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Review Article

# A correlation between intestinal microbiota dysbiosis and osteoarthritis

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## Abstract

Osteoarthritis (OA) is a degenerative disease of the articular cartilage, resulting in pain and total joint disability. Recent studies focused on the role of the metabolic syndrome in inducing or worsening joint damage suggest that chronic low-grade systemic inflammation may represent a possible linking factor. This finding supports the concept of a new phenotype of OA, a metabolic OA. The gut microbiome is fundamental for human physiology and immune system development, among the other important functions. Manipulation of the gut microbiome is considered an important topic for the individual health in different medical fields such as medical biology, nutrition, sports, preventive and rehabilitative medicine. Since intestinal microbiota dysbiosis is strongly

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associated with the pathogenesis of several metabolic and inflammatory diseases, it is conceivable that also the pathogenesis of OA might be related to it. However, the mechanisms and the contribution of intestinal microbiota metabolites in OA pathogenesis are still not clear. The aim of this narrative review is to review recent literature concerning the possible contribution of dysbiosis to OA onset and to discuss the importance of gut microbiome homeostasis maintenance for optimal general health preservation.

Keywords: Internal medicine, Metabolism, Nutrition, Pathology, Physiology, Public health, Microbiology

## 1. Introduction

Osteoarthritis (OA), is a degenerative disease characterized by the progressive deterioration of the articular cartilage, resulting in pain and total joint disability at advanced stages. Disease progression can be dependent on genetic and epigenetic factors, sex, ethnicity and age, and it is also associated with obesity, overweight, dietary factors, sedentary lifestyle, lubricin loss and sport injuries [1, 2, 3, 4, 5]. It is a multifactorial disorder with a very complicated etiology, where the triggering factor is still a "mystery". Recent studies, confirming an association between type 2 diabetes, cardiovascular diseases, obesity and OA, have focused on the role of the metabolic syndrome in inducing or exacerbating joint damage [6, 7]. There is some evidence showing that the linking factor between metabolic abnormalities and the OA onset could be represented by the persistence of a chronic low-grade systemic inflammation [8]. These findings support the idea of a new phenotype of OA, a metabolic OA, in addition to the age-related and injury-related phenotypes [9]. Intestinal microbiota and its metabolic derivates are highly associated with various aspects of the host physiology such as development, metabolism, immunity and longevity. Gut microbiome dysbiosis has been associated with the pathogenesis of various diseases, such as inflammatory bowel syndrome, obesity and cancer [10,11, 12] (Fig. 1). Recently, the involvement of intestinal microbiota in autoimmune diseases such as rheumatoid arthritis and celiac disease, has been also investigated [13, 14]. In the last decade some authors have also tried to explain the involvement of gut microbiota or its metabolic products in the development of OA [15, 16]. Indeed, it is conceivable that since dysbiosis of the intestinal microbiota is strongly associated with the pathogenesis of several metabolic and inflammatory diseases, it may also be linked to OA pathogenesis. However, the exact mechanism and the contribution of intestinal microbiota metabolites to OA pathogenesis has still not being defined and needs to be further explored. The aim of this narrative review is to review the recent literature regarding the potential relationship of microbiome dysbiosis and OA onset, and to discuss the importance of gut microbiome homeostasis


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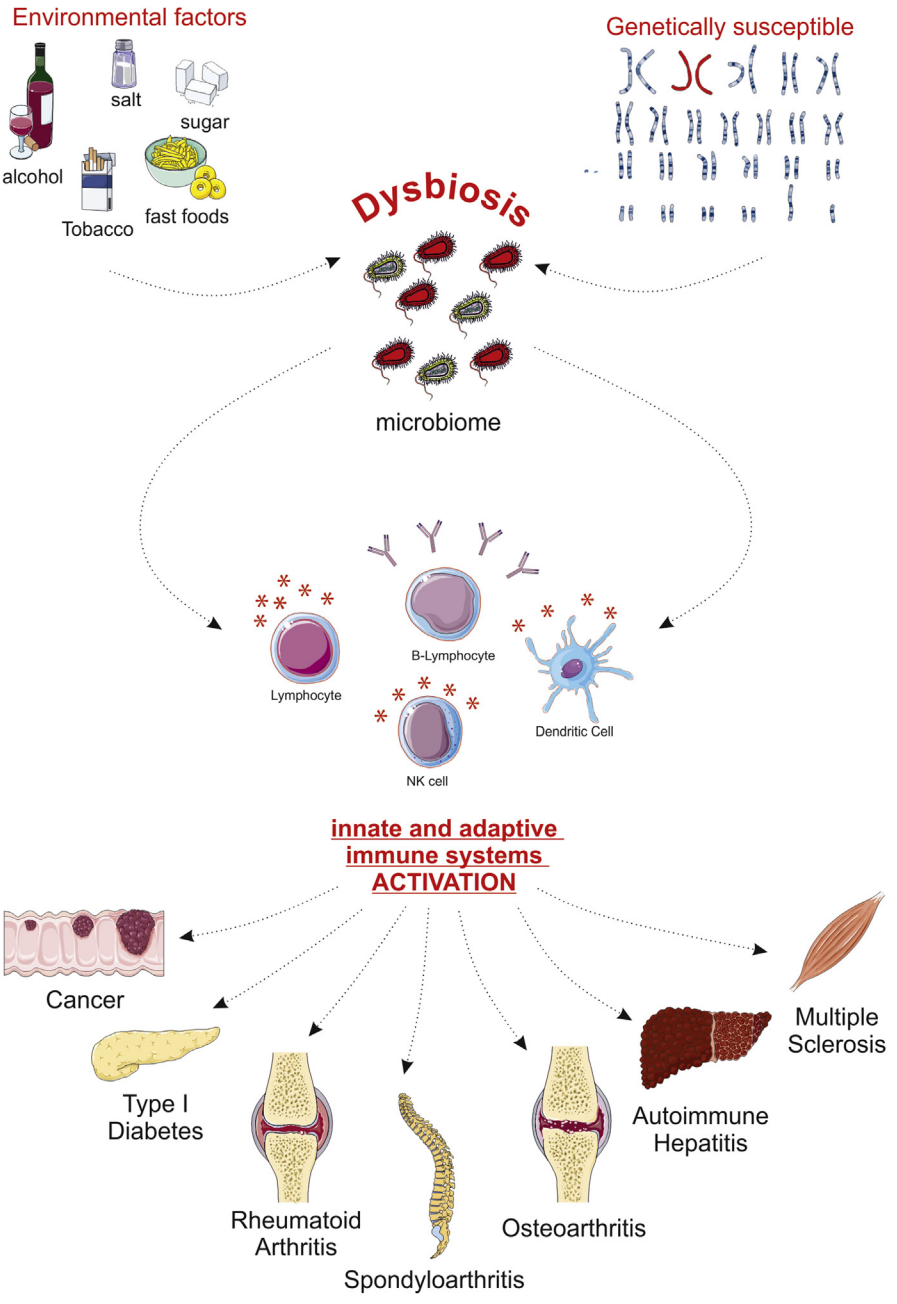


**Fig. 1.** The figure represents the main factors involved in dysbiosis of the gut microbiome. The self-antigen immune-activation by dysbiosis could lead to the development of different diseases such as cancer, Type I Diabetes, Rheumatoid Arthritis, Spondyloarthritis, Osteoarthritis, Autoimmune Hepatitis and Multiple Sclerosis. This figure was drawn using the software CorelDraw and the vector image bank of Servier Medical Art (http://smart.servier.com/). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

maintenance for the optimal general health preservation. The limitation of this review is, surely, due both to the paucity of the studies in this field and to the consequent lack of a systematic approach like PRISMA Statement or similar to provide a more balanced view on the current state of knowledge in this research field.


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## 2. Main text

### 2.1. Microbiome in health and disease

For several years, the potential role played by the microbiome in health and disease has remained unnoticed. With the advent of cutting-edge sequencing technologies understanding the composition and functions of the microbiome has been made possible. The human microbiota represents a collection of microorganisms living on the surface and inside the host body [17]. More than a 100 trillion of prokaryotic cells have been identified as having a role in supporting the biological functions of the human body. At any given time, we carry 3−6 pounds of bacteria, containing roughly 3 million protein-coding genes [18]. In the human body there are several microbial niches that are in balance with a specific nutritional condition [19]. An important role played by the gut microbiome, in particular, is maintaining the homeostasis with the host [20]. The gut microbiome is fundamental for human physiology, immune system development, digestion, fat storage, angiogenesis regulation, behavior, development and detoxification reactions [21, 22]. Some of the microorganisms of the gut microbiome encode proteins, such as enzymes required for the hydrolysis of dietary compounds, otherwise indigestible, and the synthesis of vitamins [23, 24]. The most abundant microbiota phyla living in the healthy gut are *Firmicutes*, *Bacteroidetes* and *Actinobacteria*, while *Proteobacteria*, *Fusobacteria*, *Cyanobacteria* and *Verrucomicrobia* are usually less present [25, 26]. The presence of methanogenic archaea (especially *Methanobrevibacter smithii*), *Eucarya* (predominantly yeasts), and multiple phages has also been reported [27]. However, the microbiome content varies enormously from one person to another [26]. The microbiome is extremely dynamic and can be influenced by a number of factors, such as age and travel [28], diet [29], hormonal cycles [30], therapies and illness [31]. Moreover, variations in microbiome patterns have been identified in different geographical locations, as demonstrated by He et al., [32]. In particular, it was shown that, within the same geographical location, it is the different ethnicity that can be accounted for the most to explain the interindividual dissimilarities in microbiome composition. In particular, three main poles, characterized by operational taxonomic units (OTUs) have been classified as *Prevotella* (Moroccans, Turks, Ghanaians), *Bacteroides* (African Surinamese, South-Asian Surinamese), and *Clostridiales* (Dutch) [33]. The colonization of the host body by the microbiome, determines the presence of two phenotypes, one inherited from our parents and the other acquired through the microbiome. The alteration of the gut microbiome has the ability to dramatically influence health outcomes and its homeostasis may be interrupted under certain pathological conditions. It has been shown that in genetically susceptible individuals, environmental factors (e.g., diet, smoke and alcohol) can disturb the gut microbial populations, causing dysregulations in host innate and adaptive immune systems, leading to the development of several diseases [19]. In


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recent years, it has been demonstrated that it is the interaction between the immune system and the altered gut microbiome that affects the pathogenesis of several disease states such as cancer, metabolic syndrome, inflammatory bowel syndrome, nonalcoholic fatty liver disease [12] and many autoimmune diseases, including autoimmune hepatitis, type 1 diabetes, spondyloarthritis, multiple sclerosis and rheumatoid arthritis [34]. All these findings, along with the correlation between the numerous risk factors shared by gut dysbiosis and OA such as aging, gender, obesity and quality of nutrients intake, also suggested the possible involvement of intestine microflora alterations in the pathogenesis of musculoskeletal disorders (Fig. 2).

## 2.2. Links between gut microbiome alterations and osteoarthritis-related risk factors

### *2.2.1. Aging*

Different pathophysiological mechanisms, including thinning of cartilage, oxidative damage, muscle weakening and a reduction in proprioception, have been proposed to clarify the involvement of age in OA [35]. Several studies have demonstrated that, older people also show significant difference in gut microbiome compared with young people, such as greater proportion of *Bacteroides*, and distinct abundance pattern of *Clostridium* groups [36, 37]. The variation within the gut microbiome

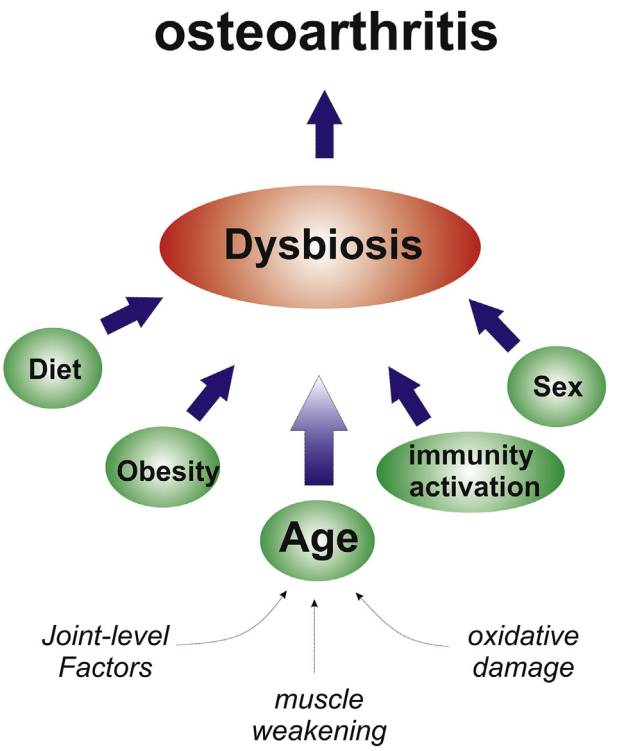


**Fig. 2.** The etiology of osteoarthritis (OA) is still unknown. Various risk factors have been reported to negatively influence OA onset including age, sex, obesity, immune activation and incorrect diet.


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may regulate the age-related physiology, such as immune responses, cognitive function, metabolic alterations and organ disorders [38, 39]. It has been revealed that in *Drosophila* the dysbiosis of intestinal microbiome greatly precedes and predicts age-related intestinal barrier dysfunction [40]. Moreover, targeting of the aging-related dysbiosis of intestinal microbiome improves these dysfunctions and maintains lifespan in *Drosophila* [40]. The variations in the gut microbiota with aging are commonly linked with physiological alterations of the gastrointestinal tract, and also, to variations in dietary patterns, all together leading to decline in cognitive and immune functions and contributing to frailty [41]. With aging, the gut microbiota is characterized by a reduced bacterial diversity, variations in the dominant species and decline in those beneficial ones [42]. More specifically, when comparing the gut microbiota of elderly with that of younger subjects, lower levels of *Firmicutes*, especially *Clostridium cluster XIVa* and *Faecalibacterium prausnitzii*, and *Actinobacteria* (mainly *Bifidobacteria*), and increased populations of *Proteobacteria,* are found [43, 44]. Moreover, recent studies demonstrate that gut microbiota may promote frailty physiopathology by stimulating chronic inflammation insurgence and anabolic resistance, suggesting its involvement in numerous others chronic inflammation-based disorders [45].

### 2.2.2. Gender

The prevalence and the severity of OA in hip, knee and hand are higher in women than in men, and they even increase with menopause [35, 46, 47]. These findings suggest that there are differences based on hormonal factors such as high estrogen levels in women, that may determine differences in cartilage volume and bone/muscle strength [48]. Gender effects on gut microbiome have been investigated in several vertebrate species, such as fish, mice, and humans [49]. However, since the inter-individual dissimilarities in microbiome composition are quite common, more studies are needed to support the idea of the effective gender influence on gut microbiome alterations.

### 2.2.3. Obesity

Another well-known risk factor for OA is obesity [35]. The biological process by which obesity promotes OA onset, is not completely understood. From the mechanical point of view, the link between obesity and OA involves excessive joint loading as a result of increased body weight. The latter, usually, leads to the physiologically decreased movement, that finally results in a decreased release of synovial fluid into the joint capsule and, thus, in the decreased tribology properties of the articular cartilage. From the molecular point of view, a more complex etiology for obesity-induced OA has been reported, encompassing chronic low-grade inflammatory state, mainly due to increased adipokine levels [50, 51]. It has been shown that intestinal


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microbiota alterations are strongly associated with the development and establishment of obesity. Obesity is associated with phylum-level changes in the microbiome (*Firmicutes*/*Bacteroidetes*), reduced bacterial diversity, and altered representation of bacterial genes and metabolic pathways [52]. In obese people, the ratio of *Firmicutes* to *Bacteroidetes* is increased, which stimulates the production of biologically active metabolites, such as short chain fatty acids (SCFAs) [53]. The formation of SCFAs is the result of a complex interplay between diet and the gut microbiota within the gut lumen environment. SCFAs represent the major carbon flux from the diet through the gut microbiota to the host and evidence is emerging for a regulatory role of SCFA in local, intermediate and peripheral metabolism [54]. Recent evidence suggests that SCFAs may regulate directly or indirectly physiological and pathological processes associated to obesity, energy regulation and metabolism. Indeed, increased levels of SCFAs represent an additional energy source, and cause an imbalance in energy regulation, leading to obesity onset. Simultaneously, SCFAs participate in glucose-stimulated insulin secretion and release of peptide hormones which control appetite. This apparent contradictory situation may indicate the involvement of additional bacteria or their metabolites that may trigger regulatory cascades and alter the general metabolic homeostasis [55]. Since there is some degree of correlation between dysbiosis of the gut microbiome and obesity, it is conceivable that the former may also be linked to other obesity-related conditions characterized by low grade chronic inflammation, including OA. OA is a low-grade inflammatory condition, and the high levels of lipopolysaccharides seen in obese people and in those affected by metabolic syndrome, may contribute to its onset. Lipopolysaccharides could be considered a major hidden risk factor that provides a unifying mechanism to explain the association between obesity, metabolic syndrome and OA [56]. However, this association also warrants further investigations.

### *2.2.4. Dietary factors*

Several dietary factors, along with quality and quantity of nutrients intake, have been reported to be involved in pathogenesis of OA. Among these, vitamins, fatty acids and magnesium seem to play a key role [57, 58]. It has been shown that low intake of vitamin D and vitamin C is a possible risk factor for knee OA, while certain food groups, such as milk and dairy products, meat and poultry are beneficial for knee OA [35]. Gut microbiome is highly molded by dietary nutrients as well [59, 60]. It is critical in the synthesis of vitamins and absorption and metabolism of otherwise inaccessible nutrients. Vitamin D regulates calcium homeostasis in the intestine, kidney and bone. It was shown that Vitamin D deficiency contributes to the pathogenesis of Crohn's disease and non-alcoholic fatty liver disease (NAFLD) and its supplementation has shown a positive effect in these patients and through regulating microbiome [61]. Moreover, magnesium deficiency has been shown to adversely affect gut microbial composition and to promote both anxiety and depressive-like


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behavior in mice [62]. Other studies in animal models have demonstrated that a high-fat diet decreases the number of bacterial species in the gut microbiome. It was shown, for example, that *A. muciniphila* decreases in obese animals and those with type 2 diabetes. While, prebiotic feeding of *A. muciniphila* normalizes its quantity and improves metabolic profiles [63]. Treatment with *A. muciniphila* also reduces inflammation, fat mass and insulin resistance induced by a high-fat diet [63]. Moreover, a fiber-rich diet has been shown to be beneficial to health because it modulates positively the gut microbiome [64]. A theory to explain nutrient-induced changes of the gut microbiome is that dietary nutrients alter the microenvironment of gut microbiome in terms of its digestion capacity, structure and immunological reactions of the host. These data suggest that nutrients affect host physiological functions depending on the gut microbiome [65, 66]. Modifications of nutrients intake, and thus of the gut microbiome microenvironment, may be an interesting strategy to prevent OA [67]. However, this aspect needs to be substantiated by additional studies.

## 2.3. The impact of lifestyle on the gut microbiome

The potential impact of lifestyle factors on the gut microbiome has been largely disregarded. Smoking habits, stress, travelling, poor healthy conditions and personal hygiene, host interactions with environment, life sharing conditions, disruptions in the circadian rhythm and lack of exercise can significantly impact the intestinal function and determine microbiome alterations [68]. Frantic life-style, consumption of industrial foods, snacks, prevalence of a high fat/high sugar "Western diet" and sedentary lifestyle are increasingly becoming predominant in daily life, resulting in phenotypically and epigenetically obvious consequences [69] (Fig. 3). In recent years, it has been shown that nutritional habits influence qualitatively and quantitatively our lives. A potentially harmful diet of nowadays, commonly known as "Western diet" is primarily the result of a combination of additive and harmful ingredients, such as animal fats and glucose in excessive quantities and lack of nutritional factors, such as vitamins and minerals, essential for our body. Moreover, wrong habits (smoking, sedentary life, alcohol abuse) and unhealthy dietary habits (fast and fatty food) may predispose people to obesity, and thus, to many other complications which may lead to the development of severe metabolic dysfunctions [70]. It is also well known that sedentary behavior is associated with an increased risk of developing several chronic diseases. In recent epidemiologic findings, it has been indicated as an independent risk factor for both morbidity and mortality [71]. Interestingly, smoking has a significant influence on gut microbiota composition. Indeed, smoking as well as lack of physical activity, can significantly impact the large bowel as are also considered risk factors for colorectal cancer [72]. Moreover, it has been demonstrated that stress has an impact on colonic motor activity via the gut-brain axis which can alter gut microbiota profiles [73]. Stress may contribute to functional


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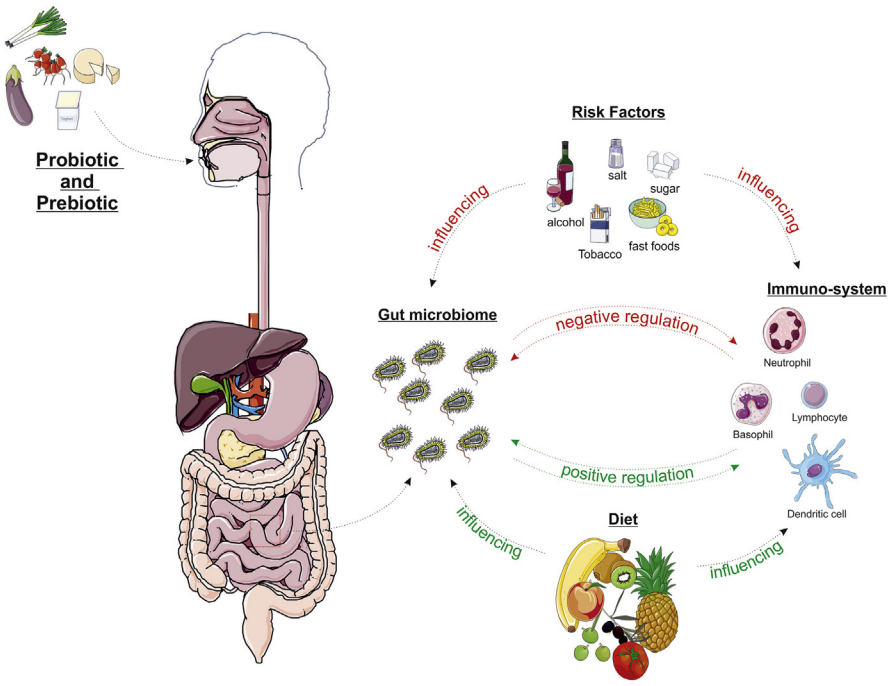


**Fig. 3.** Proposed schematic representation of how the gut microbiome is regulated. Risk factors such as alcohol consumption, tobacco, salt, sugar and fast food diet negatively influence the microbiome and the immune system. Conversely, a diet rich in fibers, improves the gut microbiome and boosts the immune system. This figure was drawn using the software CorelDraw and the vector image bank of Servier Medical Art (http://smart.servier.com/). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

bowel disorders such as irritable bowel syndrome and the associated changes in microbial populations *via* the central nervous system. Finally, sedentary lifestyle and excessive energy intake may lead to obesity. In fact, the lack of exercise influences shifts in microbial populations that seem to find some associations with obesity. In humans and animal models of obesity, shifts in gut microbiome composition could potentially contribute to adiposity through greater energy harvest [74, 75]. On the contrary, healthy lifestyle, based on a healthy diet, regular sleeping habits and physical activity helps to maintain the gut microbiome healthier [76]. It improves mental health and general physical condition, including the hematopoietic system, bone, cartilage and muscles, as well as the immune system and cardiovascular function [77, 78] among a range of additional benefits [79, 80].

## 2.4. Influence of physical activity and diet on the intestinal microbiome

Exercise is considered as a metabolism modulator and the metabolic changes it induces may be partially responsible for an improved health [81, 82] (Fig. 4). Nonetheless, the mechanisms by which exercise prevents disease occurrence and improves


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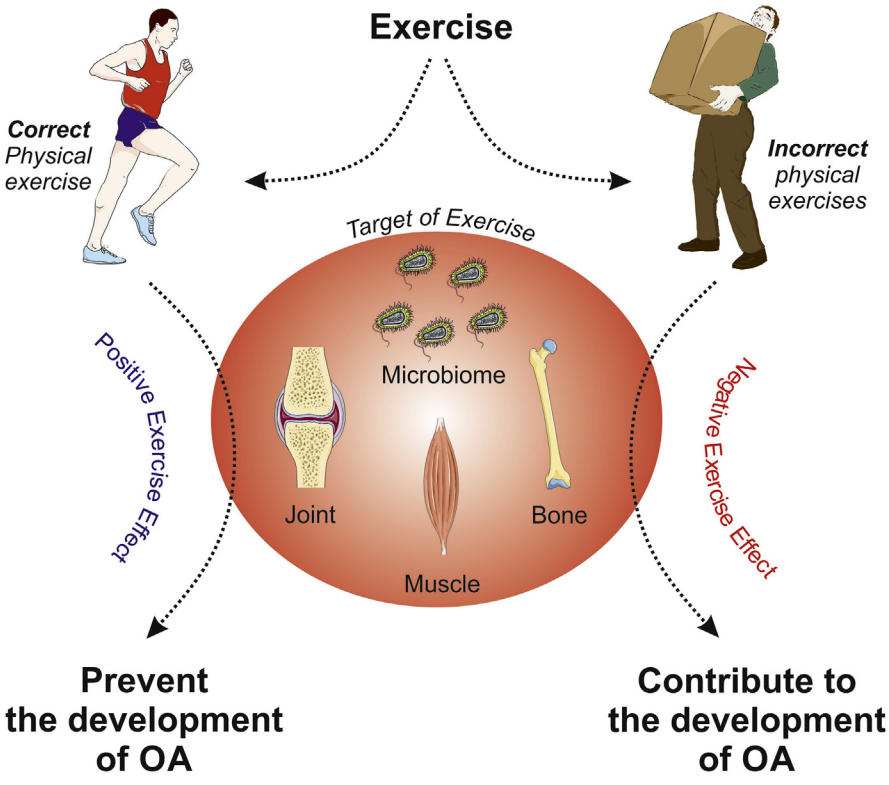


**Fig. 4.** Regular moderate physical exercise plays a role in weight control, decreases the risk of diabetes and regularizes the function of the gut microbiome. A correct physical exercise could exert positive effects on joints, muscles, bones and microbiome, consequently preventing osteoarthritis (OA) development. On the other hand, excessive and incorrect physical exercise could be a risk factor for OA. This figure was drawn using the software CorelDraw and the vector image bank of Servier Medical Art (http://smart.servier.com/). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

physical recovery following illnesses are still poorly understood. An increasing body of evidence suggests that gut microbiome can be implicated in this process. Several studies in animal models and humans have found correlations between specific alterations in the gut microbiome and physical activity. Studies on animal models demonstrated that exercise could reverse unhealthy states, such as diet-induced obesity, diabetes and endotoxin-induced toxicity, by shifting the α-diversity of gut microbiome [83, 84, 85]. These finding have been confirmed by two studies on professional athletes [86, 87]. Generally, the α-diversity of the gut microbiome refers to a "healthier" intestinal microbiota that promotes gut health and maintains essential structural, metabolic and signaling functions. In particular, in a recent study by Zhao and coauthors [88], it has been demonstrated that physical activity based on long-distance running, induced significant increase in the *Coriobacteriaceae* family, whose activity has been reported to be involved in the metabolism of bile salts and steroids as well as in the activation of dietary polyphenols in the human gut. In particular, strong positive correlations between *Coriobacteriaceae* and the steroid


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aldosterone 18-glucuronide, an important metabolite of aldosterone, have been found. The latter exerts many important functions, such as cell signaling, fuel and energy storage, and membrane integrity/stability. Evidence in literature has also shown that aldosterone levels in the plasma rise significantly in response to stress caused by long-distance running [89]. Thus, the metabolism of *Coriobacteriaceae* may be considered a potential factor contributing to explain the underlying the role of exercise in preventing disease and improving health outcomes, further suggesting the existence of a link between exercise, intestinal microbiota and health improvement. There is some indication showing that regular physical activity is also protective against developing chronic inflammatory diseases [90, 91, 92, 93]. Furthermore, exercise can determine changes in the gut microbial composition, playing a positive role in energy homeostasis and regulation [94, 95]. Aerobic physical activity modulates vagal tone, which is crucial in regulating the brain-gut microbiome axis. Exercise and the gut microbiome share several immunometabolic and physiological activities that are well recognized in cardiovascular health and other areas beyond the gut [96]. Conversely, additional investigations are essential to ascertain the anti-inflammatory and metabolic consequences of moderate exercise and the hypothetical threats of excessive exercise [97]. An intense physical activity determines a pleiotropic effect in the entire body. The physiological processes of our body undergo continuous adjustments and adaptations to the increased metabolic demand caused by the intense physical effort. Electrolyte imbalance, regulation of glycogen storage, increased oxidative stress, muscle damage, increased release of endotoxins from gram negative bacteria and systemic immune activation, are all conditions purportedly associated with intense physical activity and may determine alterations of intestinal permeability [98]. Adaptations to exercise might be influenced by the gut microbiome, which shows a significant function in the production, storage, and expenditure of energy obtained through the diet as well as in inflammation, redox reactions, and hydration status [99]. During endurance exercise, transient immunosuppression and inflammatory changes are observed, as well as the regulation of lipid and carbohydrate metabolism, mitochondrial biogenesis, oxidative stress, and dehydration [94, 100]. The gut microbiome ferments complex dietary polysaccharides, which may be used as sources of energy in the liver and in muscle cells to improve endurance performance, by maintaining glycaemia over time [101, 102]. Physical activity has been shown to control neutrophil function and migration, decrease colonic mucosal permeability, inhibit inflammatory cytokines and control the redox environment within the cell, which might help delaying fatigue symptoms in endurance athletes [103]. Given that many endurance dietary plans are based on high protein and carbohydrate levels, a key challenge is to design diets that limit the microbial profiles able to produce toxic metabolites from protein degradation whilst increasing the number of microorganisms that improve energy metabolism, thereby reducing oxidative stress and systemic inflammation [104]. Currently, the main dietary intervention to modulate gut microbiome involves the supplementation of


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probiotics. In athletes, administration of different *Lactobacillus* and *Bifidobacterium* strains might help maintaining a state of general health, enhance immune function, improve gut mucosal permeability, reduce oxidative stress and improve our ability to obtain energy from plant-carbohydrate sources [105, 106]. It is therefore important for future research to dissect the respective influences that high intensity or moderate exercise and the intestinal microbiome may have on the immune system, redox system, and energy metabolism and to track the impact of functional foods on the intestinal microbiome [106, 107].

## 2.5. Gut microbiota manipulation by nutrition boosters

Reinstatement of a healthy gut microbiota is shown to have positive effects on the treatment of dysbiosis-related diseases. The regulation of the intestinal microbiome in healthy individuals may also be helpful in disease prevention. Therefore, manipulation of the gut microbiome presents valuable avenues for therapeutic and clinical applications. To positively influence health through therapeutic modulation of the gut microbiome, the latter can be manipulated by changing the composition and/or the functional output of metabolic products. In particular, the manipulation of the gut microbiome can be reached by using targeted prebiotics, probiotics and engineered probiotics. It is correct, at this point, to make a distinction between prebiotics (indigestible and non-absorbable substances) and probiotics (live organisms). The current definition of prebiotics is proposed as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" [108]. With regards to prebiotics, their main function is to stimulate the activity and growth of bacteria in the digestive tract. The main characteristics of these substances are the ability to resist to the action of hydrolytic enzymes and to the low pH of the gastric enzymes. The gut microbiome determines the fermentation of prebiotics and the consequent transformation into SCFAs that can be used as a source of energy [109]. During the fermentation process, several metabolites are produced, many of which elicit a numberof biological activities [110]. Prebiotics are mainly composed of fibers, present in a variety of foods such as whole grain, fruit, root vegetables, and legumes. The inulin-type fructans oligofructose, fructo-oligosaccharides and the galactan galacto-oligosaccharide belong to the prebiotics groups. It has been shown that the fermentation of prebiotics such as fructo-oligosaccharides can help in the prevention of diseases such as osteoporosis, obesity, and colorectal cancer [94]. The consumption of fermentable fibers or the combinations of prebiotics represent a good strategy to activate the gut microbes and improve health benefits [111, 112]. Many are the health benefits provided by dietary fiber intake such as significantly lower risk for developing coronary heart disease, stroke, hypertension, diabetes, obesity and certain gastrointestinal diseases. Increasing fiber intake also lowers blood pressure and serum cholesterol levels, glycaemia and insulin sensitivity in non-diabetic and diabetic individuals. Fiber supplementation in obese patients significantly enhances


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weight loss. Moreover, increased fiber intake is of benefit in a number of disorders of the gastrointestinal tract, including gastroesophageal reflux disease, duodenal ulcer, diverticulitis, constipation, and hemorrhoids. Prebiotic fibers appear to enhance immune function as well [113]. It has been shown that also the diet-mediated manipulation of the gut microbiome confers health benefits to the host [114]. Within the gastrointestinal tract, probiotics play a number of functional roles, including, regulating mucin secretion, producing antimicrobial peptides, maintaining the intestinal barrier integrity and influencing cytokines' production [115]. Probiotics generally promote gut health through different mechanisms, such as regulation of pH levels and by affecting colonization resistance [114]. Currently, well-known gram-positive bacteria that confer such health benefits include *Bifidobacterium* and *Lactobacillus* [116]. Noteworthy are also the so called next-generation probiotics, referred to as a new class of organisms for exclusive pharmaceutical application. The notion of "new generation probiotics" comes from the increasing knowledge of the human microbiome, which individualizes the novel dominant members of the adult microbiota. In this sense, the literature highlights the interest towards several species such *as Faecalibacterium prausnitzii* and *Akkermansia muciniphila* as potential novel classes to be used for medical purposes [117]. Patients diagnosed with musculoskeletal diseases are reported to have a predisposition for gastrointestinal disturbances that includes dyspepsia, nausea, abdominal bloating and irregular bowel habits [118]. The intake of high-dose analgesic pharmaceuticals for musculoskeletal pain [119] has adverse effects on gastrointestinal physiology and morphology further inducing barrier integrity loss and inflammation [120]. The gut microbiome viability and growth may potentially be disrupted with the use of these medications. Probiotics and prebiotics may be endowed with therapeutic effects that can restore gastrointestinal barrier functionality and down regulate pro-inflammatory mediators by modulating the activity of, for example, *Clostridia* species, known to induce the release of pro-inflammatory mediators [121, 122]. Obesity-related OA is potentially driven by a persistent low-grade inflammatory process partaken by dysbiosis of the gut microbiome. Although further investigations are required, current evidence suggests that the condition may be prevented/treated by restoring a healthy microbial community certain prebiotics, includingthe indigestible prebiotic fiber oligofructose. The latter might reduce systemic inflammation and, probably, contribute to preserve articular cartilage damage and OA onset in obese people [8, 35].

## 3. Conclusions

The intestinal microbiota is strictly associated with the pathogenesis of numerous disorders. Interestingly, emerging evidence leads to the hypothesis that alterations in the gut microbiome could also be considered as possible triggering factors in the onset of musculoskeletal disorders such as OA. The most accredited linking


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factor between these two disorders may be represented by the common appearance of a chronic low-grade inflammation, supporting a new OA phenotype, indicated as the metabolic OA. As discussed in the present narrative review, OA and gut dysbiosis share numerous triggering risk factors such as aging, gender, obesity and nutrition. Since the gut microbiome composition may be altered by several factors such as sedentary life, use of medicines, smoking, stress, traveling, wrong dietary habits (Western diet), life sharing conditions, etc, preservation of the health status of the intestinal flora results of fundamental importance to prevent the onset of numerous diseases. Manipulation of the intestinal microbiota, along with the associated positive outcomes, may be achieved by switching to an healthy lifestyle, based on regular physical activity, healthy diet enriched by vitamins, minerals and nutrition boosters such as prebiotics and probiotics, and regular sleeping habits. In the future, it is foreseeable that the gut microbiome profile may be use as a tool to predict performance and detect potential disorders. Moreover, manipulation of the gut microbiome could be a potentially novel intervention to tackle or prevent metabolic OA. However, this field needs to be further investigated.

## Declarations

### Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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### Competing interest statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

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## References

[1] A.M. Malfait, Osteoarthritis year in review 2015: biology, Osteoarthritis Cartilage 24 (2016) 21−26. PMID: 26707989.

[2] R. Leonardi, M.C. Rusu, F. Loreto, C. Loreto, G. Musumeci, Immunolocalization and expression of lubricin in the bilaminar zone of the human temporomandibular joint disc, Acta Histochem. 114 (1) (2012 Jan) 1−5. PMID: 21955422.

[3] G. Musumeci, P. Castrogiovanni, F.M. Trovato, A.M. Weinberg, M.K. Al-Wasiyah, M.H. Alqahtani, A. Mobasheri, Biomarkers of chondrocyte apoptosis and autophagy in osteoarthritis, Int. J. Mol. Sci. 16 (2015) 20560−20575. PMID: 26334269.

[4] S. Giunta, A. Castorina, R. Marzagalli, M.A. Szychlinska, K. Pichler, A. Mobasheri, G. Musumeci, Ameliorative effects of PACAP against cartilage degeneration. Morphological, immunohistochemical and biochemical evidence from in vivo and in vitro models of rat osteoarthritis, Int. J. Mol. Sci. 16 (2015) 5922−5944. PMID: 25782157.

[5] G. Musumeci, A. Mobasheri, F.M. Trovato, M.A. Szychlinska, A.C. Graziano, D. Lo Furno, R. Avola, S. Mangano, R. Giuffrida, V. Cardile, Biosynthesis of collagen I, II, RUNX2 and lubricin at different time points of chondrogenic differentiation in a 3D in vitro model of human mesenchymal stem cells derived from adipose tissue, Acta Histochem. 116 (2014) 1407−1417. PMID: 25307495.6.

[6] G.S. Hotamisligil, E. Erbay, Nutrient sensing and inflammation in metabolic diseases, Nat. Rev. Immunol. 8 (2008) 923−934. PMID: 19029988.

[7] I. Barna, D. Nyúl, T. Szentes, R. Schwab, Review of the relation between gut microbiome, metabolic disease and hypertension, Orv. Hetil. 159 (2018) 346−351. PMID: 29480046.

[8] E.M. Schott, C.W. Farnsworth, A. Grier, J.A. Lillis, S. Soniwala, G.H. Dadourian, R.D. Bell, M.L. Doolittle, D.A. Villani, H. Awad, J.P. Ketz, F. Kamal, C. Ackert-Bicknell, J.M. Ashton, S.R. Gill, R.A. Mooney, M.J. Zuscik, Targeting the gut microbiome to treat the osteoarthritis of obesity, JCI Insight 3 (2018) pii: 95997. PMID: 29669931. [Epub ahead of print].

[9] J. Sellam, F. Berenbaum, Is osteoarthritis a metabolic disease? Jt. Bone Spine 80 (6) (2013 Dec) 568−573. Kluzek S, Newton JL, Arden NK. Is osteoarthritis a metabolic disorder? Br Med Bull 2015; 115: 111−21. PMID: 24176735.


https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[10] M. Wlodarska, A.D. Kostic, R.J. Xavier, An integrative view of microbiome-host interactions in inflammatory bowel diseases, Cell Host Microbe 17 (2015) 577–591. PMID: 25974300.

[11] W.J. Lee, K. Hase, Gut microbiota-generated metabolites in animal health and disease, Nat. Chem. Biol. 10 (2014) 416–424. PMID: 24838170.

[12] A. Fasano, T. Shea-Donohue, Mechanisms of disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases, Nat. Clin. Pract. Gastroenterol. Hepatol. 2 (2005) 416–422. PMID: 16265432.

[13] A. Lerner, T. Matthias, Rheumatoid arthritis-celiac disease relationship: joints get that gut feeling, Autoimmun. Rev. 14 (2015) 1038–1047. PMID: 26190704.

[14] K.P. Liao, L. Alfredsson, E.W. Karlson, Environmental influences on risk for rheumatoid arthritis, Curr. Opin. Rheumatol. 21 (2009) 279–283. PMID: 19318947.

[15] Y. Li, W. Xiao, W. Luo, C. Zeng, Z. Deng, W. Ren, G. Wu, G. Lei, Alterations of amino acid metabolism in osteoarthritis: its implications for nutrition and health, Amino Acids 48 (2016) 907–914. PMID: 26767374.

[16] D.T. Felson, R.C. Lawrence, P.A. Dieppe, R. Hirsch, C.G. Helmick, J.M. Jordan, R.S. Kington, N.E. Lane, M.C. Nevitt, Y. Zhang, M. Sowers, T. McAlindon, T.D. Spector, A.R. Poole, S.Z. Yanovski, G. Ateshian, L. Sharma, J.A. Buckwalter, K.D. Brandt, J.F. Fries, Osteoarthritis: new insights. Part 1: the disease and its risk factors, Ann. Intern. Med. 133 (2000) 635–646. PMID: 11033593.

[17] M. Arumugam, J. Raes, E. Pelletier, et al., Enterotypes of the human gut microbiome, Nature 473 (2011) 174–180. PMID: 21508958.

[18] N. Voreades, A. Kozil, T.L. Weir, Diet and the development of the human intestinal microbiome, Front. Microbiol. 5 (2014) 494. PMID: 25295033.

[19] E.M. Quigley, Gut bacteria in health and disease, Gastroenterol. Hepatol. 9 (2013) 560–569. PMID: 24729765.

[20] P. Debre, Challenges set by the microbiota, Biologie aujourd'hui 211 (2017) 19–28. PMID: 28682224.

[21] I. Sekirov, S.L. Russell, L.C. Antunes, B.B. Finlay, Gut microbiota in health and disease, Physiol. Rev. 90 (2010) 859–904. PMID: 20664075.

 https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[22] J.F. Cryan, S.M. O'Mahony, The microbiome-gut-brain axis: from bowel to behavior, Neuro Gastroenterol. Motil. 23 (2011) 187−192. PMID: 21303428.

[23] H.J. Flint, K.P. Scott, S.H. Duncan, P. Louis, E. Forano, Microbial degradation of complex carbohydrates in the gut, Gut Microb. 3 (2012) 289−306. PMID: 22572875.

[24] S.V. Lynch, O. Pedersen, The human intestinal microbiome in health and disease, N. Engl. J. Med. 375 (2016) 2369−2379. PMID: 27974040.

[25] P.B. Eckburg, E.M. Bik, C.N. Bernstein, et al., Diversity of the human intestinal microbial flora, Science 308 (2005) 1635−1638. PMID: 15831718.

[26] J. Qin, R. Li, J. Raes, et al., A human gut microbial gene catalogue established by metagenomic sequencing, Nature 464 (2010) 59−65. PMID: 20203603.

[27] A. Reyes, M. Haynes, N. Hanson, et al., Viruses in the faecal microbiota of monozygotic twins and their mothers, Nature 466 (2010) 334−338. PMID: 20631792.

[28] T. Yatsunenko, F.E. Rey, M.J. Manary, I. Trehan, M.G. Dominguez-Bello, M. Contreras, M. Magris, G. Hidalgo, R.N. Baldassano, A.P. Anokhin, A.C. Heath, B. Warner, J. Reeder, J. Kuczynski, J.G. Caporaso, C.A. Lozupone, C. Lauber, J.C. Clemente, D. Knights, R. Knight, J.I. Gordon, Human gut microbiome viewed across age and geography, Nature 486 (2012) 222−227. PMID: 22699611.

[29] L.A. David, C.F. Maurice, R.N. Carmody, D.B. Gootenberg, J.E. Button, B.E. Wolfe, A.V. Ling, A.S. Devlin, Y. Varma, M.A. Fischbach, S.B. Biddinger, R.J. Dutton, P.J. Turnbaugh, Diet rapidly and reproducibly alters the human gut microbiome, Nature 505 (2014) 559−563. PMID: 24336217.

[30] O. Koren, J.K. Goodrich, T.C. Cullender, A. Spor, K. Laitinen, H.K. Bäckhed, A. Gonzalez, J.J. Werner, L.T. Angenent, R. Knight, F. Bäckhed, E. Isolauri, S. Salminen, R.E. Ley, Host remodeling of the gut microbiome and metabolic changes during pregnancy, Cell 150 (2012) 470−480. PMID: 22863002.

[31] A.E. Pérez-Cobas, M.J. Gosalbes, A. Friedrichs, H. Knecht, A. Artacho, K. Eismann, W. Otto, D. Rojo, R. Bargiela, M. von Bergen, S.C. Neulinger, C. Däumer, F.A. Heinsen, A. Latorre, C. Barbas, J. Seifert, V.M. dos Santos, S.J. Ott, M. Ferrer, A. Moya, Gut microbiota

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disturbance during antibiotic therapy: a multi-omic approach, Gut 62 (2013) 1591−1601. PMID: 23236009.

[32] Y. He, W. Wu, H.M. Zheng, P. Li, D. McDonald, H.F. Sheng, M.X. Chen, Z.H. Chen, G.Y. Ji, Z.D. Zheng, P. Mujagond, X.J. Chen, Z.H. Rong, P. Chen, L.Y. Lyu, X. Wang, C.B. Wu, N. Yu, Y.J. Xu, J. Yin, J. Raes, R. Knight, W.J. Ma, H.W. Zhou, Regional variation limits applications of healthy gut microbiome reference ranges and disease models, Nat. Med. 24 (2018) 1532−1535. PMID: 30250144.

[33] M. Deschasaux, K.E. Bouter, A. Prodan, E. Levin, A.K. Groen, H. Herrema, V. Tremaroli, G.J. Bakker, I. Attaye, S.J. Pinto-Sietsma, D.H. van Raalte, M.B. Snijder, M. Nicolaou, R. Peters, A.H. Zwinderman, F. Bäckhed, M. Nieuwdorp, Depicting the composition of gut microbiota in a population with varied ethnic origins but shared geography, Nat. Med. 24 (2018) 1526−1531. PMID: 30150717.

[34] B. Singh, N. Qin, G. Reid, Microbiome regulation of autoimmune, gut and liver associated diseases, Inflamm. Allergy - Drug Targets 14 (2015) 84−93. PMID: 26817477.

[35] G. Musumeci, F.C. Aiello, M.A. Szychlinska, M. Di Rosa, P. Castrogiovanni, A. Mobasheri, Osteoarthritis in the XXIst century: risk factors and behaviours that influence disease onset and progression, Int. J. Mol. Sci. 16 (2015) 6093−6112. PMID: 25785564.

[36] P.W. O'Toole, I.B. Jeffery, Gut microbiota and aging, Science 350 (2015) 1214−1215. PMID: 26785481.

[37] M.J. Claesson, S. Cusack, O. O'Sullivan, et al., Composition, variability, and temporal stability of the intestinal microbiota of the elderly, Proc. Natl. Acad. Sci. U. S. A 108 (2011) 4586−4591. PMID: 20571116.

[38] R.I. Clark, A. Salazar, R. Yamada, et al., Distinct shifts in microbiota composition during Drosophila aging impair intestinal function and drive mortality, Cell Rep. 12 (2015) 1656−1667. PMID: 26321641.

[39] H. Li, Y. Qi, H. Jasper, Preventing age-related decline of gut compartmentalization limits microbiota dysbiosis and extends lifespan, Cell Host Microbe 19 (2016) 240−253. PMID: 26867182.

[40] V.K. Srikanth, J.L. Fryer, G. Zhai, et al., A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis, Osteoarthritis Cartilage 13 (2005) 769−781. PMID: 15978850.


https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[41] N. Salazar, L. Valdés-Varela, S. González, M. Gueimonde, C.G. de Los Reyes-Gavilán, Nutrition and the gut microbiome in the elderly, Gut Microb. 8 (2017) 82−97. PMID: 27808595.

[42] N. Salazar, S. Arboleya, L. Valdés, C. Stanton, P. Ross, L. Ruiz, M. Gueimonde, C.G. de Los Reyes-Gavilán, The human intestinal microbiome at extreme ages of life. Dietary intervention as a way to counteract alterations, Front. Genet. 5 (2014) 406. PMID: 25484891.

[43] T. Odamaki, K. Kato, H. Sugahara, N. Hashikura, S. Takahashi, J.Z. Xiao, F. Abe, R. Osawa, Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study, BMC Microbiol. 16 (2016) 90. PMID: 27220822.

[44] N. Salazar, P. López, L. Valdés, A. Margolles, A. Suárez, A.M. Patterson, A. Cuervo, C.G. de los Reyes-Gavilán, P. Ruas-Madiedo, S. Gonzalez, M. Gueimonde, Microbial targets for the development of functional foods accordingly with nutritional and immune parameters altered in the elderly, J. Am. Coll. Nutr. 32 (2013) 399−406. PMID: 24606713.

[45] A. Ticinesi, C. Tana, A. Nouvenne, B. Prati, F. Lauretani, T. Meschi, Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review, Clin. Interv. Aging 13 (2018) 1497−1511. PMID: 30214170.

[46] F.S. Hanna, A.E. Wluka, R.J. Bell, et al., Osteoarthritis and the postmenopausal woman: epidemiological, magnetic resonance imaging, and radiological findings, Semin. Arthritis Rheum. 34 (2004) 631−636. PMID: 15609268.

[47] M.C. Nevitt, D.T. Felson, E.N. Williams, et al., The effect of estrogen plus progestin on knee symptoms and related disability in postmenopausal women: the Heart and Estrogen/Progestin Replacement Study, a randomized, double-blind, placebo-controlled trial, Arthritis Rheum. 44 (2001) 811−818. PMID: 11315920.

[48] D.I. Bolnick, L.K. Snowberg, P.E. Hirsch, C.L. Lauber, R. Knight, J.G. Caporaso, R. Svanbäck, Individuals' diet diversity influences gut microbial diversity in two freshwater fish (threespine stickleback and Eurasian perch), Ecol. Lett. 17 (2014) 979−987. PMID: 24847735.

[49] C. Haro, O.A. Rangel-Zuniga, J.F. Alcala-Diaz, et al., Intestinal Microbiota Is Influenced by Gender and Body Mass Index, PLoS One 11 (2016) e0154090. PMID: 27228093.

[50] E. Thijssen, A. van Caam, P.M. van der Kraan, Obesity and osteoarthritis, more than just wear and tear: pivotal roles for inflamed adipose tissue and

 https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

dyslipidaemia in obesity-induced osteoarthritis, Rheumatology 54 (2015) 588−600. PMID: 25504962.

[51] R.C. Koonce, J.T. Bravman, Obesity and osteoarthritis: more than just wear and tear, J. Am. Acad. Orthop. Surg. 21 (2013) 161−169. PMID: 23457066.

[52] P.J. Turnbaugh, M. Hamady, T. Yatsunenko, et al., A core gut microbiome in obese and lean twins, Nature 457 (2009) 480−484. PMID: 19043404.

[53] P.J. Turnbaugh, R.E. Ley, M.A. Mahowald, et al., An obesity-associated gut microbiome with increased capacity for energy harvest, Nature 444 (2006) 1027−1031. PMID: 17183312.

[54] D.J. Morrison, T. Preston, Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism, Gut Microb. 7 (2016) 189−200. PMID: 26963409.

[55] S. Murugesan, K. Nirmalkar, C. Hoyo-Vadillo, M. García-Espitia, D. Ramírez-Sánchez, J. García-Mena, Gut microbiome production of short-chain fatty acids and obesity in children, Eur. J. Clin. Microbiol. Infect. Dis. 37 (2018) 621−625. PMID: 29196878.

[56] Z. Huang, V.B. Kraus, Does lipopolysaccharide-mediated inflammation have a role in OA? Nat. Rev. Rheumatol. 12 (2016) 123−129. PMID: 26656661.

[57] D.T. Felson, J. Niu, M. Clancy, et al., Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies, Arthritis Rheum. 56 (2007) 129−136. PMID: 17195215.

[58] Y. Li, J. Yue, C. Yang, Unraveling the role of Mg(++) in osteoarthritis, Life Sci. 147 (2016) 24−29. PMID: 26800786.

[59] W. Ren, J. Duan, J. Yin, et al., Dietary L-glutamine supplementation modulates microbial community and activates innate immunity in the mouse intestine, Amino Acids 46 (2014) 2403−2413. PMID: 25023447.

[60] W. Ren, S. Chen, J. Yin, et al., Dietary arginine supplementation of mice alters the microbial population and activates intestinal innate immunity, J. Nutr. 144 (2014) 988−995. PMID: 24670969.

[61] F.M. Trovato, P. Castrogiovanni, M.A. Szychlinska, F. Purrello, G. Musumeci, Early effects of high-fat diet, extra-virgin olive oil and vitamin D in a sedentary rat model of non-alcoholic fatty liver disease, Histol. Histopathol. 33 (2018) 1201−1213. PMID: 29855033.

[62] E.K. Crowley, C.M. Long-Smith, A. Murphy, E. Patterson, K. Murphy, D.M. O'Gorman, C. Stanton, Y.M. Nolan, Dietary supplementation with a

 https://doi.org/10.1016/j.heliyon.2019.e01134
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magnesium-rich marine mineral blend enhances the diversity of gastrointestinal microbiota, Mar. Drugs 16 (2018) E216. PMID: 29925774.

[63] A. Everard, C. Belzer, L. Geurts, J.P. Ouwerkerk, C. Druart, L.B. Bindels, Y. Guiot, M. Derrien, G.G. Muccioli, N.M. Delzenne, et al., Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity, Proc. Natl. Acad. Sci. U.S.A. 110 (2013) 9066−9071. PMID: 23671105.

[64] A. Koh, F. De Vadder, P. Kovatcheva-Datchary, F. Backhed, From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites, Cell 165 (2016) 1332−1345. PMID: 27259147.

[65] J. Tan, S. Liu, Y. Guo, et al., Dietary L-arginine supplementation attenuates lipopolysaccharide-induced inflammatory response in broiler chickens, Br. J. Nutr. 111 (2014) 1394−1404. PMID: 24330949.

[66] K. Asano, S. Yoshimura, A. Nakane, Alteration of intestinal microbiota in mice orally administered with salmon cartilage proteoglycan, a prophylactic agent, PLoS One 8 (2013) e75008. PMID: 24040376.

[67] K.H. Collins, H.A. Paul, R.A. Reimer, et al., Relationship between inflammation, the gut microbiota, and metabolic osteoarthritis development: studies in a rat model, Osteoarthritis Cartilage 23 (2015) 1989−1998. PMID: 26521745.

[68] C.A. Thaiss, M. Levy, T. Korem, L. Dohnalová, H. Shapiro, D.A. Jaitin, E. David, D.R. Winter, M. Gury-BenAri, E. Tatirovsky, T. Tuganbaev, S. Federici, N. Zmora, D. Zeevi, M. Dori-Bachash, M. Pevsner-Fischer, E. Kartvelishvily, A. Brandis, A. Harmelin, O. Shibolet, Z. Halpern, K. Honda, I. Amit, E. Segal, E. Elinav, Microbiota diurnal rhythmicity programs host transcriptome oscillations, Cell 167 (2016) 1495-1510.e12. PMID: 27912059.

[69] P. Castrogiovanni, G. Li Volti, C. Sanfilippo, et al., Fasting and fast food diet play an opposite role in mice brain aging, Mol. Neurobiol. 55 (2018) 6881−6893. PMID: 29353457.

[70] M. Crovetto, M. Valladares, V. Espinoza, F. Mena, G. Oñate, M. Fernandez, S. Durán-Agüero, Effect of healthy and unhealthy habits on obesity: a multicentric study, Nutrition 54 (2018) 7−11. PMID: 29677480.

[71] T.Y. Warren, V. Barry, S.P. Hooker, X. Sui, T.S. Church, S.N. Blair, Sedentary behaviors increase risk of cardiovascular disease mortality in men, Med. Sci. Sports Exerc. 42 (2010) 879−885. PMID: 19996993.


https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[72] R.R. Huxley, A. Ansary-Moghaddam, P. Clifton, S. Czernichow, C.L. Parr, M. Woodward, The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence, Int. J. Cancer 125 (2009) 171−180. PMID: 19350627.

[73] F. Lutgendorff, L.M. Akkermans, J.D. Söderholm, The role of microbiota and probiotics in stress-induced gastro-intestinal damage, Curr. Mol. Med. 8 (2008) 282−298. PMID: 18537636.

[74] R.E. Ley, F. Bäckhed, P. Turnbaugh, C.A. Lozupone, R.D. Knight, J.I. Gordon, Obesity alters gut microbial ecology, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 11070−11075. PMID: 16033867.

[75] A. Damms-Machado, S. Mitra, A.E. Schollenberger, K.M. Kramer, T. Meile, A. Königsrainer, D.H. Huson, S.C. Bischoff, Effects of surgical and dietary weight loss therapy for obesity on gut microbiota composition and nutrient absorption, BioMed Res. Int. 2015 (2015) 806248. PMID: 25710027.

[76] D. Rothschild, O. Weissbrod, E. Barkan, et al., Environment dominates over host genetics in shaping human gut microbiota, Nature 555 (2018) 210−215. PMID: 29489753.

[77] D.E. Warburton, C.W. Nicol, S.S. Bredin, Health benefits of physical activity: the evidence, CMAJ 174 (2006) 801−809. PMID: 16534088.

[78] F.M. Trovato, F.C. Aiello, L. Larocca, S.D. Taylor-Robinson, The role of physical activity and nutrition in the sarcopenia of cirrhosis, J Funct. Morphol. Kinesiol. 1 (1) (2016) 118−125.

[79] G. Musumeci, F.M. Trovato, K. Pichler, et al., Extra-virgin olive oil diet and mild physical activity prevent cartilage degeneration in an osteoarthritis model: an in vivo and in vitro study on lubricin expression, J. Nutr. Biochem. 24 (2013) 2064−2075. PMID: 24369033.

[80] A.P. Hills, S.J. Street, N.M. Byrne, Physical activity and health: "what is old is new again", Adv. Food Nutr. Res. 75 (2015) 77−95. PMID: 26319905.

[81] P.D. Neufer, M.M. Bamman, D.M. Muoio, et al., Understanding the cellular and molecular mechanisms of physical activity-induced health benefits, Cell Metabol. 22 (2015) 4−11. PMID: 26073496.

[82] P. Castrogiovanni, A. Di Giunta, C. Guglielmino, F. Roggio, D. Romeo, F. Fidone, R. Imbesi, C. Loreto, S. Castorina, G. Musumeci, The effects of exercise and kinesio tape on physical limitations in patients with knee osteoarthritis, J. Funct. Morphol. Kinesiol. 1 (4) (2016) 355−368.


https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[83] J.J. Choi, S.Y. Eum, E. Rampersaud, S. Daunert, M.T. Abreu, M. Toborek, Exercise attenuates PCB-induced changes in the mouse gut microbiome, Environ. Health Perspect. 121 (2013) 725−730. PMID: 23632211.

[84] C.C. Evans, K.J. LePard, J.W. Kwak, M.C. Stancukas, S. Laskowski, J. Dougherty, L. Moulton, A. Glawe, Y. Wang, V. Leone, D.A. Antonopoulos, D. Smith, E.B. Chang, M.J. Ciancio, Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity, PLoS One 9 (2014) e92193. PMID: 24670791.

[85] J.E. Lambert, J.P. Myslicki, M.R. Bomhof, D.D. B, J. Shearer, R.A. Reimer, Exercise training modifies gut microbiota in normal and diabetic mice, Appl. Physiol. Nutr. Metabol. 40 (2015) 749−752. PMID: 25962839.

[86] S.F. Clarke, E.F. Murphy, O. O'Sullivan, A.J. Lucey, M. Humphreys, A. Hogan, P. Hayes, M. O'Reilly, I.B. Jeffery, R. Wood-Martin, D.M. Kerins, E. Quigley, R.P. Ross, P.W. O'Toole, M.G. Molloy, E. Falvey, F. Shanahan, P.D. Cotter, Exercise and associated dietary extremes impact on gut microbial diversity, Gut 63 (2014) 1913−1920. PMID: 25021423.

[87] W. Barton, N.C. Penney, O. Cronin, I. Garcia-Perez, M.G. Molloy, E. Holmes, F. Shanahan, P.D. Cotter, O. O'Sullivan, The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level, Gut 67 (2018) 625−633. PMID: 28360096.

[88] X. Zhao, Z. Zhang, B. Hu, W. Huang, C. Yuan, L. Zou, Response of gut microbiota to metabolite changes induced by endurance exercise, Front. Microbiol. 9 (2018) 765. PMID: 29731746.

[89] C.E. Wade, L.C. Hill, M.M. Hunt, R.H. Dressendorfer, Plasma aldosterone and renal function in runners during a 20-day road race, Eur. J. Appl. Physiol. Occup. Physiol. 54 (1985) 456−460. PMID: 3910430.

[90] G. Musumeci, Effects of exercise on physical limitations and fatigue in rheumatic diseases, World J. Orthoped. 6 (2015) 762−769. PMID: 26601057.

[91] G. Musumeci, F. Maria Trovato, R. Imbesi, P. Castrogiovanni, Effects of dietary extra-virgin olive oil on oxidative stress resulting from exhaustive exercise in rat skeletal muscle: a morphological study, Acta Histochem. 116 (2014) 61−69. PMID: 23810034.

[92] G. Musumeci, P. Castrogiovanni, F.M. Trovato, et al., Physical activity ameliorates cartilage degeneration in a rat model of aging: a study on lubricin


https://doi.org/10.1016/j.heliyon.2019.e01134
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expression, Scand. J. Med. Sci. Sports 25 (2015) e222−e230. PMID: 25039883.

[93] H.L. Lujan, S.E. DiCarlo, Physical activity, by enhancing parasympathetic tone and activating the cholinergic anti-inflammatory pathway, is a therapeutic strategy to restrain chronic inflammation and prevent many chronic diseases, Med. Hypotheses 80 (2013) 548−552. PMID: 23395411.

[94] A. Clark, N. Mach, The crosstalk between the gut microbiota and mitochondria during exercise, Front. Physiol. 8 (2017) 319. PMID: 28579962.

[95] N.M. Koropatkin, E.A. Cameron, E.C. Martens, How glycan metabolism shapes the human gut microbiota, Nat. Rev. Microbiol. 10 (2012) 323−335. PMID: 22491358.

[96] P. Toivanen, Normal intestinal microbiota in the aetiopathogenesis of rheumatoid arthritis, Ann. Rheum. Dis. 62 (2003) 807−811. PMID: 12922950.

[97] L. Gravina, F.F. Brown, L. Alexander, et al., n-3 fatty acid supplementation during 4 weeks of training leads to improved anaerobic endurance capacity, but not maximal strength, speed, or power in soccer players, Int. J. Sport Nutr. Exerc. Metabol. 27 (2017) 305−313. PMID: 28387540.

[98] R. Codella, L. Luzi, I. Terruzzi, Exercise has the guts: how physical activity may positively modulate gut microbiota in chronic and immune-based diseases, Dig. Liver Dis. 50 (2018) 331−341. PMID: 29233686.

[99] T.D. Love, D.F. Baker, P. Healey, et al., Measured and perceived indices of fluid balance in professional athletes. The use and impact of hydration assessment strategies, Eur. J. Sport Sci. 18 (2018) 349−356. PMID: 29364084.

[100] B.K. Diduch, Gastrointestinal conditions in the female athlete, Clin. Sports Med. 36 (2017) 655−669. PMID: 28886820.

[101] Y.T. Tung, Y.J. Chen, H.L. Chuang, et al., Characterization of the serum and liver proteomes in gut-microbiota-lacking mice, Int. J. Med. Sci. 14 (2017) 257−267. PMID: 28367086.

[102] F.M. Trovato, G.F. Martines, D. Brischetto, D. Catalano, G. Musumeci, G.M. Trovato, Fatty liver disease and lifestyle in youngsters: diet, food intake frequency, exercise, sleep shortage and fashion, Liver Int. 36 (3) (2016 Mar) 427−433. PMID: 26346413.

[103] D. Houghton, C.J. Stewart, C. Stamp, et al., Impact of age-related mitochondrial dysfunction and exercise on intestinal microbiota composition, J. Gerontol. A. Biol. Sci. Med. Sci. 73 (2018) 571−578. PMID: 29045670.


https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[104] C.J. Hoffman, E. Coleman, An eating plan and update on recommended dietary practices for the endurance athlete, J. Am. Diet Assoc. 91 (1991) 325−330. PMID: 1997556.

[105] H. Hamasaki, Exercise and gut microbiota: clinical implications for the feasibility of Tai Chi, J. Integr. Med. 15 (2017) 270−281. PMID: 28659231.

[106] N. Mach, D. Fuster-Botella, Endurance exercise and gut microbiota: a review, J. Sport Health Sci. 6 (2017) 179−197.

[107] G. Musumeci, A. Mobasheri, F.M. Trovato, M.A. Szychlinska, R. Imbesi, P. Castrogiovanni, Post-operative rehabilitation and nutrition in osteoarthritis. Version 3, F1000Res 3 (2014) 116. PMID: 26962431.

[108] G.R. Gibson, R. Hutkins, M.E. Sanders, S.L. Prescott, R.A. Reimer, S.J. Salminen, K. Scott, C. Stanton, K.S. Swanson, P.D. Cani, K. Verbeke, G. Reid, Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics, Nat. Rev. Gastroenterol. Hepatol. 14 (2017) 491−502. PMID: 28611480.

[109] M. Notay, N. Foolad, A.R. Vaughn, et al., Probiotics, prebiotics, and synbiotics for the treatment and prevention of adult dermatological diseases, Am. J. Clin. Dermatol. 18 (2017) 721−732. PMID: 28681230.

[110] S. Kolacek, I. Hojsak, R. Berni Canani, et al., Commercial probiotic products: a call for improved quality control. A position paper by the espghan working group for probiotics and prebiotics, J. Pediatr. Gastroenterol. Nutr. 65 (2017) 117−124. PMID: 28644359.

[111] D. Hill, I. Sugrue, E. Arendt, et al., Recent advances in microbial fermentation for dairy and health, F1000Res 6 (2017) 751. PMID: 28649371.

[112] G. Gonzalez-Ochoa, L.K. Flores-Mendoza, R. Icedo-Garcia, et al., Modulation of rotavirus severe gastroenteritis by the combination of probiotics and prebiotics, Arch. Microbiol. 199 (2017) 953−961. PMID: 28634691.

[113] J.W. Anderson, P. Baird, R.H. Davis Jr., S. Ferreri, M. Knudtson, A. Koraym, V. Waters, C.L. Williams, Health benefits of dietary fiber, Nutr. Rev. 67 (2009) 188−205. PMID: 19335713.

[114] C. Hill, F. Guarner, G. Reid, et al., Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic, Nat. Rev. Gastroenterol. Hepatol. 11 (2014) 506−514. PMID: 24912386.


https://doi.org/10.1016/j.heliyon.2019.e01134
2405-8440/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

[115] H.J. Chung, J.H. Sim, T.S. Min, H.K. Choi, Metabolomics and lipidomics approaches in the science of probiotics: a review, J. Med. Food (2018) [Epub ahead of print]. PMID: 30004273.

[116] H.L. Lee, H. Shen, I.Y. Hwang, H. Ling, W.S. Yew, Y.S. Lee, M.W. Chang, Targeted approaches for in situ gut microbiome manipulation, Genes (Basel) 9 (2018) pii: E351 PMID: 30002345.

[117] P.W. O'Toole, J.R. Marchesi, C. Hill, Next-generation probiotics: the spectrum from probiotics to live biotherapeutics, Nat. Microbiol. 2 (2017) 17057. PMID: 28440276.

[118] F. Wolfe, S.X. Kong, D.J. Watson, Gastrointestinal symptoms and health related quality of life in patients with arthritis, J. Rheumatol. 27 (2000) 1373−1378. PMID: 10852256.

[119] R. Jones, Nonsteroidal anti-inflammatory drug prescribing: past, present, and future, Am. J. Med. 110 (2001) 4S−7S. PMID: 11165987.

[120] C. Scarpignato, R.H. Hunt, Nonsteroidal antiinflammatory drug-related injury to the gastrointestinal tract: clinical picture, pathogenesis, and prevention, Gastroenterol. Clin. North Am. 39 (2010) 433−464. PMID: 20951911.

[121] L. Vitetta, S. Coulson, A.W. Linnane, H. Butt, The gastrointestinal microbiome and musculoskeletal diseases: a beneficial role for probiotics and prebiotics, Pathogens 2 (2013) 606−626. PMID: 25437335.

[122] C.J. Steves, S. Bird, F.M. Williams, T.D. Spector, The microbiome and musculoskeletal conditions of aging: a review of evidence for impact and potential therapeutics, J. Bone Miner. Res. 31 (2016) 261−269. PMID: 26676797.

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