potentially lead to joint-related issues, including OA and facet joint [49].

An imbalanced gut microbiome can lead to gut inflammation, which, in turn, can trigger systemic inflammation. Chronic inflammation is linked to joint problems, as it can contribute to the breakdown of cartilage and joint tissues, a hallmark of OA. The gut microbiome has the potential to influence the immune system, and immune responses are closely associated with joint health. An imbalance in the gut microbiome can lead to immune dysregulation, which may contribute to joint-related autoimmune conditions or joint pain [131].

Gut bacteria produce various metabolites, including short-chain fatty acids (SCFAs), which can have anti-inflammatory properties. These metabolites may play a role in alleviating joint inflammation and pain associated with conditions like OA and facet joint syndrome. The gut-joint axis represents the intricate interplay between different systems within the body. The gut communicates with joint tissues through signaling molecules and immune responses, influencing joint health and the progression of conditions like OA and facet joint syndrome [51].

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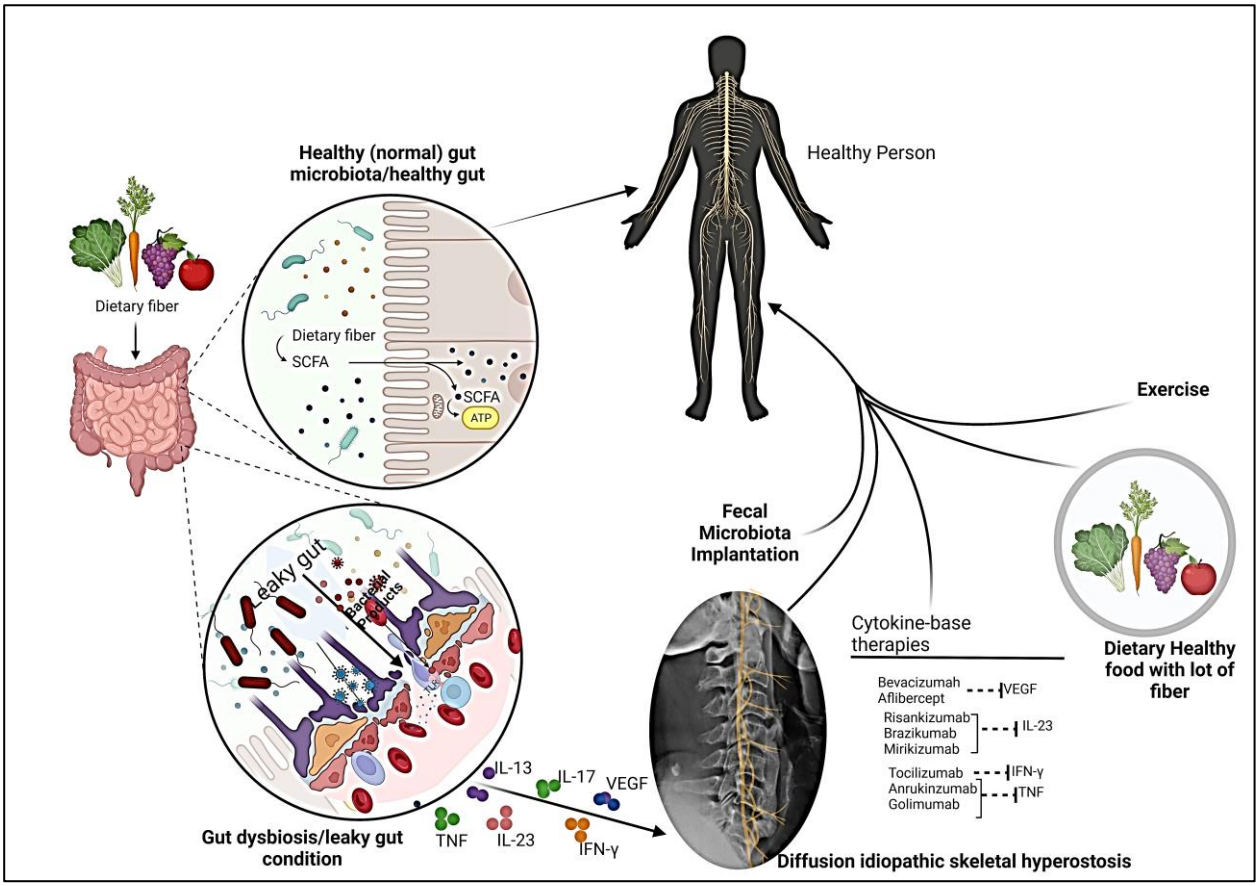

Figure 3. Relationship between gut microbiota and DISH, and regulatory factors that can possibly rescue DISH patient from the condition. Gut dysbiosis has been blamed as crucial player in DISH development, other factors such as IL-13, IL-17, VEGF, IFN-Y, TNF, IL-23 etc. has been suspected as important factors in DISH development. However, DISH management modalities include dietary food with high fiber content, exercise, cytokines administration and fecal microbiota implantation.

Gut-disc axis: DISH

The gut-disc axis is an emerging field of research that delves into the intricate relationship between the gut, particularly the gut microbiome, and conditions like Diffuse Idiopathic Skeletal Hyperostosis (DISH). DISH is a medical condition characterized by excessive bone growth along the spine, primarily affecting the thoracic and lumbar vertebrae. While this condition has long remained an enigma, the evolving science of the gut-disc axis is beginning to unravel the complex web of factors that may contribute to its development [132]. The gut, often referred to as the "second brain" due to its profound influence on overall health, is central to the gut-disc axis. It serves as the primary site for nutrient absorption, with a particular emphasis on essential minerals vital for bone health, such as calcium and vitamin D. Any disruptions within the gut that compromise nutrient absorption can potentially set the stage for abnormal bone growth, as observed in DISH. Understanding the role of the gut in the absorption of these nutrients is pivotal for comprehending the genesis of DISH [133].

One of the critical aspects of the gut-disc axis lies in the potential link between an imbalanced gut microbiome and gut inflammation, which can subsequently incite systemic inflammation. Chronic inflammation has been widely implicated in a multitude of bone and joint disorders, and it may also contribute to the development of DISH. The inflammatory response within the gut can have far-reaching consequences, ultimately leading to changes in bone structure and growth that are characteristic of DISH. Research in this area is actively examining the connection between gut inflammation and the pathogenesis of this condition [134]. Fournier et al., carried an experiment on the Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and early-phase DISH across the

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lifespan of an American population, from a total of 1536 unique images including 16710 motion segments. They found that the prevalence of early-phase DISH was 13.2% (10.4% of female and 15.8% of male individuals). The prevalence of established DISH was 14.2% (7.4% of female and 20.9% of male individuals) [134].

The gut microbiome, with its myriad of microbial inhabitants, has been shown to have a considerable impact on hormonal balance in the body. Hormones like insulin-like growth factor 1 (IGF-1) and other growth-related hormones are crucial in bone metabolism. Disturbances in the balance of these hormones have the potential to affect the rate of bone growth and remodeling. This aspect of the gut-disc axis research explores the mechanisms through which the gut microbiome may influence the excessive bone growth seen in DISH [135].

While the gut-disc axis is still in its infancy, the potential insights it offers into the development and management of conditions like DISH are significant. Researchers are actively seeking to uncover the specific mechanisms through which gut-related factors impact DISH and related spinal conditions. A thorough comprehension of this relationship may pave the way for innovative approaches to both the prevention and management of DISH.

The Gut-Ligament Axis: Exploring the Link to Lumbar Spinal Stenosis

The gut-ligament axis is an emerging area of scientific inquiry that investigates the intricate connection between the gut and various ligament-related conditions, with a particular focus on lumbar spinal stenosis. Lumbar spinal stenosis is a medical condition characterized by the narrowing of the spinal canal in the lower back, leading to a range of symptoms and discomfort. The burgeoning research in this field aims to shed light on how factors related to gut health might influence the development and progression of lumbar spinal stenosis [121,136].

The gut, often regarded as the epicenter of overall health, serves as the primary site for nutrient absorption in the human body. Essential minerals and vitamins, including calcium and vitamin D, are absorbed in the gut, and these nutrients play a crucial role in maintaining the health of bones and ligaments. Disruptions in the gut that affect nutrient absorption can potentially contribute to the development of conditions like lumbar spinal stenosis. A key focus of the gut-ligament axis is understanding how the gut influences the availability of these critical nutrients for ligament health [22,23]

Inflammation is a central theme within the gut-ligament axis. An imbalanced gut microbiome can lead to gut inflammation, which, in turn, can trigger systemic inflammation throughout the body. Chronic inflammation is often linked to various musculoskeletal disorders, including ligament-related conditions. Understanding the role of gut-related inflammation in the pathogenesis of lumbar spinal stenosis is an essential facet of ongoing research in this field [137]. The gut microbiome, a complex ecosystem of microorganisms residing in the gastrointestinal tract, has the potential to influence hormonal balance within the body. Hormones, such as those that regulate calcium metabolism and bone health, may be affected by the gut microbiome. Imbalances in these hormones can have implications for ligament health and the development of lumbar spinal stenosis. The delicate relationship between the gut microbiome and hormones is a critical area of investigation within the gut-ligament axis [138].

The Gut-Muscle Axis: Unraveling Its Connection to Spinal Sarcopenia

The gut-muscle axis is an evolving area of research that delves into the intricate connection between the gut, primarily the gut microbiome, and conditions such as spinal sarcopenia. Spinal sarcopenia is a medical condition characterized by the loss of muscle mass and function, particularly in the muscles supporting the spine. Research in this field seeks to elucidate how factors related to gut health may influence the development and progression of spinal sarcopenia [139]. The gut serves as the primary site for nutrient absorption in the human body, and this function is particularly relevant to muscle health. Essential nutrients, including protein, amino acids, and vitamins, are absorbed in the gut and play a vital role in maintaining muscle mass and function. Any disruptions in the gut that hinder nutrient absorption can potentially contribute to the development of conditions

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like spinal sarcopenia. Therefore, the gut-muscle axis investigates how gut health influences the availability of these essential nutrients for muscle health [140].

Inflammation is a central theme within the gut-muscle axis. The gut microbiome has the potential to influence hormonal balance within the body. Hormones like insulin-like growth factor 1 (IGF-1), which plays a crucial role in muscle growth and maintenance, may be affected by the gut microbiome [141,142]. Imbalances in these hormones can have implications for muscle health and the development of spinal sarcopenia. The intricate interplay between the gut microbiome and hormones is a critical area of investigation within the gut-muscle axis. While the gut-muscle axis is still in its infancy, it holds the promise of providing valuable insights into the development and management of conditions like spinal sarcopenia. Researchers are actively working to uncover the specific mechanisms through which gut-related factors influence muscle health and the pathogenesis of spinal sarcopenia. The link between gut health and spinal sarcopenia is a dynamic field of study with the potential to transform our approach to managing this condition [59].

Impact of Gut Microbiota on DISH -derived pain

The impact of gut microbiota on pain derived from Diffuse Idiopathic Skeletal Hyperostosis (DISH) is an area of emerging research that aims to uncover the intricate connections between gut health, particularly the gut microbiome, and the pain experienced by individuals with DISH. DISH is characterized by excessive bone growth along the spine and other skeletal areas, often leading to pain and discomfort. Understanding how gut-related factors may influence pain in DISH is essential for better managing and alleviating this condition [143].

The gut microbiome plays an enormous role in modulating the immune system. An imbalanced gut microbiome can influence immune responses and potentially exacerbate the inflammatory processes in the body. The immune system's role in the development of DISH and the associated pain is a subject of ongoing investigation. Researchers aim to elucidate how the gut microbiota may affect immune responses and, subsequently, the pain experienced by individuals with DISH. The gut microbiota produces various metabolites and signaling molecules. Some of these molecules may influence pain perception and sensitivity [144].

The gut is intricately connected with the brain through the gut-brain axis [17]. Communication between the gut and the brain can influence pain perception. This axis may play a role in the experience of pain by individuals with DISH, and researchers are actively investigating how gut health may impact pain perception and the brain's response to pain in these individuals.

The gut-DISH pain axis is a burgeoning area of research, and it has the potential to provide valuable insights into pain management for individuals with DISH. By unraveling the specific mechanisms through which gut-related factors influence pain, researchers aim to develop novel approaches to pain relief and management for this condition. As the understanding of the gut's impact on DISH-derived pain continues to evolve, it may lead to more effective strategies for improving the quality of life for those affected by this condition. The impact of the gut microbiota on DISH-derived pain is an exciting field that holds promise for enhancing the well-being of individuals living with this condition [145].

Fecal microbiome transplant and DISH

Fecal Microbiome Transplant (FMT) is a medical procedure that involves transferring fecal material from a healthy donor into the gastrointestinal tract of a recipient. This procedure is primarily used to restore a healthy balance of gut microbiota and treat conditions associated with gut dysbiosis. While FMT has shown promise in addressing various gastrointestinal disorders, its application in the context of Diffuse Idiopathic Skeletal Hyperostosis (DISH) is an area of emerging research and interest [146]. FMT is primarily used to replenish a healthy and diverse gut microbiota in individuals with gut-related conditions, particularly those involving dysbiosis. If research establishes a strong connection between gut dysbiosis and DISH or its symptoms, FMT could be explored as a means to restore gut microbiota balance in affected individuals [25,68].

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A balanced gut microbiome is crucial for immune system health and function. In cases where DISH may have an autoimmune component or where chronic inflammation plays a role in the condition, FMT could potentially help modulate the immune system's response. If DISH is associated with systemic inflammation and pain, FMT may be investigated as a means to reduce inflammation. The gut microbiome can influence inflammation levels throughout the body, and restoring a balanced microbiota could potentially mitigate inflammatory processes. One of the potential applications of FMT in the context of DISH could be in managing the pain associated with the condition. Chronic pain is a significant aspect of DISH, and if research suggests that the gut microbiome affects pain perception through the gut-brain axis, FMT might be explored as a means of alleviating pain [145]. It's important to note that research on the application of FMT for DISH is in its early stages. Clinical trials and studies are necessary to determine the safety and efficacy of FMT in the context of DISH.

Summary of reports related to GM and spinal musculoskeletal diseases, including DISH.

Recent reports and studies have highlighted the potential connections between the gut microbiome (GM) and spinal musculoskeletal diseases, including Diffuse Idiopathic Skeletal Hyperostosis (DISH).

Studies claimed that an imbalanced gut microbiome can lead to gut inflammation, which, in turn, may trigger systemic inflammation. This chronic inflammation is associated with various bone and joint disorders, including DISH. Studies are investigating the role of the gut microbiome in modulating the immune system, which could influence the development and progression of DISH. The gut microbiome's production of microbial metabolites and signaling molecules is under scrutiny for its potential role in pain modulation and the inflammatory processes seen in DISH.

Inflammation is a central theme in understanding the pain experienced by individuals with DISH. Chronic inflammation contributes to the discomfort and pain associated with the condition. Contemporary research is focused on the gut's role in influencing systemic inflammation, which could exacerbate the inflammatory processes in the spine and musculoskeletal system.

The gut-brain axis is receiving attention for its role in influencing pain perception. Communication between the gut and the brain may impact the experience of pain by individuals with DISH. The gut's influence on pain perception and the brain's response to pain is an area of active research.

A thorough comprehension of the gut-DISH connection may lead to innovative pain management strategies for individuals with DISH. This emerging research field holds promise for improving the quality of life for those affected by DISH by identifying new therapeutic targets and interventions. Future studies will likely delve deeper into the specific mechanisms through which the gut microbiome influences the development, progression, and pain associated with DISH.

Overall, these reports emphasize the intricate and multifaceted relationship between the gut microbiome and spinal musculoskeletal diseases like DISH.

Conclusion and perspective

Emerging field of research that examines the interplay between the gut microbiome and various spinal musculoskeletal diseases, including Diffuse Idiopathic Skeletal Hyperostosis (DISH), holds significant promise for advancing our understanding of these conditions and exploring novel treatment approaches. The gut-spine axis, as well as other gut-related axes, represents a complex and multifaceted network of interactions between the gut microbiome, the immune system, hormones, and various body systems.

The gut's impact on spinal musculoskeletal health is multifaceted. It involves the microbiome's role in nutrient absorption, systemic inflammation, hormonal regulation, immune system modulation, and even the gut-brain axis. Understanding the complexity of these interactions is essential for developing effective interventions. Research suggests that gut-related factors could influence the development and progression of spinal conditions like DISH. As such, interventions targeting the gut microbiome, such as dietary changes, probiotics, prebiotics, and fecal microbiome transplants (FMT), may hold promise for managing these conditions and reducing associated

symptoms, including pain and inflammation. The field of gut-musculoskeletal research may pave the way for personalized medicine approaches. By considering an individual's unique gut microbiome composition, healthcare providers can tailor treatments to address the specific factors contributing to spinal musculoskeletal diseases. This tailored approach could enhance treatment efficacy and patient outcomes. While significant progress has been made in understanding the gut-spine axis and its potential implications for diseases like DISH, there are still gaps in our knowledge. Further research is needed to elucidate the precise mechanisms by which gut-related factors contribute to these conditions and to establish the safety and efficacy of gut-focused interventions. As research in this area continues to evolve, we can anticipate the development of clinical applications. This might include diagnostic tools that assess an individual's gut microbiome in the context of spinal musculoskeletal diseases and targeted interventions that aim to modulate the gut to improve patient outcomes. Collaboration between experts in gastroenterology, rheumatology, orthopedics, and immunology will be vital to advancing our understanding of the gut-musculoskeletal connection. A multidisciplinary approach can help uncover the nuances of these interactions and develop comprehensive treatment strategies. Recognizing the potential influence of the gut on spinal health underscores the importance of a holistic and patient-centered approach to healthcare. This approach takes into account the whole individual, including their diet, lifestyle, and gut health, in the management of spinal musculoskeletal diseases.

In the coming years, we can anticipate a deeper exploration of the gut-spine axis and its relevance to conditions like DISH. This review has the potential to transform our approach to these diseases, offering new hope for more effective treatments and improved patient outcomes. The insights gained from this field may ultimately lead to innovative therapies that enhance the quality of life for individuals living with spinal musculoskeletal conditions.

References

1. Wójcik, G. and Szulc, A., 2018. Diffuse idiopathic skeletal hyperostosis of the spine. Journal of Education, Health and Sport, 8(12), pp.593-599.
2. Srinivasan, W., Thorell, W., McCumber, T.L., Vilburn, M. and Snow, E.L., 2023. Hyperostosis cranialis interna and an ectopic ossification on the endosteal dura deep to the trigeminal ganglion: Case analysis and clinical implications. *Translational Research in Anatomy*, *30*, p.100239.
3. Akhtar, A., Lata, M., Sunsunwal, S., Yadav, A., Lnu, K., Subramanian, S. and Ramya, T.N.C., 2023. New carbohydrate binding domains identified by phage display based functional metagenomic screens of human gut microbiota. *Communications Biology*, *6*(1), p.371.
4. Wan, X., Eguchi, A., Sakamoto, A., Fujita, Y., Yang, Y., Qu, Y., Hatano, M., Mori, C. and Hashimoto, K., 2023. Impact of broad-spectrum antibiotics on the gut–microbiota–spleen–brain axis. *Brain, Behavior, & Immunity-Health*, *27*, p.100573.
5. Holgate, R.L. and Steyn, M., 2016. Diffuse idiopathic skeletal hyperostosis: Diagnostic, clinical, and paleopathological considerations. *Clinical anatomy*, *29*(7), pp.870-877.
6. Mader, R., Pappone, N., Baraliakos, X., Eshed, I., Sarzi-Puttini, P., Atzeni, F., Bieber, A., Novofastovski, I., Kiefer, D., Verlaan, J.J. and Ambrosino, P., 2021. Diffuse idiopathic skeletal hyperostosis (DISH) and a possible inflammatory component. *Current Rheumatology Reports*, *23*, pp.1-6.
7. Mader, R., 2005. Current therapeutic options in the management of diffuse idiopathic skeletal hyperostosis. *Expert opinion on pharmacotherapy*, *6*(8), pp.1313-131
8. Cammisa, M., De Serio, A. and Guglielmi, G., 1998. Diffuse idiopathic skeletal hyperostosis. *European Journal of Radiology*, *27*, pp.S7-S11.
9. Olivieri, I., D'ANGELO, S.A.L.V.A.T.O.R.E., Palazzi, C. and Padula, A., 2013. Spondyloarthritis and diffuse idiopathic skeletal hyperostosis: two different diseases that continue to intersect. *The Journal of Rheumatology*, *40*(8), pp.1251-1253.
10. Sarzi-Puttini, P. and Atzeni, F., 2004. New developments in our understanding of DISH (diffuse idiopathic skeletal hyperostosis). *Current opinion in rheumatology*, *16*(3), pp.287-292.
11. Mazières, B., 2013. Diffuse idiopathic skeletal hyperostosis (Forestier-Rotes-Querol disease): what's new? *Joint Bone Spine*, *80*(5), pp.466-470.
12. Van der Merwe, A.E., Maat, G.J.R. and Watt, I., 2012. Diffuse idiopathic skeletal hyperostosis: diagnosis in a palaeopathological context. *Homo*, *63*(3), pp.202-215.
13. Balling, H. and Weckbach, A., 2015. Hyperextension injuries of the thoracolumbar spine in diffuse idiopathic skeletal hyperostosis. *Spine*, *40*(2), pp.E61-E67.

14. Hirasawa, A., Wakao, N., Kamiya, M., Takeuchi, M., Kawanami, K., Murotani, K., Matsuo, T. and Deie, M., 2016. The prevalence of diffuse idiopathic skeletal hyperostosis in Japan–the first report of measurement by CT and review of the literature. *Journal of Orthopaedic Science*, *21*(3), pp.287-290.
15. Ikuma, H., Hirose, T., Nakamura, D., Yamashita, K., Ueda, M., Sasaki, K. and Kawasaki, K., 2022. The prevalence and characteristics of diffuse idiopathic skeletal hyperostosis (DISH): A cross-sectional study of 1519 Japanese individuals. *Diagnostics*, *12*(5), p.1088.
16. Mader, R., 2002, October. Clinical manifestations of diffuse idiopathic skeletal hyperostosis of the cervical spine. In *Seminars in arthritis and rheumatism* (Vol. 32, No. 2, pp. 130-135). WB Saunders.
17. Ibrahim, I., Syamala, S., Ayariga, J.A., Xu, J., Robertson, B.K., Meenakshisundaram, S. and Ajayi, O.S., 2022. Modulatory effect of gut microbiota on the gut-brain, gut-bone axes, and the impact of cannabinoids. Metabolites, 12(12), p.1247.
18. Cheng, Z., Zhang, L., Yang, L. and Chu, H., 2022. The critical role of gut microbiota in obesity. *Frontiers in Endocrinology*, *13*, p.1025706.
19. Niu, G., Jian, T., Gai, Y. and Chen, J., 2023. Microbiome and plant-derived vesicles that serve as therapeutic agents and delivery carriers to regulate metabolic syndrome. Advanced Drug Delivery Reviews, p.114774.
20. Wang, L., Wang, S., Zhang, Q., He, C., Fu, C. and Wei, Q., 2022. The role of the gut microbiota in health and cardiovascular diseases. *Molecular biomedicine*, *3*(1), p.30.
21. Ou, J., Wang, Z., Liu, X., Song, B., Chen, J., Li, R., Jia, X., Huang, R., Xiang, W. and Zhong, S., 2022. Regulatory effects of marine polysaccharides on gut microbiota dysbiosis: A review. *Food Chemistry: X*, p.100444.
22. Saranya, G.R. and Viswanathan, P., 2023. Gut microbiota dysbiosis in AKI to CKD transition. *Biomedicine & Pharmacotherapy*, *161*, p.114447.
23. Rogers, G.B., Keating, D.J., Young, R.L., Wong, M.L., Licinio, J. and Wesselingh, S., 2016. From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Molecular psychiatry, 21(6), pp.738-748.
24. Fiocchi, A., Cabana, M.D. and Mennini, M., 2022. Current use of probiotics and prebiotics in allergy. *The Journal of Allergy and Clinical Immunology: In Practice*, *10*(9), pp.2219-2242.
25. Biazzo, M. and Deidda, G., 2022. Fecal microbiota transplantation as new therapeutic avenue for human diseases. *Journal of Clinical Medicine*, *11*(14), p.4119.
26. Krela-Kaźmierczak, I., Zakerska-Banaszak, O., Skrzypczak-Zielińska, M., Łykowska-Szuber, L., Szymczak-Tomczak, A., Zawada, A., Rychter, A.M., Ratajczak, A.E., Skoracka, K., Skrzypczak, D. and Marcinkowska, E., 2022. Where Do We Stand in the Behavioral Pathogenesis of Inflammatory Bowel Disease? The Western Dietary Pattern and Microbiota—A Narrative Review. *Nutrients*, *14*(12), p.2520.
27. Zhang, B., Jin, Z., Zhai, T., Ding, Q., Yang, H., Wang, J., Zhang, L. and Zhao, L., 2022. Global research trends on the links between the gut microbiota and diabetes between 2001 and 2021: A bibliometrics and visualized study. *Frontiers in Microbiology*, *13*, p.1011050.
28. Bai, J., Wan, Z., Zhang, Y., Wang, T., Xue, Y. and Peng, Q., 2022. Composition and diversity of gut microbiota in diabetic retinopathy. *Frontiers in Microbiology*, *13*, p.926926.
29. Kaltsas, A., Zachariou, A., Markou, E., Dimitriadis, F., Sofikitis, N. and Pournaras, S., 2023. Microbial Dysbiosis and Male Infertility: Understanding the Impact and Exploring Therapeutic Interventions. *Journal of Personalized Medicine*, *13*(10), p.1491.
30. Larsen, O.F., van der Grint, M., Wiegers, C. and van de Burgwal, L.H., 2022. The gut microbiota: Master of puppets connecting the epidemiology of infectious, autoimmune, and metabolic disease. *Frontiers in Microbiology*, *13*, p.1604.
31. He, X., Sun, J., Liu, C., Yu, X., Li, H., Zhang, W., Li, Y., Geng, Y. and Wang, Z., 2022. Compositional alterations of gut microbiota in patients with diabetic kidney disease and type 2 diabetes mellitus. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, pp.755-765.
32. Bresser, L.R., de Goffau, M.C., Levin, E. and Nieuwdorp, M., 2022. Gut microbiota in nutrition and health with a special focus on specific bacterial clusters. *Cells*, *11*(19), p.3091.
33. Perler, B.K., Friedman, E.S. and Wu, G.D., 2023. The role of the gut microbiota in the relationship between diet and human health. *Annual Review of Physiology*, *85*, pp.449-468.
34. You, S., Ma, Y., Yan, B., Pei, W., Wu, Q., Ding, C. and Huang, C., 2022. The promotion mechanism of prebiotics for probiotics: A review. *Frontiers in Nutrition*, *9*, p.1000517.
35. Ibrahim, S.A., Yeboah, P.J., Ayivi, R.D., Eddin, A.S., Wijemanna, N.D., Paidari, S. and Bakhshayesh, R.V., 2023. A review and comparative perspective on health benefits of probiotic and fermented foods. *International Journal of Food Science & Technology*, *58*(10), pp.4948-4964.
36. Afzaal, M., Saeed, F., Shah, Y.A., Hussain, M., Rabail, R., Socol, C.T., Hassoun, A., Pateiro, M., Lorenzo, J.M., Rusu, A.V. and Aadil, R.M., 2022. Human gut microbiota in health and disease: Unveiling the relationship. *Frontiers in microbiology*, *13*, p.999001.

37. Expósito-Almellón, X., Duque-Soto, C., López-Salas, L., Quirantes-Piné, R., de Menezes, C.R., Borrás-Linares, I. and Lozano-Sánchez, J., 2023. Non-Digestible Carbohydrates: Green Extraction from Food By-Products and Assessment of Their Effect on Microbiota Modulation. *Nutrients*, *15*(18), p.3880.
38. Ferraz, M.P., 2023. An Overview of the Relevance of Human Gut and Skin Microbiome in Disease: The Influence on Atopic Dermatitis. *Applied Sciences*, *13*(18), p.10540.
39. Li, S., Qian, Z., Yang, J., Lin, Y., Li, H. and Chen, L., 2022. Seasonal variation in structure and function of gut microbiota in Pomacea canaliculata. *Ecology and Evolution*, *12*(8), p.e9162.
40. Han, Y., Shao, D., Han, C., Huang, Q. and Zhao, W., 2022. Response of human gut microbiota under simulated microgravity. *Applied Microbiology and Biotechnology*, *106*(13-16), pp.5221-5231.
41. Ringø, E., Harikrishnan, R., Soltani, M. and Ghosh, K., 2022. The effect of gut microbiota and probiotics on metabolism in fish and shrimp. *Animals*, *12*(21), p.3016.
42. Bedu-Ferrari, C., Biscarrat, P., Langella, P. and Cherbuy, C., 2022. Prebiotics and the human gut microbiota: From breakdown mechanisms to the impact on metabolic health. *Nutrients*, *14*(10), p.2096.
43. Rinninella, E., Tohumcu, E., Raoul, P., Fiorani, M., Cintoni, M., Mele, M.C., Cammarota, G., Gasbarrini, A. and Ianiro, G., 2023. The role of diet in shaping human gut microbiota. *Best Practice & Research Clinical Gastroenterology*, *62*, p.101828.
44. Hassane, M., Jouan, Y., Creusat, F., Soulard, D., Boisseau, C., Gonzalez, L., Patin, E.C., Heuzé-Vourc'h, N., Sirard, J.C., Faveeuw, C. and Trottein, F., 2020. Interleukin-7 protects against bacterial respiratory infection by promoting IL-17A-producing innate T-cell response. *Mucosal Immunology*, *13*(1), pp.128-139.
45. Socol, C.T., Chira, A., Martinez-Sanchez, M.A., Nuñez-Sanchez, M.A., Maerescu, C.M., Mierlita, D., Rusu, A.V., Ruiz-Alcaraz, A.J., Trif, M. and Ramos-Molina, B., 2022. Leptin signaling in obesity and colorectal cancer. *International journal of molecular sciences*, *23*(9), p.4713.
46. Hamamah, S., Amin, A., Al-Kassir, A.L., Chuang, J. and Covasa, M., 2023. Dietary Fat Modulation of Gut Microbiota and Impact on Regulatory Pathways Controlling Food Intake. *Nutrients*, *15*(15), p.3365.
47. Pan, S., Guo, Y., Hong, F., Xu, P. and Zhai, Y., 2022. Therapeutic potential of melatonin in colorectal cancer: Focus on lipid metabolism and gut microbiota. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1868*(1), p.166281.
48. Mariadoss, A.V.A., Sivakumar, A.S., Lee, C.H. and Kim, S.J., 2022. Diabetes mellitus and diabetic foot ulcer: Etiology, biochemical and molecular based treatment strategies via gene and nanotherapy. *Biomedicine & Pharmacotherapy*, *151*, p.113134.
49. Liu, D., Yang, K., Gu, H., Li, Z., Wang, Y. and Wang, Y., 2022. Predictive effect of triglyceride-glucose index on clinical events in patients with acute ischemic stroke and type 2 diabetes mellitus. *Cardiovascular Diabetology*, *21*(1), pp.1-14.
50. Strikić, D., Vujević, A., Perica, D., Leskovar, D., Paponja, K., Pećin, I. and Merćep, I., 2023. Importance of Dyslipidaemia Treatment in Patients with Type 2 Diabetes Mellitus.
51. Domínguez-Balmaseda, D. and García-Pérez-de-Sevilla, G., 2022. The Relationship between the Gut Microbiota and Exercise: A Narrative Review. *Hygiene*, *2*(4), pp.152-162.
52. Bakhru, A. ed., 2023. *Nutrition and Integrative Medicine for Clinicians: Volume Two*. CRC Press.
53. Carloni, S. and Rescigno, M., 2023, September. The gut-brain vascular axis in neuroinflammation. In *Seminars in Immunology* (Vol. 69, p. 101802). Academic Press.
54. van Deuren, T., Blaak, E.E. and Canfora, E.E., 2022. Butyrate to combat obesity and obesity-associated metabolic disorders: Current status and future implications for therapeutic use. *Obesity Reviews*, *23*(10), p.e13498.
55. Bhatia, Z., Kumar, S. and Seshadri, S., 2023. Exploring the Unexplored Arena: Butyrate as a Dual Communicator in Gut–Brain Axis. In *Probiotics, Prebiotics, Synbiotics, and Postbiotics: Human Microbiome and Human Health* (pp. 153-164). Singapore: Springer Nature Singapore.
56. Guo, T.T., Zhang, Z., Sun, Y., Zhu, R.Y., Wang, F.X., Ma, L.J., Jiang, L. and Liu, H.D., 2023. Neuroprotective Effects of Sodium Butyrate by Restoring Gut Microbiota and Inhibiting TLR4 Signaling in Mice with MPTP-Induced Parkinson's Disease. *Nutrients*, *15*(4), p.930.
57. Xun, Z., Yao, X. and Ou, Q., 2023. Emerging roles of bile acids in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma. *Cellular & Molecular Immunology*, pp.1-3.
58. Lei, Y., Tang, L., Chen, Q., Wu, L., He, W., Tu, D., Wang, S., Chen, Y., Liu, S., Xie, Z. and Wei, H., 2022. Disulfiram ameliorates nonalcoholic steatohepatitis by modulating the gut microbiota and bile acid metabolism. *Nature Communications*, *13*(1), p.6862.
59. Yin, Y., Guo, Q., Zhou, X., Duan, Y., Yang, Y., Gong, S., Han, M., Liu, Y., Yang, Z., Chen, Q. and Li, F., 2022. Role of brain-gut-muscle axis in human health and energy homeostasis. *Frontiers in Nutrition*, *9*, p.2250.
60. Huang, L., Zheng, J., Sun, G., Yang, H., Sun, X., Yao, X., Lin, A. and Liu, H., 2022. 5-Aminosalicylic acid ameliorates dextran sulfate sodium-induced colitis in mice by modulating gut microbiota and bile acid metabolism. *Cellular and Molecular Life Sciences*, *79*(8), p.460.
61. Sankararaman, S., Noriega, K., Velayuthan, S., Sferra, T. and Martindale, R., 2023. Gut Microbiome and Its Impact on Obesity and Obesity-Related Disorders. *Current gastroenterology reports*, *25*(2), pp.31-44.

62. Koutoukidis, D.A., Jebb, S.A., Zimmerman, M., Otunla, A., Henry, J.A., Ferrey, A., Schofield, E., Kinton, J., Aveyard, P. and Marchesi, J.R., 2022. The association of weight loss with changes in the gut microbiota diversity, composition, and intestinal permeability: A systematic review and meta-analysis. *Gut microbes*, *14*(1), p.2020068.
63. Ali, Q., Ma, S., La, S., Guo, Z., Liu, B., Gao, Z., Farooq, U., Wang, Z., Zhu, X., Cui, Y. and Li, D., 2022. Microbial short-chain fatty acids: a bridge between dietary fibers and poultry gut health—A review. *Animal Bioscience*, *35*(10), p.1461.
64. Wilson, I.D. and Nicholson, J.K., 2017. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Translational Research, 179, pp.204-222.
65. Pezzino, S., Sofia, M., Greco, L.P., Litrico, G., Filippello, G., Sarvà, I., La Greca, G. and Latteri, S., 2023. Microbiome Dysbiosis: A Pathological Mechanism at the Intersection of Obesity and Glaucoma. *International Journal of Molecular Sciences*, *24*(2), p.1166.
66. Fikree, A. and Byrne, P., 2021. Management of functional gastrointestinal disorders. Clinical Medicine, 21(1), p.44.
67. Lindell, A.E., Zimmermann-Kogadeeva, M. and Patil, K.R., 2022. Multimodal interactions of drugs, natural compounds and pollutants with the gut microbiota. *Nature Reviews Microbiology*, *20*(7), pp.431-443.
68. Matheson, J.A.T. and Holsinger, R.D., 2023. The role of fecal microbiota transplantation in the treatment of neurodegenerative diseases: A review. *International Journal of Molecular Sciences*, *24*(2), p.1001.
69. Beyi, A.F., Wannemuehler, M. and Plummer, P.J., 2022. Impacts of gut microbiota on the immune system and fecal microbiota transplantation as a re-emerging therapy for autoimmune diseases. *Antibiotics*, *11*(8), p.1093.
70. Zheng, D., Liwinski, T. and Elinav, E., 2020. Interaction between microbiota and immunity in health and disease. *Cell research*, *30*(6), pp.492-506.
71. Donald, K. and Finlay, B.B., 2023. Early-life interactions between the microbiota and immune system: impact on immune system development and atopic disease. *Nature Reviews Immunology*, pp.1-14.
72. Costantini, C., 2022. The immune system and the microbiota: the two sides of mucosal tolerance. In *Translational Autoimmunity* (pp. 297-315). Academic Press.
73. Yagi, K., Asai, N., Huffnagle, G.B., Lukacs, N.W. and Fonseca, W., 2022. Early-life lung and gut microbiota development and respiratory syncytial virus infection. *Frontiers in Immunology*, *13*, p.877771.
74. Vojdani, A., Vojdani, E. and Vojdani, C., 2020. The Immune System: Our Body's Homeland Security Against Disease. *Integrative and Functional Medical Nutrition Therapy: Principles and Practices*, pp.285-302.
75. Edwards, C., Shah, S.A., Gebhardt, T. and Jewell, C.M., 2023. Exploiting unique features of microneedles to modulate immunity. *Advanced Materials*, p.2302410.
76. Ning, X., Lei, Z., Rui, B., Li, Y. and Li, M., 2022. Gut microbiota promotes immune tolerance by regulating RORγt+ treg cells in food allergy. *Advanced Gut & Microbiome Research*, *2022*.
77. Schuppan, D., Gisbert-Schuppan, K., Schuppan, D. and Gisbert-Schuppan, K., 2019. Immunology of the Intestine. *Wheat Syndromes: How Wheat, Gluten and ATI Cause Inflammation, IBS and Autoimmune Diseases*, pp.11-23.
78. Samih, M. and Ahami, A.O.T., 2023. Consequences of errors in the functioning of the immune system Descriptive review [Running title: Consequences of misstep of the immune system]. *International Journal of Innovation and Applied Studies*, *40*(2), pp.444-451.
79. Kogut, M.H., Lee, A. and Santin, E., 2020. Microbiome and pathogen interaction with the immune system. *Poultry science*, *99*(4), pp.1906-1913.
80. Barnig, C., Bezema, T., Calder, P.C., Charloux, A., Frossard, N., Garssen, J., Haworth, O., Dilevskaya, K., Levi-Schaffer, F., Lonsdorfer, E. and Wauben, M., 2019. Activation of resolution pathways to prevent and fight chronic inflammation: Lessons from asthma and inflammatory bowel disease. *Frontiers in immunology*, *10*, p.1699.
81. Neumann, C., Scheffold, A. and Rutz, S., 2019, August. Functions and regulation of T cell-derived interleukin-10. In *Seminars in immunology* (Vol. 44, p. 101344). Academic Press.
82. Jang, D.I., Lee, A.H., Shin, H.Y., Song, H.R., Park, J.H., Kang, T.B., Lee, S.R. and Yang, S.H., 2021. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. *International journal of molecular sciences*, *22*(5), p.2719.
83. Fang, S., Ju, D., Lin, Y. and Chen, W., 2022. The role of interleukin-22 in lung health and its therapeutic potential for COVID-19. *Frontiers in immunology*, *13*, p.951107.
84. Favalli, E.G., 2020. Understanding the role of interleukin-6 (IL-6) in the joint and beyond: a comprehensive review of IL-6 inhibition for the management of rheumatoid arthritis. *Rheumatology and therapy*, *7*(3), pp.473-516.
85. Houben, E., Hellings, N. and Broux, B., 2019. Oncostatin M, an underestimated player in the central nervous system. *Frontiers in immunology*, *10*, p.1165.

86. Dikilitas, A., Karaaslan, F., Aydin, E.Ö., Yigit, U. and Ertugrul, A.S., 2022. Granulocyte-macrophage colony-stimulating factor (GM-CSF) in subjects with different stages of periodontitis according to the new classification. *Journal of Applied Oral Science*, *30*.
87. Chang, S.H., 2019. T helper 17 (Th17) cells and interleukin-17 (IL-17) in cancer. *Archives of pharmacal research*, *42*(7), pp.549-559.
88. Lokau, J., Kespohl, B., Kirschke, S. and Garbers, C., 2022. The role of proteolysis in interleukin-11 signaling. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1869*(1), p.119135.
89. Merli, P., Quintarelli, C., Strocchio, L. and Locatelli, F., 2021. The role of interferon-gamma and its signaling pathway in pediatric hematological disorders. *Pediatric Blood & Cancer*, *68*(4), p.e28900.
90. Wu, S., Duan, C., Kong, L., Tu, X., Wang, L., Guo, Z. and Ye, J., 2021. Interleukin-10 (IL-10) participates in host defense against bacterial pathogens and promotes IgM antibody production in Nile tilapia (Oreochromis niloticus). *Aquaculture*, *531*, p.735829.
91. Soyfoo, M.S. and Nicaise, C., 2021. Pathophysiologic role of Interleukin-33/ST2 in Sjögren's syndrome. *Autoimmunity Reviews*, *20*(3), p.102756.
92. Song, X., Traub, B., Shi, J. and Kornmann, M., 2021. Possible roles of interleukin-4 and-13 and their receptors in gastric and colon cancer. *International Journal of Molecular Sciences*, *22*(2), p.727.
93. Pelaia, C., Paoletti, G., Puggioni, F., Racca, F., Pelaia, G., Canonica, G.W. and Heffler, E., 2019. Interleukin-5 in the pathophysiology of severe asthma. *Frontiers in physiology*, *10*, p.1514.
94. Kar, S., Gupta, R., Malhotra, R., Sharma, V., Farooque, K., Kumar, V., Chakraborty, S. and Mitra, D.K., 2021. Interleukin-9 facilitates osteoclastogenesis in rheumatoid arthritis. *International journal of molecular sciences*, *22*(19), p.10397.
95. Wu, J., Zhang, F., Tao, H., Nawaz, W., Chen, D. and Wu, Z., 2022. The potential roles of interleukin-25 in infectious diseases. *Frontiers in Immunology*, *13*, p.986118.
96. Ebina-Shibuya, R. and Leonard, W.J., 2023. Role of thymic stromal lymphopoietin in allergy and beyond. *Nature Reviews Immunology*, *23*(1), pp.24-37.
97. Rana, T., 2022. Influence and Implications of the Molecular Paradigm of Nitric Oxide Underlying Inflammatory Reactions of the Gastrointestinal Tract of Dog: A Major Hallmark of Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, *28*(8), pp.1280-1288.
98. Sugimura, N., Li, Q., Chu, E.S.H., Lau, H.C.H., Fong, W., Liu, W., Liang, C., Nakatsu, G., Su, A.C.Y., Coker, O.O. and Wu, W.K.K., 2022. Lactobacillus gallinarum modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. *Gut*, *71*(10), pp.2011-2021.
99. Brown, J.A., Sanidad, K.Z., Lucotti, S., Lieber, C.M., Cox, R.M., Ananthanarayanan, A., Basu, S., Chen, J., Shan, M., Amir, M. and Schmidt, F., 2022. Gut microbiota-derived metabolites confer protection against SARS-CoV-2 infection. *Gut Microbes*, *14*(1), p.2105609.
100. Parker, A., Fonseca, S. and Carding, S.R., 2020. Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. *Gut Microbes*, *11*(2), pp.135-157.
101. Huynh, U. and Zastrow, M.L., 2023. Metallobiology of Lactobacillaceae in the gut microbiome. *Journal of Inorganic Biochemistry*, *238*, p.112023.
102. Abbott, M. and Ustoyev, Y., 2019, October. Cancer and the immune system: the history and background of immunotherapy. In *Seminars in oncology nursing* (Vol. 35, No. 5, p. 150923). WB Saunders.
103. Lajqi, T., Köstlin-Gille, N., Hillmer, S., Braun, M., Kranig, S.A., Dietz, S., Krause, C., Rühle, J., Frommhold, D., Pöschl, J. and Gille, C., 2022. Gut microbiota-derived small extracellular vesicles endorse memory-like inflammatory responses in murine neutrophils. *Biomedicines*, *10*(2), p.442.
104. Strizova, Z., Smetanova, J., Bartunkova, J. and Milota, T., 2021. Principles and challenges in anti-COVID-19 vaccine development. *International Archives of Allergy and Immunology*, *182*(4), pp.339-349.
105. Bulut, O., Kilic, G. and Domínguez-Andrés, J., 2022. Immune memory in aging: a wide perspective covering microbiota, brain, metabolism, and epigenetics. *Clinical Reviews in Allergy & Immunology*, *63*(3), pp.499-529.
106. da Silva Soares, N.F., Quagliariello, A., Yigitturk, S. and Martino, M.E., 2023. Gut microbes predominantly act as living beneficial partners rather than raw nutrients. *Scientific Reports*, *13*(1), p.11981.
107. Meng, C., Feng, S., Hao, Z., Dong, C. and Liu, H., 2022. Changes in gut microbiota composition with age and correlations with gut inflammation in rats. *Plos one*, *17*(3), p.e0265430.
108. Ling, Z., Cheng, Y., Chen, F., Yan, X., Liu, X., Shao, L., Jin, G., Zhou, D., Jiang, G., Li, H. and Zhao, L., 2022. Changes in fecal microbiota composition and the cytokine expression profile in school-aged children with depression: A case-control study. *Frontiers in Immunology*, *13*, p.964910.
109. Cataldi, S., Bonavolontà, V., Poli, L., Clemente, F.M., De Candia, M., Carvutto, R., Silva, A.F., Badicu, G., Greco, G. and Fischetti, F., 2022. The relationship between physical activity, physical exercise, and human gut microbiota in healthy and unhealthy subjects: a systematic review. *Biology*, *11*(3), p.479.
110. Kiewiet, M.B., Elderman, M.E., El Aidy, S., Burgerhof, J.G., Visser, H., Vaughan, E.E., Faas, M.M. and de Vos, P., 2021. Flexibility of gut microbiota in ageing individuals during dietary fiber long-chain inulin intake. *Molecular nutrition & food research*, *65*(4), p.2000390.

111. Princisval, L., Rebelo, F., Williams, B.L., Coimbra, A.C., Crovesy, L., Ferreira, A.L. and Kac, G., 2022. Association between the mode of delivery and infant gut microbiota composition up to 6 months of age: a systematic literature review considering the role of breastfeeding. *Nutrition Reviews*, *80*(1), pp.113-127.
112. Thomas, M.S., Blesso, C.N., Calle, M.C., Chun, O.K., Puglisi, M. and Fernandez, M.L., 2022. Dietary influences on gut microbiota with a focus on metabolic syndrome. *Metabolic Syndrome and Related Disorders*, *20*(8), pp.429-439.
113. Aljumaah, M.R., Bhatia, U., Roach, J., Gunstad, J. and Peril, M.A.A., 2022. The gut microbiome, mild cognitive impairment, and probiotics: A randomized clinical trial in middle-aged and older adults. *Clinical Nutrition*, *41*(11), pp.2565-2576.
114. Ye, S., Shah, B.R., Li, J., Liang, H., Zhan, F., Geng, F. and Li, B., 2022. A critical review on interplay between dietary fibers and gut microbiota. *Trends in Food Science & Technology*, *124*, pp.237-249.
115. Gasaly, N. and Gotteland, M., 2022. Interference of dietary polyphenols with potentially toxic amino acid metabolites derived from the colonic microbiota. *Amino acids*, pp.1-14.
116. Schoeler, M. and Caesar, R., 2019. Dietary lipids, gut microbiota and lipid metabolism. *Reviews in Endocrine and Metabolic Disorders*, *20*, pp.461-472.
117. Zhou, X., Xing, J., Tang, X., Sheng, X., Chi, H. and Zhan, W., 2020. Interleukin-2 (IL-2) interacts with IL-2 receptor beta (IL-2Rβ): its potential to enhance the proliferation of CD4+ T lymphocytes in flounder (Paralichthys olivaceus). *Frontiers in Immunology*, *11*, p.531785.
118. Yoo, J.Y., Groer, M., Dutra, S.V.O., Sarkar, A. and McSkimming, D.I., 2020. Gut microbiota and immune system interactions. *Microorganisms*, *8*(10), p.1587.
119. Adejuyigbe, B., Kallini, J., Chiou, D. and Kallini, J.R., 2023. Osteoporosis: Molecular Pathology, Diagnostics, and Therapeutics. *International Journal of Molecular Sciences*, *24*(19), p.14583.
120. Li, Z., Yang, H., Hai, Y. and Cheng, Y., 2023. Regulatory Effect of Inflammatory Mediators in Intervertebral Disc Degeneration. *Mediators of Inflammation*, *2023*.
121. Chen, D.Q., Xu, W.B., Xiao, K.Y., Que, Z.Q., Feng, J.Y., Sun, N.K., Cai, D.X. and Rui, G., 2023. Gut microbiota and spinal stenosis: a two-sample Mendelian randomization study.
122. Moțățăianu, A., Șerban, G. and Andone, S., 2023. The Role of Short-Chain Fatty Acids in Microbiota–Gut–Brain Cross-Talk with a Focus on Amyotrophic Lateral Sclerosis: A Systematic Review. *International Journal of Molecular Sciences*, *24*(20), p.15094.
123. Morimoto, T., Kobayashi, T., Kakiuchi, T., Esaki, M., Tsukamoto, M., Hirata, H. and Mawatari, M., Gut-spine axis: a possible correlation between gut microbiota and spinal degenerative diseases. *Frontiers in Microbiology*, *14*, p.1290858.
124. Qin, L., Li, J., Guo, K., Lu, M., Zhang, Y., Zhang, X., Zeng, Y., Wang, X., Xia, Q., Zhao, P. and Zhang, A.B., 2022. Insights into the structure and composition of mineralized hard cocoons constructed by the oriental moth, Monema (Cnidocampa) flavescens Walker. *Insect Biochemistry and Molecular Biology*, *151*, p.103878.
125. Lassmann, Ł., Pollis, M., Żółtowska, A. and Manfredini, D., 2022. Gut Bless Your Pain—Roles of the Gut Microbiota, Sleep, and Melatonin in Chronic Orofacial Pain and Depression. *Biomedicines*, *10*(7), p.1528.
126. Hinton, J., 2019. A radiographic exploration of vitamin D deficiency at the eighteenth-century fortress of Louisbourg, NS.
127. Howell, B.M. and Harrod, R.P., Future Directions for an Anthropology of Aging. *Perspectives on*, p.314.
128. Zi, C., Wang, D., Gao, Y. and He, L., 2023. The role of Th17 cells in endocrine organs: Involvement of the gut, adipose tissue, liver and bone. *Frontiers in Immunology*, *13*, p.1104943.
129. Wu, X., Al-Abedalla, K., Abi-Nader, S., Daniel, N.G., Nicolau, B. and Tamimi, F., 2017. Proton pump inhibitors and the risk of osseointegrated dental implant failure: a cohort study. Clinical implant dentistry and related research, 19(2), pp.222-232.
130. Guan, Z., Jia, J., Zhang, C., Sun, T., Zhang, W., Yuan, W., Leng, H. and Song, C., 2020. Gut microbiome dysbiosis alleviates the progression of osteoarthritis in mice. *Clinical Science*, *134*(23), pp.3159-3174.
131. Ferrillo, M., Giudice, A., Migliario, M., Renó, F., Lippi, L., Calafiore, D., Marotta, N., de Sire, R., Fortunato, L., Ammendolia, A. and Invernizzi, M., 2023. Oral–Gut Microbiota, Periodontal Diseases, and Arthritis: Literature Overview on the Role of Probiotics. *International Journal of Molecular Sciences*, *24*(5), p.4626.
132. Pariente, E., Pini, S.F., Olmos, J.M., Fierro, P., Landeras, R., Ramos, C., Martínez-Taboada, V.M. and Hernández, J.L., 2023. Early stages of diffuse idiopathic skeletal hyperostosis (DISH) and chronic inflammation: the Camargo Cohort Study. *Clinical Rheumatology*, pp.1-12.
133. Rathour, D., Shah, S., Khan, S., Singh, P.K., Srivastava, S., Singh, S.B. and Khatri, D.K., 2023. Role of gut microbiota in depression: Understanding molecular pathways, recent research, and future direction. *Behavioural Brain Research*, *436*, p.114081.
134. Fournier, D.E., Leung, A.E., Battié, M.C. and Séguin, C.A., 2023. Prevalence of diffuse idiopathic skeletal hyperostosis (DISH) and early-phase DISH across the lifespan of an American population. *Rheumatology*, p. kead362.
135. Shafik, B.M., Kamel, E.R., Mamdouh, M., Elrafaay, S., Nassan, M.A., El-Bahy, S.M., El-Tarabany, M.S. and Manaa, E.A., 2022. Performance, blood lipid profile, and the expression of growth hormone receptor (GHR)

and insulin-like growth factor-1 (IGF-1) genes in purebred and crossbred quail lines. *Animals*, *12*(10), p.1245.
136. Ge, W. and Ding, J., 2023. Investigation of the causal relationship between gut microbiota and discitis: A Mendelian randomisation study.
137. Rosales-Antequera, C., Viscor, G. and Araneda, O.F., 2022. Inflammation and oxidative stress as common mechanisms of pulmonary, autonomic and musculoskeletal dysfunction after spinal cord injury. *Biology*, *11*(4), p.550.
138. Shin, J.H., Park, Y.H., Sim, M., Kim, S.A., Joung, H. and Shin, D.M., 2019. Serum level of sex steroid hormone is associated with diversity and profiles of human gut microbiome. *Research in microbiology*, *170*(4-5), pp.192-201.
139. Gibbons, D., Ahern, D.P., Curley, A.E., Kepler, C.K. and Butler, J.S., 2021. Impact of sarcopenia on degenerative lumbar spondylosis. *Clinical spine surgery*, *34*(2), pp.43-50.
140. Liu, Y., Xu, L., Yang, Z., Wang, D., Li, T., Yang, F., Li, Z., Bai, X. and Wang, Y., 2023. Gut-muscle axis and sepsis-induced myopathy: The potential role of gut microbiota. Biomedicine & Pharmacotherapy, 163, p.114837.
141. Ahmad, S.S., Ahmad, K., Lee, E.J., Lee, Y.H. and Choi, I., 2020. Implications of insulin-like growth factor-1 in skeletal muscle and various diseases. *Cells*, *9*(8), p.1773.
142. Al-Samerria, S. and Radovick, S., 2021. The role of insulin-like growth factor-1 (IGF-1) in the control of neuroendocrine regulation of growth. *Cells*, *10*(10), p.2664.
143. Yamada, K., Ieguchi, M., Takahashi, S. and Nakamura, H., 2022. Life Expectancy Is Poor in Patients with Diffuse Idiopathic Skeletal Hyperostosis-Related Pyogenic Vertebral Osteomyelitis. *Spine Surgery and Related Research*, *6*(6), pp.654-663.
144. Tanios, M., Brickman, B., Norris, J., Ravi, S., Eren, E., McGarvey, C., Morris, D.J. and Elgafy, H., 2023. Spondyloarthropathies That Mimic Ankylosing Spondylitis: A Narrative Review. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders, 16, p.11795441231186822.
145. Sethi, A., Ruby, J.G., Veras, M.A., Telis, N. and Melamud, E., 2023. Genetics implicates overactive osteogenesis in the development of diffuse idiopathic skeletal hyperostosis. *Nature Communications*, *14*(1), p.2644.
146. Froeynes, W., 2023. *My tinnitus story: a symptom medical science has not understood*. Tinnire forlag.