Editorial　　　　　　　　　　　　　　　　　　　　　　　　**Open Access**

New Development in Osteoporosis Treatment: The Synergistical Osteogenic Effects with Vitamin D$_3$, Menaquinone-7, Genistein and Zinc

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Bone is a dynamic tissue that undergoes continual adaptation during vertebrate life to attain and preserve skeletal size, shape, and structural integrity and to regulate mineral homeostasis. Two processes, remodeling and modeling, underpin development and maintenance of the skeletal system [1]. Bone modeling is responsible for growth and mechanically induced adaptation of bone and requires the processes of bone formation and bone removal (resorption). Bone remodeling is responsible for removal and repair of damaged bone to maintain integrity of the adult skeletal and mineral homeostasis. Bone homeostasis, which maintains bone mass, is skillfully regulated through osteoclasts, osteoblasts and osteocytes, which are major cells in bone tissues. Bone homeostasis is regulated through various physiological systems including many hormones and cytokines and immune systems, and it is disturbed through various pathophysiological states that induce osteoporosis. Aging induces a reduction in bone mass with a decrease in osteoblastic bone formation and an increase in osteoclastic bone resorption. Osteoporosis with its accompanying decrease in bone mass is widely recognized as a major public health problem. The most dramatic expression of the disease is represented by fractures of the proximately femur, and the number of which increase as the population ages [2,3]. Moreover, bone loss has been shown to stimulate in various pathophysiologic states including inflammation, obesity, diabetes, and cancer cell bone metastasis [4]. Malnutrition or undernutrition is often observed with increasing ages, and it appears to be more intense in patients with hip fracture than in the general aging population [5]. The deficiency in both micronutrients and macronutrients appears to be strongly implicated in the pathogenesis and consequences of hip fracture in the osteoporotic elderly. This may generate the concept that bone homeostasis is regulated through various nutritional and food factors in maintaining bone health in long life. There is growing evidence that nutritional and functional food factors have a role in the prevention of bone loss with increasing age [6]. Food life style may help to prevent bone loss with aging. Chemical factors including vitamins and minerals in food and plants, which regulate bone homeostasis, have been to be notice. Recent studies have been shown that these factors stimulate osteoblastic bone formation and suppress osteoclastic bone resorption in osteoporosis animal models and human subjects [6], thereby increasing bone mass. Supplemental intake of ingredients plays an important role in maintaining bone health and in the prevention of bone loss. This may provide a new tool in the treatment of osteoporosis.

Calcium, phosphorus and vitamin D, which are nutrients, were noticed in maintaining bone health and in the prevention of osteoporosis. Calcium and phosphorus are essential elements in bone composition and are regulated through calcium-regulating hormones including parathyroid hormone, 1, 25-dihydroxyvitamin D$_3$ and calcitonin. Nutrient vitamin D$_3$ is converted to hydroxyVitamin D3 [25(OH)D$_3$] in the liver and then 1,25-dihydroxyVitamin D$_3$ [1,25(OH)$_2$D$_3$] in the kidney which are its active metabolite. These forms are hormone recognized to play a critical function in bone metabolism. This is evidenced by formation of poorly mineralized bone during vitamin D3 deficiency leading to rickets in children and osteomalacia in adults. This is largely a consequence of the necessity for vitamin D to promote efficient calcium absorption in the small intestine. Any decline in serum calcium concentrations due to inadequate calcium absorption leads to a secondary hyperparathyroidism that catabolizes the skeleton to maintain a physiological level of calcium necessary for normal cellular metabolism [7]. Although vitamin D supplementation is commonly used to combat osteoporosis, currently the optimal dose of vitamin D required for fracture prevention is contentious. While a minimum of 10 ng/mL of 25(OH)D$_3$ is sufficient to prevent rickets and osteomalacia [8], recent studies have demonstrated that a minimum threshold 25(OH)D$_3$ level of 29.7 ng/mL is necessary for protection from fracture [9]. However, there is a paucity of data as to the optimal vitamin D concentration for fracture prevention and to complicate matters it is now appreciated that vitamin D plays a number of extra-skeletal roles including promotion of innate and adaptive immune function, prevention of cancers, and prevention of hypertension [8,9]. The doses of vitamin D needed to achieve these extra-skeletal actions may be considerable higher than that needed to effect its actions on the skeleton [10]. Recent meta-analysis have suggested that supplementation of greater than 400 IU of vitamin D may reduce fractures [11], however the mechanism is unclear and may be associated in part with decreased risk of falling as a consequence of improved neuromuscular function [12]. In a clinical study of bedridden older patients with chronic secondary hyperparathyroidism, low dose (400 IU/d) vitamin D supplementation led to a significant increase in amino-terminal propeptide of type I procollagen, a marker of *in vivo* bone formation. These gains were complete negated by high dose (1200 IU/d) vitamin D supplementation, while indices of bone resorption did not significantly change with either regimen [13]. In another study, wintertime vitamin D supplementation of healthy men led to a significant dose-dependent decline in bone specific alkaline phosphatase, a marker of *in vivo* mineralization [14]. As the vast majority of studies involve vitamin D supplementation in the context of antiresorptive therapy, typically a bisphosphonate, it becomes extremely difficult to assess and effects of vitamin D alone on bone turnover given that antiresorptive agents themselves potently suppress bone formation as a consequence of coupling. Furthermore, the amelioration of secondary hyperparathyroidism by vitamin D supplementation is often associated with a decline in bone turnover [15]. This may be a consequence of reduced parathyroid hormone (PTH)-driven bone resorption leading to reduced bone formation as a consequence of coupling. Vitamin D further appears to have hallmarks of an anti-inflammatory agent as vitamin D deficiency has been linked to a number of different inflammatory conditions including inflammatory bowel disease and rheumatoid arthritis. In a population-based prospective cohort, vitamin D intake was inversely correlated with risk of rheumatoid arthritis [8], an inflammatory

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autoimmune disease. Furthermore, vitamin D insufficiency promotes the development of autoimmunity in animal models of inflammatory bowel disease [9].

Vitamin K is known as a blood coagulative factor. There are three types of vitamin K: vitamin K_1 (phylloquinone), vitamin K_2 (menaquinone), and vitamin K_3 (menadione). Menaquinone-4 (MK-4), with four isoprene units, not only enhances mineralization but also increases amount of osteocalcin, which has a high affinity to calcium and/or hydroxyapataite, in human osteoblasts. MK-4 has been shown to inhibit bone resorption and inhibits bone loss in ovariectomized rats. Menaquinone-7 (MK-7) with seven isoprene units is very abundant in fermented soybean. Dietary vitamin K intake has beneficial effects on bone. MK-7 has a stimulatory effect on osteoblastic bone formation due to increasing protein synthesis including osteocalcin [16]. Also, MK-7 has an inhibitory effect on osteoclastogenesis [17]. Suppressive effects of MK-7 on osteoclasts may be partly mediated through the pathway of Ca^{2+}- and cyclic AMP-dependent signaling. The actions of MK-7 on osteoblasts and osteoclasts are accomplished by down regulating basal and cytokine-induced the nuclear factor kappa B (NF-κB) activation, by increasing IκB mRNA, in a γ-carboxylation–independent manner [18]. Vitamin K_2 is a transcriptional regulator of bone-specific genes that act through steroid and xenobiotic receptors (SXRs) to promote expression of osteoblastic markers. The intake of dietary MK-7 has a preventive effect on bone loss caused in ovariectomized rats, an animal model for osteoporosis, *in vivo*. The intake of dietary MK-7 with fermented soybean can stimulate γ-carboxylation of osteocalcin in normal human subjects. Dietary MK-7 may be useful in the prevention and treatment of osteoporosis. Intake of fermented soybean, which largely contains MK-7, has been shown to have preventive effects on bone fracture in Japan.

Genistein is a functional food factor, which is largely contained in soybeans and fermented soybeans. Genistein has been shown to have a stimulatory effect on osteoblastic bone formation and a suppressive effect on osteoclastic bone resorption, thereby increasing bone mass [19,20]. Genistein has regulatory effects on protein synthesis and gene expression, which are related to bone formation in osteoblastic cells and bone resorption in osteoclastic cells. Genistein has been shown to directly evoke apoptosis of mature osteoclastic cells. Oral administration of genistein has been shown to prevent on bone loss in ovariectomized rats, indicating a role in the prevention of osteoporosis. Moreover, the intake genistein has been shown to have a restorative effect on osteoporosis in human subjects, suggesting a role in the treatment of bone loss [21,22]. Zinc plays a pivotal role as an essential nutritional factor in the growth of animals and human. Bone growth retardation is a common finding in various conditions associated with dietary zinc deficiency. Bone zinc content has been shown to decrease in aging, skeletal unloading and postmenopausal conditions, suggesting its role in bone disorder.

Zinc has been demonstrated to have stimulatory effects on osteoblastic bone formation and mineralization due to stimulating cellular protein synthesis and the gene expression of the transcription factors runt-related transcription factor 2 (Runx 2), which is related to differentiation into osteoblastic cells [23,24]. Moreover, zinc has been shown to inhibit osteoclastic bone resorption due to inhibiting osteoclast-like cell formation from bone marrow cells and stimulating apoptotic cell death of mature osteoclasts [23,25]. Zinc has a suppressive effect on the receptor activator of nuclear factor (NF)-κB ligand (RANKL)-induced osteoclastogenesis. The intake of zinc causes an increase in bone mass. Oral administration of zinc compound has potent-restorative effects on bone loss under various pathophysiologic conditions including aging, skeletal unloading, aluminium bone toxicity, calcium- and vitamin D-deficiency, adjuvant arthritis, estrogen deficiency, diabetes, and fracture healing [24]. Zinc compounds may be designed as new supplementation factor in the prevention and treatment of osteoporosis.

Interestingly, the osteogenic effects of vitamin D_3 [26-29], MK-7 [30,31] and genistein [32-38] have been found to be synergistically enhanced with combination of zinc and also have potential suppressive effects on osteoclastic bone resorption. Such effects may be based on protein synthesis and gene expression, which are related to osteoblastic bone formation and osteoclastic bone resorption. Oral administration with combination of vitamin D_3, MK-7, genistein and zinc has been shown to have a synergistic-preventive effect on bone loss in aged and ovariectomized rats, an animal model for osteoporosis. Moreover, supplemental intake of their ingredient has potent effects on osteoporosis in human subjects. Such combination of biomedical food factors may be a potential useful tool in maintaining bone health and in the prevention and treatment of osteoporosis in various pathophysiological states. Anti-resorptive agents have long been the preferred standard of care for the amelioration of bone loss. Although in general anti-resorptive agents do an excellent job of preventing additional bone loss, they do not allow for adequate regeneration of lost bone mass. Drugs, which are used clinically in the treatment of osteoporosis, are mainly based on the action of osteoclastic bone resorption. An intensive effort has begun to identify or develop anabolic agents capable of rebuilding lost bone mineral density. At present, teriparatide, a fragment of human parathyroid hormone is the only United State Food and Drug Administration (FDA) approved anabolic agent currently available. This agent represents a significant leap forward but as a biologic based agent its use is limited by high cost and the need for daily injection. Furthermore, therapy is not recommended for more than 2 years due to the potential for osteosarcoma. As a consequence there is intense interest in the identification of additional anabolic agents. Clinical compounds that stimulate bone formation are under development. Supplements with chemically pure ingredients of vitamin D_3, MK-7, genistein and zinc, which have potential osteogenic effects, will be expected to use as new drug for osteoporosis

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