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MINI-REVIEW

Nutritional properties and plausible benefits of Pearl millet (*Pennisetum glaucum*) on bone metabolism and osteoimmunology: a mini-review

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Abstract

Bone is a hard connective tissue that undergoes a systematic renewal. This highly dynamic organ is made up of four different types of cells, however, bone formation is commonly attributed to osteoblasts and bone resorption to osteoclasts. Bone tissue formation occurs during embryonic development and in certain post-birth pathological conditions. The immune system could influence the functions of bone cells, and the crosstalk between hematopoietic, immune, and bone cells is known as osteoimmunology. Indeed, cytokines produced by immune cells, including TNF-α and IL-6, are critically implicated in bone pathogenesis. It is well established that diet plays an important role in bone health and function. Indeed, an antioxidant nutraceuticals-rich diet, of which pearl millet is one, can be effective in treating osteoporosis. Pearl millet (PM) is an African native cereal that constitutes the staple food for African Sahel region inhabitants as well as for many peoples in rural regions in India. Pearl millet grains' content in amino acids, minerals, and phytochemicals may contribute to promoting bone health and metabolism. Accordingly, in the current review, we discuss the putative effects of PM nutrients, with a focus on polyphenols, bone metabolism and osteoimmunology. In the light of our previous studies and others from the literature, we suggest that PM whole grains can be effective in the prevention and management of bone pathogenesis.

Keywords: PM whole grains, nutrients, polyphenols, osteoblasts, osteoclasts, osteoimmunology, TNF-α.

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1 Introduction

Made up of 206 bones, the skeletal system, or skeleton, of the human body plays a key role in positioning and protecting the other organ systems, supporting the body, and storing minerals. Inside certain bones, hematopoiesis, which corresponds to the process by which blood cells are formed, occurs within the bone marrow [1]. Bone tissue formation occurs during embryonic development and in certain post-birth pathological conditions, including fracture [2]. Indeed, a complex process called bone remodeling by which four types of cells: osteoblasts, osteocytes, bone lining cells, and osteoclasts act together to heal the fracture[3]. A failure in bone remodeling can cause pathological destructive bone diseases such as osteoporosis that predominantly affects menopausal women [4].

Bone resorption (destruction) by osteoclasts is the first phase in the complex process of bone remodeling [3]. For some time, given that osteoclasts are derived from immune cells, the relationship between immune and skeletal systems has been clear. Therefore, the study of interactions between these systems is defined as osteoimmunology [5]. Cytokines including TNF-α and IL-6 play fundamental roles in osteoimmunology [6]. It is now well established that TNF-α and IL-6 constitute important modulators of immune-mediated bone diseases including postmenopausal osteoporosis [7]. The use of drugs for osteoporosis-related fracture has been criticized chiefly for its costs and side effects, whereas, nutritional-based strategies are highly recommended [8]. Indeed, it is well established that antioxidant nutraceuticals-rich herbal medicines such as pearl millet can be effective in treating osteoporosis.

Pearl millet or *Pennisetum glaucum* (L.) is a minor cereal domesticated somewhere in West Africa for almost 4500 years ago, then it has spread to other continents over time [9]. Pearl millet is one of the four major types of millet family [10]. In addition to the valid '*Pennisetum glaucum*' taxonomic name, pearl millet is also called *Pennisetum americanum* or *Pennisetum typhoides* [11]. It is called *Bajara* in India [12], *Bechna* in local south-west Algerian Arabic, or *Innely* in *Zenatia*, a Berber dialect. Moreover, pearl millet has many vernacular names in Sub-Saharan Africa [13]. Pearl millet grain is the staple food for African Sahel region inhabitants as well as for many peoples in rural regions in India. Previous studies have already demonstrated the antioxidant [14], immunomodulatory [15], and anti-cancer properties of pearl millet[16]. In the traditional medicine of the South of Algeria, mild millet is used alone or in combination with other medicinal plants to boost bone remodeling. Herein, in light of researches which have been undertaken on pearl millet nutritional composition and impact on metabolism, the current review aims to provide a body of evidence on the effectiveness of pearl millet grains for bone homeostasis.

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2 Overview on bone metabolism and osteoimmunology

Osteogenesis is a process by which connective bone tissue is formed from bone marrow mesenchymal stem cell during both fetal and postnatal periods [17], whereas, bone remodeling is a complex process involving bone resorption by osteoclasts and bone formation by osteoblasts [1]. Bone remodeling occurs along with the bone normal development and following certain traumatisms like fracture which is the most frequent traumatic large-organ injury [18]. This process occurs in three consecutive phases: osteoclastic resorption, reversal period, and osteoblastic formation[19]. The process of bone remodeling promotes the fracture healing through the coordination of several cell types chiefly osteoclasts, osteocytes, bone lining cells, and osteoblasts which are all assembled into a temporary anatomic structure called basic multicellular unit (BMU) [20]. Furthermore, molecules including parathyroid hormone (PTH), bone morphogenetic proteins (BMP) which belong to the transforming growth factor beta (TGFbeta) superfamily, insulin-like growth factors (IGFs), osteoprotegerin (OPG), receptor activator of NF-kappa B ligand (RANKL), alkaline phosphatase, prostaglandin E2 (PGE2), Runx2, and cytokines are involved as well in bone remodeling resulting in restored bone integrity [1].

Recently, there has been an increasing interest in the immune regulation of bone metabolism. Thus, the study of interactions between skeletal and immune systems is defined as osteoimmunology in which osteoblasts play a pivotal role[5]. Indeed, osteoblasts can secrete several cytokines including macrophage chemoattractant protein-1 (MCP-1), TGF-β, IL -1β, IL-6, and TNF-α in response to various stimuli [1,6]. It is now well established that TNF-α and IL-6 constitute important modulators of immune-mediated bone diseases including postmenopausal osteoporosis [7]. TNF-α is produced mainly by monocytes, but can also be secreted by osteoblasts, T cells and other cell types [22]. Nanes *et al.* [23] have shown that higher concentrations of TNF-α stimulate osteoclastogenesis through receptor activator of nuclear factor κB receptor (RANK)/RANKL pathway. In line with these findings, TNF-α suppressed osteoblast differentiation through NF-κB and mitogen-activated protein kinases (MAPK) pathways. In addition, TNF-α can stimulate NF-κB signaling and inhibit Wnt signaling that is the main canonical pathway of osteoblastic differentiation [23]. TNF-α also suppressed BMP-2-induced osteoblast differentiation and activated NF-kB signaling [24]. Moreover, TNF-α mitigated the expression of the Runx2 transcription factor, a downstream effector of p38 MAPK, which is required for osteoblast differentiation [25]. TNF-α induced the production of IL-6 pro-inflammatory cytokine and nitric oxide (NO), which modulates osteoclast recruitment and activity, in osteoblastic MC3T3-E1 cells [26]. Indeed, TNF-α induced oxidative stress that stimulates osteoclastogenesis and enhances bone resorption [27]. IL-6 is another cytokine that exhibits many roles in bone physiology [28]. IL-6 has been reported to promote osteoclastogenesis through enhanced RANKL expression in response to sustained PTH elevation, vitamin D3, and ovariectomy [3]. Moreover, a combination of IL-6, TNF-α, and IL-1β treatment has been found to increase RANKL/OPG ratio in SCP-1 human osteoblastic cell line accompanied with significant increase in osteoclast resorption activity [29].

Although the above-mentioned cytokines have been established to modulate bone resorption, they may have a dual role in bone remodeling [22]. Indeed, they are also recognized to boost osteoblast differentiation and contribute to bone formation [7].

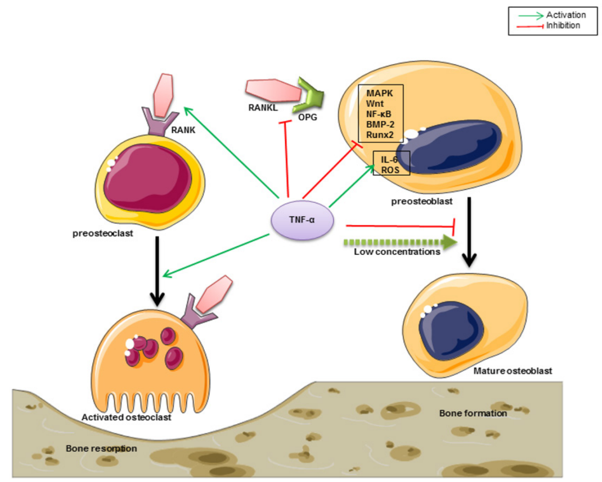

Figure 1: Illustration of some TNF-α-mediated biological processes of bone. BMP-2: bone morphogenetic proteins, NF-κB: nuclear factor- kB, MAPK: mitogen-activated protein kinases, OPG: osteoprotegerin, RANK: receptor activator of NF-kappa B, RANKL: receptor activator of NF-kappa B ligand, Runx2; Runt-related transcription factor 2, TNF-α: tumor necrosis factor-alpha, Wnt: Wingless type

3 Nutrient composition of pearl millet grains

PM is an important source of food security, nutrition and health in the arid and semi-arid tropics [30]. Indeed, PM grains possess considerable amounts of proteins, fat, carbohydrates, minerals, vitamins, and phytochemicals [15,31,32].

3.1 Proteins

Protein content in PM grains ranges between 8.8 and 16.1 %[31,32]. It has been established that cereal grains are notably deficient in lysine which is an essential amino acid that must be supplied from an exogenous diet [33]. Yet, PM contains a balanced amino acid profile with considerable amounts of lysine that can reach 2.9 g/ 100 g proteins [34]. Moreover, arginine that can be interconverted to proline and ultimately incorporated into collagen is estimated at 4.23 g/ 100 g proteins in PM grains [31]. Interestingly, digestibility of these essential amino acids has been found higher in pearl millet than in corn [35]. Civitelli *et al.* [36] argue for an adequate lysine intake for the management of fractures and osteoporosis due to its stimulating effects on intestinal calcium absorption and renal conversion. In the same vein, Fini *et al.* [37] emphasize the importance of lysine and arginine for bone remodeling, in part, through improving type I collagen synthesis by osteoblasts in both normal and osteopenic bone.

3.2 Lipids

PM grains contain the highest level of lipids as compared to wheat, barley, rye, and sorghum [32]. Our earlier findings showed that lipids represent 4.5 % in PM grains, and more than 72% of the fatty acids are unsaturated [15]. Among essential fatty acids, α-linolenic acid occupied only 3.2 % of total fatty acids in PM grains, however, this amount is the highest when compared to maize and rice [38]. Recently, it has been shown that α-linolenic acid-rich flaxseed oil improves HFD-induced bone loss, most likely by promoting osteogenesis [39]. On the other hand, T cells activation, which may delay fracture healing, is abolished by PM lipids treatment [15].

3.3 Starch and dietary fibers

Starch is one of the major nutrients in cereals, and it constitutes the main source of energy in plant foods [32]. PM starch content is comparable to that of sorghum which has a starch content of about 67.5%. However, it is relatively higher than that of barley and rye (53.6% and 58.0%, respectively) [32]. The portion of starch that resists digestion as it passes through the gastrointestinal tract is known as resistant starch [40]. There is an increasing interest in resistant starch for both its potential health benefits and functional properties [41]. A recent study has shown that resistant starch attenuates bone loss in ovariectomized mice in part by regulating bone-marrow inflammation [42]. Interestingly, the resistant starch proportion can reach 6.14 % in heat-moisture treated-PM starch [43]. Resistant starch is commonly grouped with dietary fibers on the basis of their indigestibility [44]. Thereby, PM whole grains showed a reasonable level of dietary fiber estimated to be 14.95 % [32].

3.4 Minerals

Minerals are minor constituents in cereal grains, however, they are as important as other nutrients [45]. The mineral content of PM whole grains ranges between 1.82 and 2.1 % [32,46]. The overall mineral content in PM grains is high when compared to commonly consumed cereals as reported by Nambiar *et al.*[12]. Indeed, PM whole grains contained phosphorus (P), calcium (Ca), magnesium (Mg), and potassium (K) with an amount of 2879, 508.6, 1488, and 2798 mg/kg, respectively [32]. Moreover, PM grains contain trace minerals such as zinc and iron with a concentration of 65.9 and 199.8 mg/kg, respectively [32], however, processing such as decortication influences the overall mineral content in PM [47]. Minerals contribute to the transformation of type I collagen produced from osteoblasts to mineralized extracellular matrix in bone tissue [48]. The impact of dietary intake of calcium, magnesium, phosphorus, and potassium on bone development had been extensively discussed [49]. Hence, it is obvious that a rational intake of foods that are rich in minerals such as calcium and phosphorus is positively associated with bone formation and density [50]. In addition to its role as a cofactor of a large number of enzymes, zinc may exert protective properties against bone loss by suppressing osteoclastogenesis [51].

3.5 Vitamins

Nambiar *et al.* reported that PM whole grains are important sources of certain vitamins, mainly some of the B-complex vitamins [12]. Indeed, levels of thiamine (B1), riboflavin (B2), Niacin (B3), and folic acid (B9) are approximately 0.33, 0.25, 2.3, and 0.046 mg/100 g, respectively. Thus, vitamin A and vitamin C occupy a proportion of 0.13 and 0.73 mg/100 g, respectively in PM whole grains [12,31]. The so-called B-vitamins and vitamin C are water-soluble, and their function as a coenzyme is the most salient characteristic of this class of vitamins. Whereas vitamin C is well known for its antioxidant proprieties, the fat-soluble vitamin A, also known as provitamin A and preformed vitamin A, exerts much of its effects both on rhodopsin conformational change following light-induced bleaching and at the gene level [52].

3.6 Phytochemicals

Phytochemicals or plant secondary metabolites are plant-derived chemicals or compounds. Hence, bioactive phytochemicals that protect or promote health are known as nutraceuticals which occur at the intersection of food and pharmaceutical industries[53]. The well-documented phytochemicals are mainly phenolics (or polyphenols), alkaloids, and terpenes [54]. Cereals contain significant amounts of phytochemicals [45] among which phenolics are the most studied in PM grains [15,16,32,55–58]. Previous researches have shown that total phenolic content in PM whole grains ranges from 1660 to 2580 µg gallic acid equivalents (GAE)/g DM [15,59]. Furthermore, flavonoids are estimated to be 2350 µg catechin equivalents (CE)/g DM [59]. Our previous research has demonstrated that hydroxycinnamic acids are the most abundant phenolic compound in PM whole grains [15]. There is an increasing body of evidence that polyphenols, including hydroxycinnamic acids, are effective in improving bone health through promoting bone remodeling and mitigating the damaging effects of oxidative stress that takes part in bone-resorptive processes [60]. In addition, PM polyphenols modulated MAPK pathways both in osteoblasts and T cells [15,16].

4 Pearl millet grains phenolics benefits on bone health and functions

Recently, a big interest has been given to traditional diet which has an impact on the prevention and management of a number of pathologies including rheumatic diseases [61,62]. As far as bone tissue is concerned, epigenetic alterations have been established as key factors of osteogenesis, homeostasis, and diseases of pathologic bone remodeling [63,64]. Indeed, there is a common agreement that nutrients can regulate gene expression in many biological processes [61,64]. Among nutrients, dietary polyphenols have been reported to have a positive impact both on bone health and function [60]. Several polyphenol-rich foods including olive, extra virgin olive oil, green tea, plum, and blueberry, have been shown to exert an osteoprotective activity under normal and inflammatory conditions [62,65–68]. There are many PM-based traditional diets in different regions in Africa and Asia [47,57,69,70]. According to our previous studies, PM grains are rich in polyphenols that exert immunomodulatory and anti-cancer, against osteosarcoma, activities [15,16]. To the best of our knowledge, no single study discussed the potential effects of PM grains on bone yet.

Beside the aforementioned benefits of PM nutrients on bone remodeling, in this section we emphasize the plausible benefits of PM phenolic compounds on bone remodeling and osteoimmunology. Some studies have already demonstrated the effects of ferulic acid, a major phenolic compound in PM grains, on gene expression of the principal proteins that play a pivotal role in bone remodeling and osteoimmunology chiefly RANKL and NF-κB [71]. Ferulic acid promoted osteogenesis of human bone marrow-derived mesenchymal stem cells (MSC) by up-regulating β-catenin, which constitutes the major player of Wnt signaling, expression and activity [72]. Ferulic acid treatment also increased the expression of alkaline phosphatase (ALP), Runx2, and Ostrix (Osx) osteoblast markers in MSC [72]. Another research has revealed that ferulic acid can protect against osteoporosis in glucocorticoid-treated neonatal rats in part through inhibition of NF-κB signaling [73]. On the other hand, ferulic acid suppressed osteoclast differentiation in RAW 264.7 monocyte/macrophage cells via the inhibition of RANKL dependent NF-κB signaling pathway [71]. The same authors showed that ferulic acid mitigates the gene expression of TRAP, MMP-9 and Cathepsin K which all mediate bone resorption activity of mature osteoclasts [71].

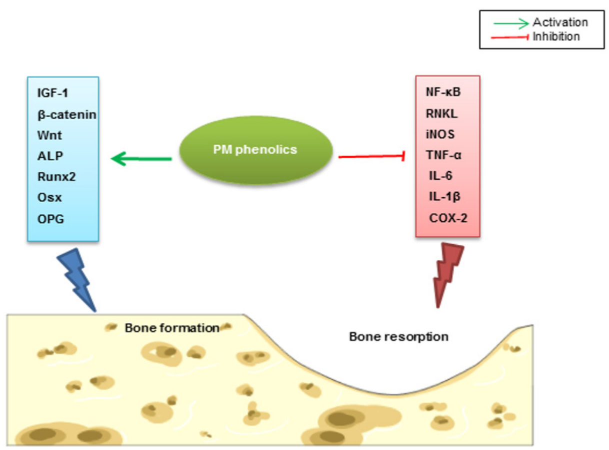

Figure 2: Putative effects of PM phenolics on bone metabolism. ALP: alkaline phosphatase, COX-2: cyclooxygenase-2, IGF-1: insulin-like growth factor-I, IL-1β: interleukin-1β, IL-6: interleukin-6, iNOS: inducible nitric oxide synthase, OPG: osteoprotegerin, Osx: Ostrix, NF-κB: nuclear factor-kB, RNKL: receptor activator of NF-kappa B ligand, Runx2: Runt-related transcription factor 2, TNF-α: tumor necrosis factor-alpha, Wnt: Wingless type

p-coumaric acid, the most abundant phenolic compound in PM grains [15], stimulates longitudinal growth of the long bone through increasing the expression of insulin-like growth factor 1 (IGF-1) in adolescent male rats [74]. Neog and Rasool [75] demonstrated that p-coumaric inhibits osteoclastogenesis and bone resorption by enhancing OPG/RANKL ratio and down-regulating iNOS and TNF-α, IL-6, IL-1β, and COX-2 inflammatory mediators in the rheumatoid arthritis animal model. Hence, inhibiting TNF-α, IL-6, and IL-1β cytokines expression by the suppression of NF-κB signaling may improve bone loss and other complications [76]. Interestingly, the inhibition effects of bone resorption by green tea polyphenols were associated with reduced splenic TNF-α and COX-2 expression in a chronic inflammation-induced bone loss model [66]. Green tea polyphenols also alleviated ROS-induced oxidative stress in cultured rat calvarial osteoblast [77]. Dried plum polyphenols restored TNF-α-dependent decrease of Runx2, Osterix and IGF-I levels in osteoblast [78]. Overall, PM phenolics may promote osteogenesis and mitigate osteoclastogenesis in part through modulating oxidative stress, Wnt and NF-κB signaling pathways.

5 Conclusion

Polyphenols of PM grains may contribute to the prevention, management and treatment of some bone pathogenesis by their positive impact on osteoimmunology revealed by their immunomodulatory effects. However, the synergetic effect between whole-grain PM nutrients is possibly more powerful than that of individual components. Further *in vitro* and *in vivo* studies should be conducted to check the impact of PM nutrients on bone biology in normal and pathological conditions.

Limitations: the putative effects of the pearl millet grains on bone homeostasis were based on those exerted by some pearl millet nutrients and phytochemicals. Yet, the detailed mechanisms ought to be checked experimentally.

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