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Vegetarian Diets and Skeletal Integrity: Mechanisms, Risks, and Future Perspectives

Maciej Łapiński [MŁ]
ORCID https://orcid.org/0009-0008-4509-8618
e-mail: maciek.lapinski.99@gmail.com
Medical University of Bialystok, 1 Jana Kilińskiego Street, 15-089 Białystok, Poland

Aleksandra Zimnoch-Włodarczyk [AZW]
ORCID https://orcid.org/0009-0009-3851-2726
e-mail: a.zim.wlo@gmail.com
Beskid Oncology Center, City Hospital of John Paul II in Bielsko-Biała
Department of Gynecology and Obstetrics and Gynecologic Oncology,
21 Stanisława Wyspiańskiego Street, 43-300 Bielsko-Biała, Poland.

Oksana Zinko [OZ]
ORCID https://orcid.org/0009-0009-7581-0896
e-mail: oksankazinko@gmail.com
Gajda-Med District Hospital, 19 Teofila Kwiatkowskiego Street, 06-102 Pułtusk, Poland.

Michał Napierała [MN]
ORCID: https://orcid.org/0009-0005-9543-3881
e-mail: xmichael121@gmail.com
Medical University of Silesia in Katowice,
15 Poniatowskiego Street, 40-055 Katowice, Poland.

Kinga Ciecierska [KC]
ORCID: https://orcid.org/0009-0004-6888-8672
e-mail: kingaa.ciecierska@gmail.com
Mazovian Dental Center Ltd.,
1 Nowy Zjazd Street,00-301 Warsaw, Poland.

Krystyna Wasilkowska [KW]
ORCID: https://orcid.org/0009-0007-6890-3459
e-mail: vasilkova9595@gmail.com
St. Luke's Hospital in Bolesławiec,
4 Jeleniogórska Street, 59-700 Bolesławiec, Poland.

Sylwia Łatkowska [SŁ]
ORCID: https://orcid.org/0009-0004-1251-6554
e-mail: latkowskasm@gmail.com
Zdrowie Plus Non-Public Health Care Center (NZOZ),
58 Wojciechowskiego Street,Warsaw, Poland.

Maja Sadowska [MS]
ORCID: https://orcid.org/0009-0001-5198-6848
e-mail: majasadowska7@wp.pl
Medical University of Bialystok, Jana Kilińskiego 1 street, 15-089 Białystok, Poland

Abstract

Background. Osteoporosis affects over 200 million people worldwide. While vegetarian diets reduce risks of cardiovascular diseases, they raise concerns regarding the intake of nutrients key to skeletal homeostasis, such as vitamin B12 and calcium.

Aim. This review analyzes the impact of vegetarian diets on osteoporosis risk and bone physiology.

Material and methods. We synthesize current knowledge on nutrient deficiencies, the gut microbiota-bone axis, and biochemical markers including IGF-1 and homocysteine.

Results. Vegetarians, especially vegans, exhibit lower bone mineral density and higher fracture risk compared to omnivores. The paper discusses mechanisms such as reduced bioavailable calcium and protein intake, downregulation of the IGF-1 axis, and hyperhomocysteinemia driven by vitamin B12 deficiency. Additionally, we address the potential immunomodulatory role of the gut microbiome.

Conclusions. We conclude that plant-based diets are associated with compromised skeletal integrity if not properly balanced. Careful nutritional planning and targeted supplementation are essential to optimize these dietary models for fracture prevention.

Key words: osteoporosis, vegetarian diet, bone mineral density, IGF-1, microbiome, fracture risk.

1. Introduction

Osteoporosis is a systemic metabolic bone disease characterized by decreased bone mass, deterioration of bone tissue microarchitecture, and increased bone fragility, which leads to an increased risk of fractures, particularly in the elderly and postmenopausal women [1–3]. It is a common condition affecting over 200 million people worldwide, with an estimated one-third of women and one-fifth of men over 50 at risk of osteoporotic fractures [1,4]. This disease imposes a significant economic and health burden on healthcare systems, and projections indicate a 50% increase in incidence over the next decade [1,4]. Fractures are the most serious clinical complication and most often involve the vertebral bodies, hips, distal radius, and proximal humerus. They are associated with increased risk of disability and higher mortality [1,2]. Many people today choose to follow vegetarian diets, believing that they improve health by reducing the risk of cardiovascular disease, type 2 diabetes, obesity, and some cancers [5,6]. These diets are consistently associated with lower body mass index (BMI), lower total cholesterol levels, lower blood pressure, and a lower incidence of hypertension and coronary heart disease [5–7]. There is a widespread belief that well-planned and managed vegetarian diets can provide all the necessary nutrients, although there are concerns in the scientific literature about marginal intake of specific nutrients that are key to skeletal homeostasis, such as vitamin B12, iron, calcium, zinc, and vitamin D [8,9]. Despite proven metabolic benefits, numerous studies and meta-analyses indicate that individuals following vegetarian diets, and particularly vegan diets, have lower bone mineral density (BMD) compared to omnivores [10,11]. Understanding the pathogenesis of osteoporosis in the context of plant-based diets requires an analysis of the complex interactions between nutritional factors and bone physiology. This process is modulated by hormonal, genetic, environmental, and immunological factors [1,12]. For individuals on a meat-free diet, this basic mechanism is compounded by specific dietary conditions, such as lower protein, calcium, and vitamin B12 intake, as well as unique metabolic profiles that include levels of insulin-like growth factor 1 (IGF-1) and homocysteine [13–15]. This review article aims to comprehensively present the impact of a vegetarian diet on the risk of developing osteoporosis. The following sections will discuss in detail the mechanisms linking dietary restrictions to bone health, including the impact of macro- and micronutrient deficiencies, the role of the gut microbiota-bone axis, and the significance of biochemical markers such as IGF-1 and homocysteine. The conflicting literature reports will also be analyzed, as well as potential protective factors of plant-based diets, which will enable us to draw conclusions about the safety and optimization of these dietary models in the context of fracture prevention.

2. Materials and methods

To prepare this review, a multi-stage analysis of scientific literature was conducted, focusing on the identification, characterization, and clinical assessment of the impact of plant-based diets on skeletal integrity and bone metabolism. Electronic databases PubMed, Scopus, and Google Scholar were searched using advanced search strategies based on keywords in the field of clinical nutrition, endocrinology, and orthopedics. The search included medical terms (MeSH) and key phrases such as "osteoporosis," "vegetarian diet," "vegan diet," "bone mineral density" (BMD), "fracture risk," "IGF-1," "homocysteine," and "gut microbiota-bone axis."

To precisely narrow the results to the most relevant studies, individual keywords were combined using Boolean logic operators (AND, OR). This allowed for the effective combination of dietary patterns with specific physiological outcomes (e.g., "vegetarian diet AND fracture risk" or "microbiome AND bone metabolism").

The time frame of the review was divided functionally, depending on the topic being discussed. Articles published prior to 2015 were primarily used to outline the historical background of bone physiology and established nutritional deficiencies (calcium, vitamin D). However, for analyzing complex pathophysiological mechanisms, such as the immunomodulatory role of the gut microbiota, genetic polymorphisms (e.g., SOX4), and the specific influence of biochemical markers like homocysteine and IGF-1, the analysis was limited to reports from 2015–2025, with a particular emphasis on works published after 2020 to ensure the timeliness of the epidemiological and mechanistic data presented. Only full-text original and review papers in English that provided quantitative data on clinical outcomes—including large-scale cohort studies such as EPIC-Oxford and Adventist Health Study-2—were included in the final analysis, rejecting reports that did not meet the criteria for scientific reliability.

3. Pathogenesis and mechanisms of regulation of bone metabolism

Understanding the impact of nutritional factors on the skeletal system requires a prior exploration of the complex pathophysiological mechanisms underlying osteoporosis. The central mechanism leading to the development of this disease is an imbalance in the bone remodeling process, which involves a disproportion between bone formation, which is the responsibility of osteoblasts, and bone resorption, which is mediated by osteoclasts [1–3]. In a physiological state, these processes remain in dynamic balance, but in the course of osteoporosis, osteoblasts are inactivated while osteoclasts are over-activated, resulting in loss of mineral density and increased bone fragility [16,17].

3.1. Hormonal and genetic modifiers

Hormonal and endocrine factors play a key role in regulating this process. Estrogen deficiency, observed particularly in postmenopausal women, is the main etiological factor that directly impairs bone metabolism and indirectly stimulates the secretion of pro-inflammatory cytokines, such as TNF-α and IL-6 [1,3]. These cytokines increase bone resorption and inhibit bone formation, accelerating bone tissue degradation [18,19]. In addition to sex hormones, other endocrine disorders are also important, including testosterone deficiency, changes in parathyroid hormone secretion, and hypogonadism [3]. Modern research also points to metabolic and systemic factors in the development of the disease. Advanced age, obesity, hyperinsulinemia, metabolic syndrome, and chronic inflammation significantly contribute to the pathogenesis of osteoporosis [1,4]. A cohort study of nearly 24,000 participants showed that the incidence of osteoporosis increased sharply with higher TyG-BMI, a marker of lipid-glucose metabolism and adiposity, with those in the highest quartile having more than three times the risk of those in the lowest quartile [20]. Genetic factors, which account for 50–85% of the variation in bone mineral density (BMD), remain significant [12]. Polymorphisms in genes such as estrogen receptor, vitamin D receptor (VDR), type I collagen A1 (COLIA1), and transcription factor SOX4 are strongly correlated with the risk of developing the disease [12]. In particular, polymorphisms of the SOX4 gene can increase the risk of osteoporosis more than fivefold in the presence of specific haplotypes [12]. The genetic background is compounded by environmental factors and lifestyle, including inadequate intake of calcium and vitamin D, lack of physical activity, smoking, and chronic stress, which through neuroendocrine mechanisms increases bone resorption [1,21]. It is also worth mentioning the phenomenon of ferroptosis and oxidative stress associated with iron overload, which can inhibit bone formation and promote bone resorption [18,19].

4. The relationship between a vegetarian diet and bone mineral density and the risk of fractures

An analysis of the impact of plant-based diets on bone parameters indicates significant epidemiological differences between vegetarians and omnivores. Numerous cross-sectional studies and meta-analyses consistently show that individuals following vegetarian diets, and especially vegan diets, have lower bone mineral density (BMD) compared to omnivores. [11,22]. The reduction in BMD in vegetarians is usually moderate, at around 4% in the femoral neck and lumbar spine, but in vegans, this reduction is more pronounced, reaching 6% in the lumbar spine [10,11,23]. Although these differences are considered clinically insignificant in some studies, they translate into tangible health risks in the long term [10,24]. Subgroup

analyses indicated that both lacto-vegetarians and vegans have lower BMD in key skeletal locations than meat-eaters [11,22].

4.1. Fracture risk and the BMI paradox

The consequence of reduced bone density is an increased risk of fractures. Vegans are the most at risk, showing a 55% higher risk of fractures overall, with a particular emphasis on hip and lower limb fractures, compared to those on a traditional diet [23,25]. This risk is particularly evident in people over 50 years of age [23]. Vegetarians who consume dairy products and eggs also have a higher risk of hip fracture—about 25% compared to omnivores, although data on other fracture locations are less clear in this group [23,25,26]. Importantly, the risk of developing osteoporosis appears to be more pronounced in people who follow a plant-based diet for a long time, i.e., for ten years or more [22].

An important modifier of the observed risk is the body mass index (BMI). Vegetarians, especially vegans, often have a lower BMI and less body fat than the general population [27,28]. A higher BMI is a protective factor for bones, and differences in body mass account for a significant portion of the observed association between a vegetarian diet and the risk of osteoporosis [29,30]. Statistical analyses show that the differences in fracture risk are stronger before BMI is considered as a confounding variable, but even after adjusting for this indicator and for calcium and protein intake, the risk remains statistically significant [25,31]. This suggests the existence of additional mechanisms that are independent of body mass and that affect the integrity of the skeleton in this dietary group.

Despite substantial evidence suggesting concerns with plant-based diets in the context of bone health, the literature also contains contradictory reports. Some studies have found no significant difference in BMD between lacto-ovo-vegetarians and omnivores, or suggested that adequate calcium and vitamin D intake can neutralize the observed risk. [32,33]. There is evidence that a well-planned lacto-vegetarian diet, including dairy products and eggs, may have a protective effect against osteopenia, likely due to higher intake of calcium, potassium, and magnesium [32,34]. Furthermore, high consumption of fruits, vegetables, legumes, and nuts, characteristic of plant-based diets, is associated with the provision of protective components, such as phytoestrogens and antioxidants, which in certain populations, such as postmenopausal women, correlated with a lower risk of osteoporosis [32]. These discrepancies underscore the need for a more in-depth analysis of specific nutritional deficiencies and the molecular mechanisms that will be discussed in the following sections.

5. Nutrient deficiencies and skeletal homeostasis

The impact of vegetarian diets on the skeletal system is inextricably linked to the macro- and microelement profile characteristic of this diet model. Plant-based diets, particularly vegan diets, often have lower levels of nutrients that are key to maintaining skeletal homeostasis, such as calcium, vitamin D, vitamin B12, protein, and omega-3 fatty acids [13,28]. Excluding dairy products from a vegan diet poses a particular challenge, leading to significantly lower intake of bioavailable calcium, which is directly correlated with a higher risk of osteoporosis in this subgroup [35]. Furthermore, vitamin D status is often lower in people on plant-based diets, which, combined with insufficient exposure to sunlight, further increases the risk of bone resorption [22,36]. Another important factor is the bioavailability of minerals. Although plant-based diets can be rich in minerals, the presence of antinutrients, such as phytic acid and oxalates, can significantly inhibit the absorption of calcium and zinc [37]. The bioavailability of zinc, an element necessary for the synthesis of bone matrix, is lower in plant products, which necessitates a higher intake of this micronutrient by vegetarians in order to maintain its proper status in the body [38]. It is also important to pay attention to protein intake, which may be lower in vegetarian diets and have a different amino acid profile than in traditional diets. While adequate protein intake is necessary for maintaining bone mass, a deficiency can contribute to a decrease in bone mineral density [11,35]. However, plant-based diets also provide protective components, such as magnesium, potassium, vitamin K, and antioxidants, which can neutralize the negative effects of deficiencies, provided the diet is carefully balanced [32].

6. Biochemical and Endocrine Mechanisms

6.1. The role of the growth hormone and insulin-like growth factor 1 (IGF-1) axis

One of the key endocrine mechanisms through which a vegetarian diet can affect bone metabolism is the modulation of insulin-like growth factor 1 (IGF-1) levels. Observational studies consistently show that vegetarians, especially vegans, have lower circulating IGF-1 concentrations compared to meat-eaters [14,39]. One analysis found that the average serum IGF-1 concentration was significantly lower in men on a vegan diet compared to the control group [40]. IGF-1 is a strong stimulator of osteoblasts and plays a key role in maintaining bone mineral density, and IGF-1 levels are positively correlated with BMD; thus, reduced IGF-1 is associated with lower BMD and elevated fracture risk [26,40]. The underlying mechanism of this phenomenon is multifactorial. A vegetarian diet typically involves lower protein and specific amino acid intake, including branched-chain amino acids (BCAAs), which are known stimulators of the growth hormone (GH)–IGF-1 axis [40,41]. A reduced supply of these amino

acids can result in a weakened stimulation of IGF-1 production. Furthermore, high intake of phytoestrogens, typical of diets rich in soy and plant products, is associated with lower levels of serum IGF-1 and higher levels of IGF-binding proteins (IGFBP) [42]. Although this hormonal profile may be beneficial in terms of reducing the risk of hormone-dependent cancers, such as prostate or breast cancer, in the context of the skeletal system, it may be a predisposing factor for osteoporosis [14].

6.2. Hyperhomocysteinemia and mechanisms of bone tissue damage

Another important link in the pathogenesis of osteoporosis in vegetarians is the disturbed metabolism of homocysteine, mainly resulting from vitamin B12 deficiency. Vitamin B12 is a necessary cofactor in the process of remethylation of homocysteine to methionine, and its deficiency, common in the vegan and vegetarian population, leads to the accumulation of homocysteine in the blood [43]. An elevated level of homocysteine is a recognized, independent risk factor for low bone density and fractures, acting through a number of toxic mechanisms [43].

Homocysteine has a detrimental effect on bone and vascular tissue primarily by inducing oxidative stress. It generates reactive oxygen species (ROS) that break down the body's antioxidant defenses, leading to vascular endothelial dysfunction [44]. Dysfunction of the endothelium and reduced production of nitric oxide (NO) can disrupt microcirculation in bone tissue, negatively affecting its nutrition and repair processes [45]. Furthermore, the reactive homocysteine metabolite, homocysteine thiolactone, causes N-homocysteinylation of proteins, which leads to changes in their structure and function [46]. In the context of bone, this process may affect collagen, the main component of the organic bone matrix, weakening its biomechanical properties and increasing its susceptibility to fractures [47]. Additional homocysteine pathogenetic mechanisms include neurotoxic effects and influence on epigenetic processes. Homocysteine acts as an agonist of NMDA and AMPA receptors, leading to increased intracellular calcium levels and cell apoptosis, as well as promoting microglial activation and inflammation [48]. Studies on cardiomyocytes also showed that homocysteine induces ferroptosis through the β-catenin/GPX4 pathway [15]. However, whether analogous mechanisms operate in bone tissue remains to be investigated. Moreover, exposure to homocysteine leads to global DNA hypomethylation, which can disrupt the expression of genes crucial for the differentiation and function of osteoblasts [44]. The combination of these phenomena, from oxidative stress, through the modification of structural proteins, to vascular and epigenetic disorders, creates a comprehensive picture of bone pathology induced by vitamin B deficiencies in plant-based diets.

7. Microbiome-bone axis

Modern research on the pathophysiology of osteoporosis is increasingly focusing on the role of the microbiome, defining the gut-bone axis as a key regulatory system that links gut bacterial metabolism to skeletal integrity. The gut microbiota is often referred to as the second human genome due to its genetic diversity. It has a significant impact on the skeletal system, regulating immune processes, nutrient absorption, and intestinal barrier function [49,50]. Both animal model studies and clinical observations in humans confirm the existence of strong correlations between the composition of the microbiota and the state of bone tissue, which opens up new perspectives for understanding the impact of a plant-based diet rich in prebiotic fiber on the risk of fractures [51].

7.1. Immunomodulation and bacterial metabolites

One of the fundamental mechanisms of the microbiome's effect on bones is immunomodulation. Intestinal bacteria and their metabolites influence the metabolic reprogramming of immune cells, which is critical for maintaining immune homeostasis and controlling bone metabolism [50,52]. This process is closely related to the balance between Treg and Th17 lymphocytes, which determines the differentiation of osteoclasts and the intensity of bone resorption [53]. The observed reduction in inflammatory and oxidative stress biomarkers in vegetarians and vegans, resulting from changes in the metabolic activity of the microbiota and the reduction in the number of pathobionts (e.g., Enterobacteriaceae), may be associated with reduced activation of osteoclastogenic cytokines, thereby protecting bone tissue from excessive resorption [54]. Furthermore, a healthy microbiota profile strengthens the integrity of the intestinal barrier, reducing its permeability and limiting the systemic translocation of pro-inflammatory mediators, such as lipopolysaccharide (LPS), which in dysbiotic conditions can contribute to bone mass loss [50,55]. Bacterial metabolites, including short-chain fatty acids (SCFA), tryptophan derivatives, and bile acids, play a key role in this communication. These compounds affect the homeostasis of the extracellular matrix of bone, mineral absorption, and bone cell differentiation [2,56]. Vegetarian diets, through their high supply of plant substrates, stimulate the intensive production of SCFA (acetate, propionate, butyrate), which leads to a decrease in the pH of the intestinal contents [54]. The acidic environment of the gut not only inhibits the growth of pathogens, but also increases the solubility and bioavailability of minerals, including calcium and magnesium, which may be a key mechanism compensating for lower calcium intake in plant-based diets [57]. Microbiota also increases the extraction of energy and nutrients from food, which is necessary for bone growth and mineralization, especially during puberty,

where dysbiosis can lead to long-term complications, including osteopenia [58]. Additionally, the gut-brain-bone axis involves hormonal and neuroimmune regulation, including the production of serotonin in the gut, which interacts with bone cells to regulate bone mass [2]. In a therapeutic context, modulation of the gut microbiota is a promising strategy for preventing bone metabolic disorders. Research has shown that germ-free mice experience less bone loss after estrogen deficiency, and probiotic treatment with Lactobacillus acidophilus and Bifidobacterium can protect against bone loss caused by oophorectomy by reducing osteoclastogenic cytokines [51]. Specific types of bacteria, such as Prevotella histicola, have also been identified as potentially protective against postmenopausal osteoporosis [51]. This is consistent with the microbiological profiles observed in vegetarians, who have a significantly higher prevalence of Prevotella and Bacteroidetes bacteria compared to omnivores, suggesting that a plant-based diet naturally promotes a bacterial profile with osteoprotective potential [54,59]. The use of probiotics and natural plant-derived compounds, such as polyphenols, may offer safer and multimodal therapeutic options, supporting bone microarchitecture and inhibiting bone resorption [55,56].

8. Conclusions

An analysis of available literature indicates that the relationship between the use of a vegetarian diet and the risk of developing osteoporosis is a complex and multifactorial phenomenon. Although plant-based diets have documented benefits in preventing lifestyle diseases such as obesity, type 2 diabetes, and cardiovascular disease, they are also associated with measurable reductions in bone mineral density and increased risk of fractures, particularly in the vegan population. The mechanism of this phenomenon primarily involves deficiencies in key nutrients, such as calcium, vitamin D, protein, and vitamin B12, which are necessary for proper bone remodeling. Specific biochemical pathways play a significant role in the pathogenesis of osteoporosis in vegetarians. Reduced IGF-1 levels, resulting from lower protein and branched-chain amino acid intake, weaken osteoblast stimulation, while B vitamin deficiencies lead to hyperhomocysteinemia. Homocysteine, through the induction of oxidative stress, modification of bone matrix proteins, endothelial dysfunction, and epigenetic and neurotoxic mechanisms, is a significant factor in damaging bone tissue. At the same time, new research on the gut microbiota-bone axis suggests that appropriate modulation of the bacterial flora through a diet rich in fiber and polyphenols may be a compensatory mechanism, although its protective potential requires further clinical research.

In light of the presented evidence, careful meal planning and targeted supplementation are key to the safety of plant-based diets. Vegetarians and vegans should pay special attention to

ensuring adequate intake of calcium, vitamin D, and vitamin B12 from natural sources, fortified foods, and supplements to minimize the risk of fractures. Further long-term prospective studies are needed to precisely determine the impact of various subtypes of vegetarian diets on bone health and to develop personalized dietary strategies that allow for the metabolic benefits of plant-based diets without compromising skeletal integrity.

Disclosure

Author Contributions

Conceptualization, M.Ł.; methodology, M.Ł., M.N. and A.Z.W.; validation, M.Ł., S.Ł., K.C. formal analysis, S.Ł., M.N., M.S.; investigation, O.Z., M.N., K.W.; resources, M.Ł., A.Z.W., M.S.; data curation, A.Z.W., K.W., S.Ł.; writing- original draft preparation, M.Ł., O.Z., M.S.; writing- review and editing, M.Ł., O.Z., K.C.; supervision, M.Ł., K.W., K.C.

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