



Original Article

## Nutritional and Dietary Modulation of Immune Responses in Bone and Joint Diseases

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### ABSTRACT

Inflammation, immunity dysfunction, and development of diseases of bones and joints such as osteoporosis, osteoarthritis, and rheumatoid arthritis were recognized as the factors contributing to disability and poor quality of life. The current research proved that inflammation and dysfunction of immunity contribute to bone and joint diseases. Nutrition and bone physiology received special attention since there was much interest in the effect of nutrients on immunity and the processes in bone tissue. Among those nutritional compounds necessary for bone matrix mineralization and collagen formation, one could mention vitamin D, vitamin K, calcium, magnesium, zinc, and vitamin C. Micronutrients were critically important for physiological processes in bones. In addition to those, bioactive compounds present in food contributed to changes in inflammatory status and activity of immune cells as well as reduced oxidative stress. Special diets were suggested as an option to change inflammatory process and develop bone and joint pathology. Recently, new data about the role of microflora in the relationship between nutrition, immune system functioning, and bone and joint diseases became available.

**Keywords:** Nutrition, immune response, bone and joint diseases, vitamin C, K, E and omega acids, cytokines, osteoporosis.

### INTRODUCTION

Bone and joint health represent critical factors of the body functioning, allowing for the maintenance of mobility and stability in a person. Thus, bone and joint disorders may be viewed as serious illnesses affecting numerous individuals across the globe. They can greatly reduce the quality of a person's life by making their life painful and causing mobility loss. Osteoporosis, OA, and RA are considered to be the most frequent bone and joint conditions, which attract much attention from scientists since they appear frequently in people [1]. Besides, the increase in the number of elderly people, a sedentary way of life, and prevalence of metabolic illnesses play an immense role in the emergence of the mentioned disorders.

Osteoporosis refers to a condition that negatively influences the skeletal system. In particular, it impacts bone density and structure of the latter negatively. Consequently, people are exposed to fractures, which occur at the level of the hips, spine, and wrists because of fragile bones. Osteoporosis can occur due to a person's age, hormones disturbance, like deficiency of estrogen among post-menopausal women, and poor nutrition with a lack of calcium and vitamin D.

Whereas osteoarthritis was considered to be only a "wear-and-tear" disease previously, it now falls under the category of complicated disorders involving a combination of mechanical, metabolic, and inflammatory factors in the process of pathogenesis. In the end, there will be damage to cartilage tissue, alteration of bone structure below the joint, development of osteophytes, and joint space narrowing. Furthermore, inflammatory and metabolic processes exacerbate the progression of the disease [2]. Other risk factors for osteoarthritis are obesity, joint injury, and biomechanical misalignment.

If untreated, rheumatoid arthritis is an autoimmune inflammatory disease that causes synovitis, pannus development, and the breakdown of cartilage and bone. Joint deformities and incapacity are caused by abnormalities in the immune system's

functioning, such as the involvement of T and B cells and cytokine production [3]. The disease's start is significantly influenced by both hereditary and environmental variables, such as pathogenic organisms and cigarette smoking.

Due to the delicate balance between bone formation and degradation, a healthy bone structure necessitates the immune system's full operation. Conversely, when the immune system performs well, the equilibrium is upset, which increases bone resorption and joint degeneration. TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are the main inflammatory mediators that support osteoclast differentiation, inhibit osteoblast activity, degrade cartilage tissues, and maintain synovitis [4].

Several nutritional elements contribute positively to both bone and immune system functioning. In particular, nutrients are key to the proper bone development, immune system regulation, oxidation, and inflammation. To begin with, macronutrients such as protein are needed for the formation of bone density. Secondly, mineral nutrients including calcium, vitamin D, magnesium, and vitamin K are important for the creation of bone tissues. Finally,  $\omega$ -3 fatty acids, antioxidant, and polyphenols are anti-inflammatory [5].

Insight into the relationship between nutrition, immune regulation, and musculoskeletal disorders will provide potential approaches that can help reduce the incidence of bone and joint diseases.

### **Osteoimmunology of Bone and Joint Disorders**

The development of bone and joint disorders is being studied by researchers as processes that are characterized by interaction between the immune system and the bones. This field is called osteoimmunology. The malfunctioning of the immune system causes inflammation, disruption of cell signaling, and imbalance within the tissues leading to bone and joint diseases.

### **Osteoporosis**

Osteoporosis is the condition that leads to bone mass loss because of the weakening of the bones. Development of osteoporosis is connected with the loss of minerals in bones and bone deterioration. The balance of bone tissue turnover is the result of regulation of bone formation and bone resorption. Bone formation is regulated by the functioning of osteoblasts, whereas bone resorption – osteoclasts.

When the development of osteoporosis happens, there is a disturbance in bone resorption and formation processes. Resorption of bones is possible with involvement of inflammatory and immunological conditions. Inflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6 contribute to the activation of osteoclastogenesis. These cytokines stimulate production of RANKL in osteoblasts and stromal cells.

Moreover, osteoprotegerin (OPG) functions as a decoy receptor that inhibits the activity of RANKL and RANK ligand interaction and is normally expressed at a low level in cases of inflammation resulting in bone resorption. Inflammation characterized by low intensity and common in older individuals (referred to as inflammaging), coupled with insufficient hormone production (e.g., estrogen), is some of the factors capable of triggering cytokine release and cause bone resorption. Other immune cells, for instance, T lymphocytes, can be involved in bone resorption as a result of the capacity to produce RANKL and osteoclastogenic factors.

Oxidative stress and other signaling pathways, for example, NF- $\kappa$ B and MAPK, can impede osteoblast maturation and prolong osteoclast life span.

### **Osteoarthritis**

Osteoarthritis is a multi-factorial joint disorder characterized by the degeneration of cartilage, formation of osteophytes, inflammation of subchondral bone and synovium membrane. For a long time osteoarthritis was viewed as a purely mechanical disorder. Nowadays scientists believe that there is also an inflammatory/ metabolic aspect of osteoarthritis.

Chondrocytes, which are unique cells found in cartilage, are believed to be important in the onset of this illness. Pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 are produced by chondrocytes in response to any type of damage, ageing process, or metabolic stress. The generation of these mediators results in the activation of several pathways, such as the MAPK and NF- $\kappa$ B pathways, which produce the catabolic enzymes ADAMTS and MMPs. Proteoglycans and Collagen Type II are examples of ECM molecules that are harmed by enzymes.

Furthermore, synovitis is also another important contributor in OA pathogenesis because it stimulates activation of synovial cells with subsequent production of inflammatory mediators, cytokines, and enzymes resulting in the destruction of cartilage by them in a more intense manner. Remodeling occurs in subchondral bone, leading to subchondral sclerosis and bone cysts formation.

It is noteworthy that there are several metabolic contributors for OA, namely obesity. Leptin, adiponectin, and resistin activate adipocytes in adipose tissue; hence, causing systemic inflammation with the destruction of cartilage. Consequently, OA is a joint disorder where all components are interacting, including cartilage, bone, synovium, and others.

### **Rheumatoid Arthritis**

A chronic, systemic autoimmune illness that mostly affects synovial joints, rheumatoid arthritis (RA) is characterised by systemic symptoms, progressive joint degeneration, and ongoing inflammation. Autoreactive T and B cells are activated as a result of a breakdown in immunological tolerance, which drives the immunopathology of RA.

Immune cells such as CD4<sup>+</sup> T cells, B cells, macrophages, dendritic cells, and plasma cells invade the synovial membrane in RA. Together, these cells generate a variety of pro-inflammatory cytokines that maintain the inflammatory milieu, including TNF- $\alpha$ , IL-6, IL-1, and IL-17. In particular, T helper 17 (Th17) cells are important because they produce IL-17, which increases osteoclastogenesis and neutrophil recruitment.

B cells contribute to the pathogenesis of disease by generating autoantibodies such rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs). By activating complement pathways, these autoantibodies produce immune complexes that worsen inflammation. Another important cell type that contributes to synovial inflammation and tissue death is macrophages, which emit high levels of TNF- $\alpha$  and IL-1.

Another critical feature of rheumatoid arthritis includes the involvement of pannus, which is a destructive, hyperplastic synovial tissue capable of degrading the cartilage and bone tissues. The FLS present in the pannus become very invasive and release enzymes responsible for matrix degradation and inflammatory mediators. In the area where bones are present, an elevated level of RANKL is observed, leading to the breakdown of bones [8].

Not only does RA involve joint destruction; however, it is also associated with several systemic effects such as cardiovascular risks, fatigue, and osteoporosis owing to chronic inflammation. Uncontrolled signaling pathways such as JAK-STAT and NF- $\kappa$ B are involved in inflammation.

### **Nutritional Modulation of Immune Pathways**

Nutrition is regarded as an essential factor for determining the effectiveness of immune responses and inflammation control, two biological phenomena associated with bone and joint physiology. Besides acting as building blocks for tissue maintenance and repair, nutrition serves as regulatory signals affecting immune cells' actions, cytokine production, oxidative stress defense, gut microbiome composition, and bone metabolism. The relationship between nutrition and immunity is quite complex, and inappropriate nutrition can play a significant role in promoting or reducing the severity of particular inflammatory processes linked to musculoskeletal disorders.

One of the major mechanisms through which nutrition may affect immunity is cytokine production. Such cytokines as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 were identified as key mediators responsible for inducing bone loss and arthritis development. There are nutritional compounds that could alter cytokine genes' transcription and secretion. For example, PUFA  $\omega$ -3, comprising omega-3 oils from marine sources, have displayed their strong anti-inflammatory properties by blocking the activity of pro-inflammatory cytokines and inducing the synthesis of resolvins and protectins. On the contrary, high levels of saturated fats and refined sugars contribute to the increased signaling capacity of inflammatory cytokines [9].

Oxidative stress is another important element that connects nutrition and immunity. Reactive oxygen species (ROS) are created in normal metabolic processes, and increased production of these molecules occurs as a result of inflammation. This process leads to damage of cell structures, such as lipids, proteins, and DNA. Overproduction of oxidative stress affects the process of cartilage degradation, osteoclast activity, and osteoblasts' functioning. Vitamins C and E, selenium, and polyphenols contained in fruit and vegetable products are capable of neutralizing the effect of ROS and prevent cells from damage. Moreover, antioxidants affect signaling cascades like NF- $\kappa$ B, which decreases inflammatory response.

Nutrition further influences the activity and differentiation of immune cells. The supply of sufficient amounts of proteins is necessary for the development and functioning of immune cells like lymphocytes and macrophages. Micronutrients like zinc, iron, and vitamin A are important nutrients responsible for proper immune cell development and regulation of antigen presentation and cytokine signalling. Another important nutrient with immunoregulatory effects is vitamin D, which regulates both innate and adaptive immunity through its ability to inhibit inflammatory Th1 and Th17 cells and stimulating regulatory T-cells. Such modulation helps decrease chronic inflammation, which may prove useful in autoimmune diseases, e.g., rheumatoid arthritis [10].

The gut flora is recognised to have a major role in mediating the link between diet and the immune system. Diet has a major impact on the species richness and diversity of gut bacteria, which in turn control the immune response and the body's levels of systemic inflammation. A high-fiber diet encourages the growth of microbes that emit short-chain fatty

acids (SCFAs), such as butyrate, acetate, and propionate. They improve intestinal barrier function, reduce inflammation, and affect immune cell physiology. Dysbiosis is associated with increased intestinal permeability and systemic inflammation, which can lead to joint and bone issues.

Nutrition has a direct effect on bone metabolism. Vitamin D and calcium play important roles in regulating bone mineral content and calcium balance. Vitamin K takes part in osteocalcin activation, an important protein in bone mineralization. Magnesium provides structural stability and affects the action of parathyroid hormone. Moreover, there are several bioactive components, such as flavonoids and phytoestrogens, that can inhibit osteoclasts and activate osteoblasts, thus promoting bone formation [11].

The overall dietary pattern also plays an important part in regulating immune pathways. For instance, the Mediterranean diet, which comprises many vegetables, fruits, whole-grain products, nuts, olive oil, and fish, is known to be associated with reduced inflammation and improved musculoskeletal outcomes. In comparison, the typical Western diet pattern, which involves eating plenty of processed food, sugar, and fats, is associated with chronic inflammation and higher risks of suffering from bone and joint problems [12].

To summarize, the effects of nutrition on immune pathways may include inflammation modulation, oxidative stress management, regulation of immune cells' activity, modulation of gut bacteria, and bone metabolism.

### **Micronutrients and Bone–Immune Regulation**

Micronutrients have an important part to play in the delicate balancing act between bone metabolism and immunity. Not only do they serve as building blocks of bones, but they are also involved in the regulation of signal transduction mechanisms, enzymatic reactions, and immune responses. A deficiency or imbalance in specific micronutrients may cause problems in bone remodeling, induce inflammation, and make the body prone to bone-related disorders [13].

#### **Calcium**

Calcium is the most prevalent mineral in the body and one of the building blocks of bone tissue, where it is mainly deposited in the form of hydroxyapatite crystals. An optimal level of calcium consumption is vital for ensuring bone mineral density and proper skeletal function. Bones act as a dynamic storehouse of calcium ions and ensure steady concentrations of the mineral in blood serum necessary for physiological activities like muscle contractions, nerve conduction, and coagulation of blood.

In cases when an individual lacks dietary calcium, his or her organism will compensate by producing excess amounts of parathyroid hormone (PTH). Increased amounts of PTH activate osteoclasts that absorb bone mass and release calcium ions into the bloodstream [14]. Overstimulation of this process leads to continuous bone loss and higher risks of fractures. Moreover, calcium ions participate in intracellular signaling processes that facilitate activation, growth, and cytokine secretion of immune cells. In particular, calcium signaling plays a crucial role in activating T-cells, which underlines its indirect impact on immune regulation.

#### **Vitamin D**

Vitamin D is one of the vitamins that are highly soluble in fats and serves as an important player in calcium-phosphorus balance and bone mineralization. The role of this vitamin is associated with increased mineral absorption and availability for the formation of bones. Vitamin D deficiency leads to improper bone mineralization that results in pathologies like osteomalacia in adults or osteoporosis.

Another well-known role of vitamin D is related to its involvement in immunomodulation. This vitamin affects innate and adaptive immune responses by influencing its active form – calcitriol (1,25-dihydroxyvitamin D). There are specific receptors for this hormone (VDR) on immune cells, including macrophages, dendritic cells, and T/B lymphocytes. This vitamin reduces pro-inflammatory reactions by suppressing the functioning of Th1 and Th17 cells, thus lowering the number of released interferon-gamma (IFN- $\gamma$ ), IL-2, and IL-17. In addition, vitamin D favors the growth and development of regulatory T cells that contribute to immune tolerance [15]. Also, vitamin D stimulates innate immunity by stimulating the synthesis of antimicrobial peptides, like cathelicidins.

#### **Vitamin K**

Vitamin K is among the fat-soluble vitamins playing a crucial role in the post-translational modification of certain proteins involved in bone modeling. Vitamin K is known to be a cofactor for gamma-glutamyl carboxylase, the enzyme responsible for the creation of gamma-carboxyglutamic acid (Gla) through carboxylation of glutamic acid from certain proteins. Carboxylation of certain proteins is essential in the activation of osteocalcin, which is the bone-forming protein formed in osteoblasts [16].

In case of vitamin K deficiency, there will be less carboxylation of osteocalcin, meaning that osteocalcin will not be able to attach with calcium. It means that the bones cannot absorb enough calcium, hence, causing bone fractures. According to

recent researches, vitamin K has anti-inflammatory effects on the body as well since it can regulate cytokines and interfere with NF- $\kappa$ B pathways in bones.

### **Vitamin C**

Vitamin C or ascorbic acid is one of the most significant water-soluble vitamins which take part in collagen synthesis – one of the most crucial elements in terms of bone, cartilage, and connective tissues development. Vitamin C serves as a co-factor that is essential for activity of enzymes responsible for prolyl and lysyl hydroxylation during collagen formation and contributes to stabilization and collagen fibril cross-linking. Synthesis of collagen is especially vital for bone strength and cartilage formation.

One more role of vitamin C consists in its powerful antioxidant capacity; this vitamin plays an essential part in protecting human body from oxidative stress-induced cellular damage. Since oxidative stress induces bone resorption and decreases osteogenesis by activating osteoclasts, and since vitamin C reduces oxidative stress and increases osteogenesis [17], vitamin C can improve bone mineral density and protect bones from inflammatory changes.

Finally, the last role of vitamin C consists in immune system boosting. This vitamin facilitates activities of neutrophils, lymphocytes, and phagocytes and provides anti-inflammatory effects which prevent bones' inflammation.

### **Macronutrients and Immune Function**

In this context, macronutrients play a vital part in modulating the immune response and the condition of muscles and skeletal bones. Besides acting as energy and structural components, macronutrients play an essential role in regulating the inflammatory pathway, immune signaling, and metabolic process related to bone and joint disorders. In the category of macronutrients, dietary lipids and specifically omega-3 fatty acids have attracted much attention for their immunomodulation and anti-inflammatory characteristics [18].

### **Fatty Acids (Omega-3)**

Omega-3 PUFAs consist of essential fatty acids with potent anti-inflammatory effects. Sources of omega-3 PUFA include marine-based foods like fatty fish and fish oils. The modulation of immune responses occurs via omega-3 PUFA because they act on the membrane, signal transduction, and gene expression processes.

Inflammation modulation through the impact of omega-3 fatty acids on immune response takes place through the reduction of pro-inflammatory mediators. It occurs due to competition with arachidonic acid (belonging to omega-6 fatty acids), which makes it possible to include the fatty acids into cell membranes' composition. As a consequence, fewer eicosanoids including prostaglandins and leukotrienes are synthesized because they initiate pro-inflammatory reactions. In addition to it, there is an inhibition of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 pro-inflammatory cytokines synthesis responsible for different disease development [19].

Apart from it, EPA and DHA work as substrates for the production of SPM such as resolvins, protectins, and maresins. Such bioactive components stimulate inflammation resolution via accelerating the migration of inflammatory cells, reducing cytokine production, and restoration of tissue homeostasis. Thus, in contrast to traditional anti-inflammatory drugs that are able only to inhibit the inflammatory process, omega-3 fatty acids additionally provide inflammation resolution. Additionally, omega-3 fatty acids affect the function of immunological cells. By regulating the function of T cells, B cells, macrophages, and dendritic cells, they prevent the activation of pro-inflammatory pathways such nuclear factor-kappa B (NF- $\kappa$ B). Additionally, omega-3 fatty acids have the ability to shift the balance of T-cell responses from pro-inflammatory Th1 and Th17 phenotypes to a more anti-inflammatory profile, which is particularly significant in autoimmune disorders [20].

In the context of bone health, omega-3 fatty acids have been shown to inhibit osteoclastogenesis and promote osteoblast activity, thereby supporting bone formation and reducing bone resorption. Their anti-inflammatory effects also help mitigate cartilage degradation and synovial inflammation in joint diseases.

The therapeutic use of omega-3 fatty acids in rheumatoid arthritis has been validated by multiple clinical investigations. Patients who took EPA and DHA supplements reported significant improvements in their symptoms, including improved physical performance, less joint discomfort, and less morning stiffness. It is noteworthy that a number of studies have demonstrated that patients receiving treatment with supplements containing omega-3 fatty acids require fewer NSAIDs [21].

In conclusion, omega-3 fatty acids are thought to be significant dietary elements that influence immune response modulation. They are highly intriguing nutrients in cases of bone and joint problems because of their anti-inflammatory, immunomodulatory, and bone remodelling qualities.

### **Dietary Patterns and Immune Modulation**



In turn, in comparison with one-component nutrition, dietary patterns proved to have a considerable impact on immune response as well as bone and joint disorders. In other words, whole diets mean a complex of bioactive components and their synergistic effects on inflammation regulation, reduction of oxidative stress, metabolism regulation, and changes in composition of gut microbiota. As far as the effect of dietary patterns on immune response and musculoskeletal system is concerned, particular focus should be put on the Mediterranean and plant-based diets [22].

### **Mediterranean Diet**

In keeping with the Mediterranean dietary pattern, the daily ration consists of a variety of fruits, vegetables, legumes, nuts, seeds, and whole grains in addition to a significant amount of olive oil as the primary source of fatty food. The Mediterranean dietary pattern is characterised by moderate eating of fish and seafood, low consumption of dairy products, and restricted consumption of red meat. Because of this, the Mediterranean diet is characterised by a high consumption of fibre, vitamins, minerals, and monounsaturated fats including omega-3 fatty acids and oleic acid.

In addition to this, the Mediterranean diet provides an important anti-inflammatory response. An ingredient that is found in the Mediterranean diet and is highly rich in polyphenol components, such as oleocanthal, is known to provide a potential anti-inflammatory activity like that of non-steroidal drugs due to its mechanism of action by blocking the COX and NF- $\kappa$ B pathways. Plants that act as antioxidants and help protect tissues from oxidative damage are also present in the Mediterranean diet.

Furthermore, pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-6, and CRP, are produced less frequently owing to the effects of the Mediterranean diet on cytokine production.

The use of the Mediterranean diet in cases involving bone and joint disorders has been associated with better outcomes with conditions such as osteoarthritis and rheumatoid arthritis. Studies have found that patients who follow the Mediterranean diet receive an improvement in terms of joint pain and inflammation, physical activity, and overall disease activity. The special aspect of the Mediterranean diet involves bone protection through the intake of certain nutrients, such as calcium, magnesium, and vitamin K, which support bone mineralization [24].

One more mechanism of the Mediterranean diet protecting health relates to the effect it has on gut bacteria. Following this diet creates optimal conditions for bacteria responsible for producing SCFAs, such as butyrate, that possess anti-inflammatory effects and increase the gut barrier strength.

### **Plant-Based Diets**

In general, plant-based diet refers to food obtained from plants like fruits, vegetables, grains, legumes, nuts, and seeds with lower content or even absence of animal foods. Meals of this kind are rich in nutrients such as fibers, vitamins, minerals, antioxidants, and phytochemicals. This food helps to decrease the inflammatory response and modulate immune activity.

First of all, plant-based diet is characterized by high concentration of antioxidants. These include phytochemicals - carotenoids, flavonoids, polyphenols, etc. Antioxidants can neutralize ROS which makes them valuable in the treatment of bone and joint disorders that develop because of osteoporosis or cartilage damage due to oxidative stress.

Fibers in plant-based diet are the substrate of gut microbiota and result in production of SCFAs. This substance has an anti-inflammatory impact on the body and controls immune cells and decreases pro-inflammatory cytokine levels and improves gut barrier functioning. Besides, gut bacteria help to avoid the emergence of dysbiosis typical of autoimmune inflammatory disorders like rheumatoid arthritis [25].

Meatless food sources have a low content of saturated fatty acids and a high concentration of unsaturated fatty acids, resulting in decreased inflammation within the body. The low levels of adiposity following intake of meatless food sources reduce adipokine secretion, where adipokines are pro-inflammatory cytokines produced by adipose tissue cells that induce joint inflammation and subsequent disease formation.

Furthermore, the vegetarian diet can affect the immune cell signaling pathway associated with NF-kappa B and MAPK pathways that decrease the transcription of inflammation-inducing genes [26]. Phytochemical compounds have the ability to act immunomodulatory by activating regulatory T-cells and limiting an unnecessary immune reaction.

Studies show that a vegetarian diet could potentially improve cases of inflammatory joints due to the alleviation of their symptoms and disease activities, such as joint pains and stiffness; however, further research needs to be carried out.

### **The Gut-Joint Axis and Gut Microbiota**

Gut microbiota, which consists of trillions of microorganisms, including bacteria, viruses, fungi, and archaea, is an important part of immune homeostasis. Recently, the presence of a gut-joint axis was suggested. The interaction between

the gut microbiome and the musculoskeletal system occurs through bidirectional interaction via different mechanisms, such as immunity, metabolism, and hormones. This relationship plays a significant role in bone and joint conditions.

When it comes to the healthy gut microbiome, it provides the organism with the right immune homeostasis in which the organism is tolerant to antigens and immunized against pathogens. Commensal bacteria interact with epithelial cells of the intestines and immune cells, including dendritic cells, macrophages, and lymphocytes, to provide normal cytokine production and maturation of immune cells. When the imbalance occurs, a condition known as dysbiosis, then there appears the immune dysregulation.

The occurrence of dysbiosis can now be considered a possible cause for the pathogenesis of bone and joint diseases, including osteoporosis, osteoarthritis, and rheumatoid arthritis. Dysbiosis causes the increase in intestinal permeability known as "leaky gut syndrome." As a result, the translocation of antigens like LPS along with other components of bacteria into the bloodstream occurs. This leads to triggering an immune response and hence results in the formation of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 causing systemic inflammation and injury [27].

As far as rheumatoid arthritis development is concerned, certain modifications in the microbiome population have been correlated with this condition. The activation of auto-reactive cells in response to some bacteria that reside in the intestine causes the intolerance of the body's immune system resulting in continuous synovial inflammation. In the same way, dysbiosis may influence bone metabolism through promoting osteoclastogenesis while inhibiting osteoblast functions in osteoporosis.

The SCFA's include butyrate, propionate, and acetate, which are metabolic end-products resulting from fibre fermentation by the intestinal microbiota. Metabolites that contribute to the maintenance of the structural function of the gut lining by fortifying tight junctions in epithelial cells such that no toxins cross into the bloodstream [28]. In particular, butyrate has been shown to have a vital role in modulating inflammation and immunity.

Butyrate facilitates the modulation of T-cell regulatory cells (Tregs) by controlling cell proliferation and differentiation, thus contributing to proper immune tolerance as well as the suppression of inflammation. Also, butyrate contributes to the regulation of pro-inflammatory cytokine production and helps regulate NF- $\kappa$ B signaling pathways. Additionally, it has been shown to promote bone metabolism by inhibiting osteoclastogenesis.

Composition of gut microbiota is significantly affected by diet, lifestyle, exposure to antibiotics, and other environmental conditions. High-fibre, fruit-, vegetable- and whole grain-rich diet promotes growth of beneficial microorganisms and facilitates SCFAs production, while highly processed food, excessive sugar and fat consumption lead to inflammation and development of intestinal dysbiosis [29].

All things considered, gut-joint axis constitutes an important connection between nutrition, immune system functioning, and skeletal and joint integrity. Modulation of the gut microbiome via various therapeutic interventions, including dietary measures, is one promising direction of research in the area of bone and joint disease prevention and treatment.

### **Disease-Specific Nutritional Implications**

There are several effects of nutrition on bone and joint disorders in terms of occurrence, management, and progression. It is so because bone and joint disorders can be caused by various causes such as auto-immune, degenerative, or metabolic conditions. Consequently, the type of intervention used to manage such disorders needs to consider their cause.

#### **Rheumatoid Arthritis**

Rheumatoid arthritis is a medical condition whereby a patient suffers from autoimmune response resulting in inflammation and damage to joints. As the condition involves an inflammatory component, some nutritional interventions can work to alleviate the problem.

Some polyunsaturated fatty acids such as omega-3 polyunsaturated fatty acids such as EPA and DHA play important roles in alleviating inflammation and regulating the body's immunity against the disease. For instance, omega-3 fatty acids help block the secretion of inflammatory factors such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 as well as others, which aid in generating pro-resolving mediators, leading to reduction of inflammation. There are clinical studies that prove patients using omega-3 fatty acids experience reduced joint pains and stiffness, reduced activity score, and use fewer NSAIDs [34].

Another diet that has been shown to have beneficial outcomes in the management of RA is one that is based on the Mediterranean diet. The diet contains several antioxidants, polyphenols, and healthy fats, reducing systemic inflammation levels. Observing this diet leads to better physical performance, lessened disease severity, and improved quality of life [35].

In addition, antioxidants like berries, leafy greens, nuts, and seeds can help neutralize the reactive oxygen species (ROS) effect, hence minimizing oxidative stress and tissue damage. In some functional foods, like curcumin and catechins, regulating the immune system and inflammation levels have also been proven. As such, anti-inflammatory diets can serve as additional treatment to pharmacological therapy.

### **Osteoarthritis**

The disease is mainly viewed as a degenerative disorder. However, inflammation and oxidative stress are part of osteoarthritis, leading to cartilage tissue destruction.

Sources of food that have a high level of antioxidants are highly recommended to alleviate oxidative stress, which significantly contributes to cartilage degeneration. Nutritional elements such as vitamins C and E, polyphenols contained in plant foods can help prevent oxidative damage to the chondrocytes as well as suppress the pathways of inflammation (NF- $\kappa$ B pathway) which in turn inhibits the synthesis of matrix metalloproteinase enzymes responsible for the breakdown of the cartilage [36].

Another treatment option for osteoarthritis is the consumption of a healthy diet that will ensure a balanced body mass index. By doing so, one will be able to reduce the load on the joints as well as reduce the production of inflammatory mediators by the adipose tissue.

Anti-inflammatory nutrients like Omega-3 can help ease joint pains. Other studies are also looking into how the Mediterranean diet can be used to stop the progress of arthritis.

### **Osteoporosis**

Osteoporosis is associated with lower bone mineral mass and higher fragility leading to fractures due to imbalance in the processes of bone remodeling. Nutritional intervention can prevent bone diseases and ensure good skeletal health.

First of all, a proper amount of calcium is critical since it is required for bone mineralization and maintenance of bone mass. Deficiency in dietary calcium increases parathyroid hormone levels in the body stimulating bone turnover and accelerating bone loss [37].

Secondly, vitamin D enhances intestinal absorption of calcium and is important for bone mineralization. This vitamin also helps muscles work effectively contributing to prevention of falls and fractures. Furthermore, it has anti-inflammatory properties that can prevent bone destruction.

Finally, vitamin K ensures osteocalcin activation. This protein plays a role in calcium binding. Magnesium, in turn, strengthens bones and regulates calcium balance. Appropriate protein intake also plays a significant role because protein makes up bone matrix.

Thus, proper nutrition rich in micronutrients and proteins is necessary for proper bone maintenance and prevention of bone fractures. These, together with exercise, are the basis for treating and preventing osteoporosis.

### **CONCLUSION**

As can be seen at the moment, bone and joint diseases such as osteoporosis, osteoarthritis, and rheumatoid arthritis are complex diseases in which, alongside the problems with the structure, there is active involvement of inflammation and malfunctioning of immunity. The field of osteoimmunology found the connection between the function of immunity and metabolism in bone cells.

Nutrition has become an essential and modifiable parameter that can affect these processes at various levels. The process of immunoregulation, regulation of inflammatory pathways, decrease of oxidative stress, and bone turnover and cartilage health maintenance are among such processes. Not only micronutrients like calcium, vitamin D, vitamin K, and vitamin C but also macronutrients, especially omega-3 fatty acids, play a role in sustaining skeletal health and inflammatory response control. Moreover, diets like Mediterranean diet and vegetarian diets and functional food components like curcumin and green tea polyphenols can be mentioned due to their simultaneous effects on several pathogenic mechanisms.

Moreover, recent knowledge about the gut-joint axis stresses the significance of nutrition regarding its effect on immunological processes via modulation of the gut microbiota.

Although dietotherapy can be seen as an alternative form of treatment for bone and joint disorders, it cannot completely replace the current medicines therapy because the well-being of the patient will improve by combining both forms of treatment along with a number of adjustments in lifestyle and exercise routine.



Additional research needs to be done to identify nutrient-gene interactions, individualization of nutrition therapy, and conduct further clinical trials. Therefore, the combination of all these forms of treatment is still considered the most effective treatment of bone and joint disorders.

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### Author Contributions

Sanghita Mitra: Data Collection, Formal Analysis, Writing – Original Draft

Rojina Khatun: Resources, Writing-Editing

Malavika Bhattacharya: Conceptualisation, Supervision

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