REVIEW ARTICLE

Bridging the Gap: Investigating the Interplay of Polyunsaturated Fatty Acids and Osteoporosis

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Abstract

Osteoporosis, a common skeletal disorder characterized by diminished bone density and strength, poses a significant public health challenge worldwide, particularly among the aging population. This abstract explores the rising importance of omega-3 fatty acids in the management and preventing of osteoporosis. This comprehensive review delves into the molecular process underlying the effect of fatty acids on the metabolism of bone. Preclinical and clinical research data elucidates the beneficial effects of omega-3 fatty acids on bone density, bone formation, and the reduction of bone resorption. Additionally, the anti-inflammatory characteristics of these fats were examined, shedding light on their potential to mitigate the prolonged low-grade inflammation related to osteoporosis.

Keywords: Inflammation, Omega-3 fatty acids, Omega-6 fatty acids.

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Introduction

Osteoporosis is a common and potentially debilitating medical condition characterized by the weakening of bones, which leads to a reduced total bone density and an elevated risk of fractures. It is often called the "silent disease" because it develops gradually over many years without obvious symptoms until a fracture occurs. Osteoporosis is a significant global health concern, particularly affecting older adults, and it may have a significant impact on an individual's standard of living. Currently, approximately 617 million individuals, which equates to 8.5% of the global population, are 65 years of age or older. Following a recently released report, this proportion is anticipated to surge to approximately 1.6 billion individuals, representing a significant increase to 17% of the world's population by the year 2050.[1] At the same time, osteoporosis is acknowledged as a significant global economic challenge. While osteoporosis can affect both men and women, it is indeed more commonly observed in certain demographic groups, especially postmenopausal women.[2] This is because estrogen, a hormone known to be protective for healthy bones, decreases after menopause.[3]

Various factors influencing bone mass and health can be categorized as nonmodifiable or modifiable. Unaltered factors, which encompass age, gender, race, and genetics, remain beyond one's control. In contrast, factors that can be altered, including dietary choices and lifestyle habits like smoking, alcohol, and exercise, are amenable to change.[4] Presently, management for osteoporosis involve two primary approaches: Pharmacological and nonpharmacological interventions. The pharmacological approach includes anti-resorption, anabolic, and dual-effect drugs. These include medications, such as bisphosphonates, estrogen, denosumab, teriparatide, and strontium ranelate.[5] Nevertheless, it is worth noting that the use of these pharmaceutical agents can lead to various side effects. Nonpharmacological treatments primarily revolve around adopting healthy lifestyle practices, consuming balanced diets, and engaging in regular physical exercise. These nonpharmacological measures complement clinical treatments and contribute to the prevention of osteoporosis.

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Recently, dietary supplements like n-3 polyunsaturated fatty acids (PUFAs), calcium and vitamin D, and regular physical activity have emerged as potential strategies to improve bone metabolism and lower the risk of osteoporosis.[6,7] Osteoporosis and dietary choices are intricately connected, as the foods we consume have a vital function in the process of bone regeneration as well as repair. This study delves into the repercussions of consuming saturated and PUFAs on chronic inflammation, osteogenesis, bone structure, and strength. Additionally, it investigates the theory, that the consumption of dietary polyunsaturated fats exerts a positive influence on osteogenesis. This effect potentially mitigates bone depletion by reducing inflammation and activating bone resorption through vital cellular and molecular mechanisms, particularly in the context of our aged population.

Biological Factors Impacting Bone Metabolism

Bone is a highly active tissue, undergoing continuous remodeling to fulfill the body's requirements for calcium (Ca) and phosphorus (P), and to repair minor structural damage.

This intricate process involves osteoblasts responsible for building bone and osteoclasts responsible for breaking it down. Osteoclasts are cells accountable for the breakdown (resorption) of bone tissue during regular bone remodeling and in pathological conditions where there is an elevated level of bone resorption. Osteoblasts, the cells responsible for bone formation, arise from the precursor cells recruited from nearby bone marrow stromal cell populations. These recruited precursor cells distinct into osteoblasts, which then mineralize and produce bone matrix.

Bone remodeling can be enhanced in reaction to various factors, encompassing mechanical stress, cytokines, hormonal signals, as well as the influences of growth and dietary elements. Three proteins that together form a ligand called receptor-activated nuclear kappa-β ligand (RANKL) largely regulate the process of osteoclast formation, its corresponding receptor, receptor activator of nuclear factor kappa-B (RANK), and a counteracting decoy receptor called osteoprotegerin (OPG). Receptor activator of nuclear factor kappa-B is a protein situated in the membrane, expressed in osteoclast precursors as well as mature osteoclasts.[8] Receptor-activated nuclear kappa-β ligand is present in both soluble forms produced by various cells, such as osteoblasts and activated T cells. The interaction between RANKL and RANK initiates osteoclast differentiation while also preventing its cell death. RANKL triggers the activation of mature osteoclasts and facilitates osteoclast differentiation. It achieves this by binding to its receptor, RANK, which prompts the differentiation of osteoclasts into their mature form. Acting as a non-signaling receptor for RANKL, OPG acts by blocking the interaction between RANKL and RANK, thereby preventing the activation. Disturbances in the RANK–RANKL–OPG system, characterized by unproportioned rise RANKL activity, has been associated with development of numerous skeletal disorders, including osteoporosis and bone diseases. Elevated bone resorption has the potential to augment the generation of superoxide anions and/or impede the activities of antioxidant enzymes leading to concurrent skeletal destruction.[9]

Omega-3 Fatty Acids

Omega-3 fatty acids and omega-6 fatty acids are two distinct classes of PUFAs, each with its own set of functions and sources. Omega-6 (n-6) and omega-3 (n-3) are the primary categories of PUFAs[10] which can be found in both plants and animals. Linoleic acid (18:2n-6) and alpha-linolenic acid (18:3n-3) are produced by plants, consequently, they are abundant in various seeds, nuts, seed oils, and their derivative products such as margarine. Linoleic acid (18:2n-6) and alpha-linolenic acid (18:3n-3) cannot be synthesized in animals, and as a result, these two fatty acids are considered essential. After consumption, linoleic acid and alpha-linolenic acid can be transformed into various other fatty acids by a series of desaturation and elongation reactions. Linoleic acid can undergo conversion into γ-linolenic acid (GLA) (18:3n-6) through the action of Δ6-desaturase enzymes. These enzymes utilize NADPH and molecular oxygen for this process and are typically situated on the endoplasmic reticulum. γ-linolenic acid can be elongated by the enzyme elongase 5 to form dihomo-γ-linolenic acid (DGLA). Elongases are a group of enzymes responsible for elongating fatty acids by adding carbon atoms to their hydrocarbon chains. Dihomo-γ-linolenic acid is an important precursor for the synthesis of various bioactive compounds, including prostaglandins and leukotrienes, which play roles in the immune system and inflammation regulation in the body. The enzyme Δ5-desaturase can further desaturate DGLA to yield arachidonic acid (ARA). Δ5-desaturase is responsible for introducing a double bond at the Δ5 position along the carbon chain of DGLA, converting it into ARA. Employing the identical cascade of enzymes implicated in the metabolic pathway of n-6 PUFAs, α-linolenic acid can undergo conversion into timnodonic acid, frequently recognized as eicosapentaenoic acid (EPA). This conversion typically involves desaturation and elongation reactions catalyzed by specific enzymes, similar to how γ-linolenic acid is metabolized to DGLA and ARA in the n-6 pathway. In mammals, the liver is primarily responsible for the desaturation and elongation in fatty acids.

The regulation of Δ6- and Δ5-desaturases are governed by various factors, including nutritional status, hormones, and feedback inhibition by end products.[11] The genes *FADS1* and *FADS2* are responsible for the desaturation reactions that transform these fatty acids precursors into LC-PUFAs like ARA and EPA. Genetic polymorphisms can lead to variations in the efficiency of Δ5-desaturase and Δ6-desaturase enzymes encoded by *FADS1* and *FADS2* genes.[12] Subsequently, transformation of ARA into osbond acid (22:5n-6) and the conversion of EPA into cervonic acid, known as docosahexaenoic acid (DHA, 22:6n-3), involve complex pathways. ALA is the most commonly consumed omega-3 fatty acid, abundant in leafy vegetables, walnuts, soybeans, and various seed and vegetable oils. In contrast, EPA and DHA are primarily obtained from fatty fish like salmon and are also available in supplements containing fish oil.

Omega-3 Fatty Acids and their Effects on Bone Strength and Density

Reduction of the density of bone minerals occurs due to an intricate interplay between the bone-forming actions of osteoblast cells and the bone-resorbing activities of osteoclast cells. Omega-3 fatty acids have emerged as effective agents, promoting bone health by mitigating the effects of osteoporosis. Studies have indicated that these fatty acids can suppress osteoclast activity, thereby contributing to the preservation of bone mass.[13] Studies have revealed, elevated levels of DHA and EPA in erythrocytes are linked with decreased osteoporotic risk in postmenopausal Korean women.[14] The administration of fish oil has been observed to downregulate the activity of critical factors such as macrophage colony-stimulating factor (M-CSF), microphthalmia-associated transcription factor (MITF), and RANK. The inhibition of these factors ultimately leads to a suppression of bone resorption.[15] Research has demonstrated, a substantial intake of omega-3 fatty acids can effectively counteract, osteoclastic activity triggered by omega-6 fatty acids within mesenchymal stem cells. Simultaneously, it promotes the process of osteoblastogenesis.[16] Interestingly, Levental and fellow researchers have illustrated that DHA fosters osteogenic differentiation by stabilizing membrane raft microdomains.[17] This stabilization, in turn, triggers Akt activity and subsequently promotes osteoblastogenesis in baby hamster kidney cells. Moreover, nanoemulsion-EPA has been found to activate the p38 pathway, leading to an augmentation of osteoblastic differentiation in D1 cells, which are mouse mesenchymal stem cells. This activation results in increased alkaline phosphatase (ALP) activity, mineralization, and the expression of the osteoblastic transcription factor Runx2.[18] An investigation was conducted to determine the positive impact of ω-3 fatty acids on various factors influencing bone elongation, including the proliferation of chondrocytes, their differentiation, and the

production of extracellular matrix (ECM). In this report, it is observed that mice expressing the *fat-1* gene display a notable increase in bone growth. This is evident through the elongation of the tail in both male and female *fat-1* mice. The enhanced growth can be attributed to the growth plates being thicker, with increased thickness in the proliferative, prehypertrophic, and hypertrophic zones. Furthermore, there is a greater population of proliferative and prehypertrophic chondrocytes, as well as a more pronounced expression of key ECM proteins, specifically collagen type II and collagen type X.[19]

Free fatty acid receptor 4 (FFAR4), also recognized as G protein-coupled receptor 120, a specific cell surface receptor for omega-3 fatty acids (FAs), is expressed in osteoblasts, osteoclasts, and mesenchymal stem cells (MSCs).[20] Eicosapentaenoic acid and DHA exhibit anti-osteoclastogenesis and pro-osteoblastogenesis effects by engaging the FFAR4-barr2 signaling pathway.[21] In addition, EPA and DHA have been documented to inhibit osteoclastogenesis by suppressing NF-κB activation in MSCs through PPARγ mediation, subsequently resulting in reduced levels of tumor necrosis factor (TNF)-α and IL-6.[22] Furthermore, DHA and EPA exerted inhibitory effects on osteoclastogenesis by reducing the expression of RANKL. This in turn resulted in a decrease in RANKL's binding to the RANK, leading to the inhibition of NF-κB.[23]

Growing evidence consistently demonstrates the crucial roles that FAs play in bone metabolism. Studies have highlighted strong connection in between ω-3 PUFA and estrogen, and evidence indicates that ω-3 FAs positively influence bone turnover in developing animals. In particular, giving ovariectomized rats eicosapentaenoic acid (EPA 20:5 ω-3) has been linked to a decrease in bone mineral loss.[24] In a study, 4-week-old rats were divided into two groups: one receiving a diet with 10% fish oil and the other with corn oil. The results indicated that rats on the diet enriched with omega-3 experienced a 60% decrease in osteoclast count and an 80% reduction in resorption of bone compared with the control group. To date, single animal research has specifically examined the impact of ω-3 PUFA on bone fracture repair. This study utilized transgenic mice with the *fat-1* gene, which can internally transform ω-6 to ω-3 PUFAs.[25] Another study showed a notable enhancement in production of calluses with the healing of fractures within this group. Their findings indicated a positive correlation between ω-3 PUFAs supplementation and improved fracture healing. Histological examinations also revealed that the natural presence of omega-3 PUFAs promoted local endochondral ossification and accelerated the restructuring of calcified calluses post-fracture. Study on postmenopausal women indicated that consuming a diet rich in saturated fats led to an elevated risk of hip fractures. Conversely, increased intake of monounsaturated and PUFAs was associated with a reduced overall fracture risk.[26] More recently, an investigation[27] showed the connection between omega-3 FAs and enhanced skeletal health among osteoporosis patients. After examining recent randomized controlled trials, four investigations highlighted notable positive effects, whereas five showed no discernible variation in outcomes. Researchers noted that drawing definitive conclusions about the connection between ω-3 and bone health was constrained by the limited number and modest size of the studies. Additional clinical research has shown that increased intake of ω-3 FAs and a reduced ω6:ω-3 ratio are correlated with higher bone mineral density.[28–30] Further, the existence of favorable indicators for bone formation[31] and a decrease in proinflammatory cytokines in the peripheral blood were also demonstrated.[32] An additional study demonstrated a positive correlation between tissue levels of omega-3 PUFAs and bone density in postmenopausal women. Moreover, increased erythrocyte levels of EPA + DHA were associated with a reduced risk of osteoporosis among postmenopausal Korean women.[33] In another research, the impact of lipids combined with calcium intake was examined among older women with consistently low dietary calcium intake.[31] Participants were randomly divided into two groups: One received a combination of GLA and EPA, while the other group received coconut oil as a placebo. Both groups received 600 mg/day of calcium in the form of calcium carbonate. Following 18 months later, the group receiving, GLA and EPA combination maintained their lumbar spine BMD, whereas the placebo group experienced a 3.2% decline. This research indicated that the consumption of GLA and EPA, which both counteract the effects of ARA through prostanoid derivatives, enhanced bone health in older women.

Discussion

We assessed the most recent clinical and preclinical data in this evaluation to assess the implications of saturated and polyunsaturated fats on bone formation and persistent inflammation. Recent investigations indicate fats, especially those rich in ω-3 FAs, communicate effectively from stroma and hematopoietic bone cells. These fats demonstrate notable anti-inflammatory effects, inhibiting osteoclastogenesis while promoting osteoblastogenesis. As a result, they assist in preventing bone resorption and enhance bone density and repair. Although certain mechanisms underlying these benefits at the cellular and biochemical levels are not fully understood, substantial evidences is pointing to the significant role of polyunsaturated fats in regulating inflammation and mitigating bone loss.

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