Osteoporosis Treatment with Functional Food Factor: Vitamin K$_2$

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Bone homeostasis is maintained through a delicate balance between osteoblastic bone formation and osteoclastic bone resorption [1]. Numerous pathological processes have the capacity to disrupt this equilibrium leading to conditions where the rate of bone resorption outpaces the rate of bone formation leading to osteoporosis, a devastating bone disease that is widely recognized as a major public health threat. Bone loss is accelerated with increasing age, inducing elderly osteoporosis. Postmenopausal osteoporosis, a consequence of ovarian hormone deficiency, is the archetypal osteoporotic condition in women after menopause and leads to bone destruction through complex and diverse metabolic and biochemical changes [2]. Moreover, osteoporosis is induced through obesity, diabetes, and inflammation and cancer cell bone metastasis. The most dramatic expression of this disease is represented by bone fractures.

Malnutrition or under nutrition is often observed with increasing ages, and it appears to be more intense in patients with hip fracture than in the general aging population [3]. 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. There is growing evidence that nutritional and functional food factors have a role in the prevention of bone loss with increasing age [4]. Food life style may help to prevent bone loss with aging. Chemical compounds in food and plants, which regulate bone homeostasis, have been to be notice. Recent studies have been shown that nutritional and functional food factors, which are present in fruit and vegetables, stimulate osteoblastic bone formation and suppress osteoclastic bone resorption in animal models and human subjects, thereby increasing bone mass [4]. Supplemental intake of ingredients, which reveal osteogenic effects, 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, which is proposed as “biomedical osteoporosis treatment” [4].

Yamaguchi has been demonstrated that various nutritional and functional food factors stimulate osteoblastic bone formation and suppress osteoclastic bone resorption, thereby increasing bone mass [4]. Here, menaquinone-7 (MK-7), a kind of vitamin K$_2$, is focused. Vitamin K is a fat-soluble vitamin that was originally identified as an essential factor for blood coagulation. Vitamin K is an essential cofactor for the post-translational carboxylation of certain protein-bound glutamate residues of osteocalcin, a synthesized by osteoblasts, which are converted into gamma-(y)-carboxyglutamate (Gla) by y-carboxylase [5]. These Gla residues form calcium-binding sites that are essential for the activity of the proteins. There are three types of vitamin K: vitamin K$_1$ (phyloquinone), vitamin K$_2$ (menaquinone), and vitamin K$_3$ (menadione). Vitamin K$_2$ is a sole compound, but vitamin K$_1$ is a series of vitamins with multiisoprene units (one to four) at the 3-position of the naphthoquinone. Vitamin K$_1$ (menaquinone-4; MK-4) has four isoprene units. MK-4 is essential for the γ-carboxylation of osteocalcin [5]. MK-4 has been shown to inhibit bone loss, which may be related to its side chain, in ovariectomized rats [6]. Natural MK-7 with seven isoprene units is very abundant in the fermented soybean (natto). It has been shown that serum MK-7 concentration in women living in Tokyo, where the fermented soybean is consumed, is about ten times higher than that of those living in Europe [7]. These differences may result from the intake of fermented soybean.

There is growing evidence for the roles of vitamin K$_2$ in bone health in human subjects [8,9]. Clinically, vitamin K$_2$ maintains lumbar Bone Mineral Density (BMD) and prevents osteoporotic fractures in patients with osteoporosis. Osteocalcin, which is newly synthesized by osteoblasts, is released into circulation. For this reason, the circulating levels of osteocalcin are considered sensitive markers of bone formation [10]. A poor vitamin K status will lead to production of under carboxylated (inactive) osteocalcin (unOC) [11]. In postmenopausal women, a clear association between elevated unOC and increased fracture risk is found [12]. Significantly lower levels of vitamin K$_1$ and vitamin K$_2$ are found in the serum obtained from elderly patients within a few hours after a hip fracture [12]. A daily vitamin K$_2$ supplement of 80 μg seems to be necessary to reach a premenopausal carboxylatedosteocalcin/total osteocalcin ratio [13]. An adult daily intake of about 100 μg of vitamin K$_1$ is recommended for the maintenance of hemostasis [14]. The Food and Drug Administration (FDA) has mandated that adult parenteral preparations should provide a supplemental amount of 150 μg vitamin K$_1$ per day in addition to that present naturally [15]. Although this supplemental daily amount is probably beneficial in preventing vitamin K deficiency, it may be excessive for patients taking vitamin K antagonists, such as warfarin, and jeopardize their anticoagulation treatment. Natural forms of vitamin K have no proven toxicity.

Yamaguchi et al. found that MK-7, which was isolated from fermented soybean (natto), reveals stimulatory effects on calcification in the femoral tissues obtained from normal young rats in vitro [16]. This was the first time finding, which MK-7 has been demonstrated to reveal anabolic effect on bone tissues. The action of MK-7 on bone calcification has been shown to have the same effect as MK-4. MK-7 has partially been converted to MK-4 in the body. MK-7 may have an important role in the regulation of bone metabolism. Culture with MK-7 caused a significant increase in biochemical components (alkaline phosphatase activity, DNA and calcium contents) in the femoral-cortical and trabecular bone tissues obtained from aged rats in vitro [17]. The effect of MK-7 in increasing bone components in the femoral tissues is completely depressed by an inhibitor of protein synthesis in vitro [17]. Moreover, MK-7 has been demonstrated to increase differentiation and proliferation of osteoblastic cells in vitro.

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MK-7 reveals suppressive effects on osteoclastic bone resorption in vitro [19]. MK-7 is found to suppress bone resorption induced by various bone-resorbing factors (including parathyroid hormone and prostaglandin E₂) in vitro in the femoral tissues obtained from young and aged rats in vitro [19]. Osteoclast-like cells are formed from bone marrow cells in the presence of bone-resorbing factors. This osteoclast-like cell formation is found to suppress after culture with MK-7 [19]. This suppressive effect is potentially seen at the later stage of differentiation of bone marrow cells. MK-7 suppresses osteoclastic cell formation induced by activator of protein kinase C, although it does not have an inhibitory effect on cyclic AMP signaling-induced increase in osteoclast-like cell formation [19]. Suppressive effects of MK-7 on osteoclastic cell formation may be partly mediated through calcium-dependent protein kinase C signaling [19]. Moreover, the suppressive effect of MK-7 on mature osteoclasts isolated from rat femoral tissues has also been demonstrated [19]. MK-7 suppresses the number of mature osteoclasts. Such an effect is also seen by calcitonin, dibutyryl cyclic AMP or calcium chloride [19]. Suppressive effects of MK-7 on osteoclasts are abolished by dibucaine or staurosporine, which are inhibitors of Ca²⁺-dependent protein kinases. Suppressive effects of MK-7 on mature osteoclasts may be partly mediated through the pathway of Ca²⁺- and cyclic AMP-dependent signaling [19].

Molecular mechanism by which MK-7 reveals osteogenic effects is under elucidation. MK-7 may activate γ-carboxylase that converts into γ-carboxyglutamate of the glutamate residues of osteocalcin in osteoblastic cells. MK-7 may also stimulate synthesis of various proteins including osteocalcin in osteoblastic cells [19]. Activation of the nuclear factor-kappa B (NF-kB) signal transduction pathway is essential for osteoclast formation and resorption [20]. By contrast, NF-kB signaling potently antagonizes osteoblast differentiation and function [20]. The action of MK-7 on osteoblast and osteoclast formation and their cell activity is accomplished by downregulating basal and cytokine-induced NF-kB activation, by increasing IkB mRNA, in a γ-carboxylation-independent manner [20]. MK-7 is found to prevent repression by tumor necrosis factor-α of Smad signaling induced by either transforming growth factor-β or bone morphogenetic protein-2 [20]. MK-7 further antagonizes receptor activator of NF-kB (RANK) ligand (RANKL)-induced NF-kB activation in osteoclast precursors [20]. These findings provide a novel mechanism to explain the dual pro-anabolic and anti-catabolic activities of MK-7. As described above, moreover, suppressive effects of MK-7 on mature osteoclasts may be partly mediated through the pathway of Ca²⁺- and cyclic AMP-dependent signaling [19]. Vitamin K₂ has also been shown to be a transcriptional regulator of bone-specific genes that act through steroid and xenobiotic receptors (SXRs) to promote expression of osteoblastic markers [21]. The effect of MK-7 on gene expression remains to be elucidated.

MK-7 has been demonstrated to play a role in the prevention and treatment of osteoporosis. Preventive and restorative effects of dietary MK-7 on bone loss in ovariectomized (OVX) rats, an animal model for oopostmenopausal osteoporosis, has been found [22,23]. OVX rats were given experimental diets containing fermented soybeans (natto including MK-7, 9.4 μg/100 g diet) with or without added MK-7 (37.6 μg/100 g diet) for 77 days [24]. Feeding produced a significant elevation of MK-7 and MK-7 concentrations in the serum of OVX rats [24]. OVX-induced bone loss was prevented after feeding with diets containing natto with MK-7 added (37.6 μg/100 g diet) [22]. Thus, supplementation of MK-7 has been shown to have preventive and restorative effects on bone loss in osteoporosis animal model. This effect may be partly contributed to MK-4 that is formed after degradation of MK-7 in body. Moreover, the effect of prolonged intake of dietary MK-7 on bone loss in OVX rats has been shown [23]. OVX rats were given experimental diets containing natto (including MK-7, 9.4 μg/100 g diet) with or without supplemental MK-7 (containing 14.1 or 18.8 μg/100 g diet) for 150 days [23]. Feeding produced a significant elevation of the serum MK-7 concentration of OVX rats [23]. Serum γ-carboxylated osteocalcin concentration was significantly decreased after OVX. This decrease was prevented after supplementation of MK-7 (18.8 μg/100 g diet) [23]. OVX caused a significant decrease in femoral dry weight, femoral calcium content, and mineral density. These decreases were significantly prevented after supplementation of MK-7 (total, 18.8 μg/100 g diet) [23]. Co-relationship with dietary MK-7 intake and bone formation markers in OVX rats showed a good co-relationship [23]. Thus, prolonged intake of MK-7 has been shown to have preventive and restorative effects on OVX-induced bone loss. MK-7 may be useful in the prevention and treatment of osteoporosis.

Change in circulating MK-7 and γ-carboxylated osteocalcin (Glaosteocalcin) concentrations in normal individuals with the intake of fermented soybean has been demonstrated [24,25]. Forty-eight volunteers (45 men and 3 women) were divided into three groups of 16 volunteers each (15 men and 1 woman), and each group was given sequentially natto (50 g) containing three different amounts of MK-7 once a day for 14 days as follows: either regular natto with MK-7 865 μg/100 g diet of natto, reinforced natto containing MK-7 1295 μg/100 g, or MK-7 1730 μg/100 g [25]. Serum MK-7 was not found in normal individuals who had not eaten natto. Serum MK-7 and γ-carboxylated osteocalcin concentrations were significantly raised 7, 10, and 14 days after the start of the intake of reinforced natto containing MK-7 1295 or 1730 μg/100 g [25]. Serum γ-carboxylated osteocalcin concentration was significantly elevated at 14 days after the intake of natto containing either 1295 or 1730 μg of MK-7/100 g diets as compared with that after regular natto intake [25]. The intake of reinforced natto that contains more MK-7 than regular natto may play a role in the prevention of age-related bone loss.

Moreover, the effect of low-dose MK-7 supplementation on bone health has been shown [26]. Healthy postmenopausal women (n=244) received for 3 years placebo or MK-7 (180 μg MK-7/day) capsules [26], circulating uncarboxylated osteocalcin (ucOC) and carboxylated Oc (cOC) were measured; the ucOC/cOC ratio served as marker of vitamin K status. Measurements occurred at baseline and after 1, 2, and 3 years of treatment. MK-7 intake significantly improved vitamin K status and decreased the age-related decline in bone mineral content and bone mineral density at the lumbar spine and femoral neck, but not at the total hip [26]. Bone strength was also favorably affected by MK-7. MK-7 significantly decreased the loss in vertebral height of the lower thoracic region at the mid-site of the vertebrae. Supplement of MK-7 may help postmenopausal women to prevent bone loss.

Functional food factors may play an important role in the prevention and treatment of bone loss in various disease states including inflammation, obesity, diabetes, bed rest (weightlessness), and cancer cell bone metastasis. Drugs, which are used clinically in the treatment of osteoporosis, are mainly based on the action of osteoclastic bone resorption. Clinical compounds that stimulate bone formation are under development.

There may be intense interest in the identification of additional
anabolic agents. Analogues of functional food chemicals may be developed as novel drugs that reveal potent-osteogenic effects for the treatment of osteolysis. Supplements with chemically pure ingredients of functional food factors, which reveal potential osteogenic effects, will be used as a new biomedical drug for osteoporosis with lower toxicity.

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