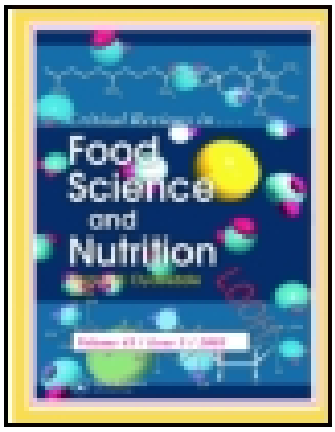

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Effect of the Types of Dietary Fats and Non-dietary Oils on Bone Metabolism

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Effect of the types of dietary fats and non-dietary oils on bone metabolism

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Abstract

Nutrients, beyond calcium and vitamin D have a role on bone health, and in treatment and prevention of osteoporosis. Quality and quantity of dietary fat may have consequences on skeletal health. Diets with highly saturated fat content produce deleterious effects on bone mineralization in growing animals. Conversely, dietary n-3-long chain polyunsaturated fatty acids play an important role in bone metabolism and may help in prevention and treatment of bone disease. Some reports suggest a correlation between the dietary ratio of n-6 and n-3 poly unsaturated fatty acids and bone formation. Specific dietary fatty acids were found to modulate prostanoid synthesis in bone tissue and improve bone formation in both animal and clinical trials. The skeletal benefits of dietary isoprenoids are extremely documented. Higher isoprenoids intakes may relate to higher bone mineral density. Dietary supplements containing fish oil, individual polyunsaturated fatty acids, and isoprenoids could be used as adjuvant with bone medications in osteoportic conditions but their doses must be considered to avoid detrimental effect of over dosages.

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Key words: Bone, saturated fat, polyunsaturated fat, isoprenoids

Introduction

The integrity of the skeleton is maintained by continuous remodeling of bone throughout life. To accommodate this process, a fine balance between bone resorption and bone formation is required. Imbalance in these processes leads to pathological conditions characterized by low or high bone density Osteoporosis is a disease defined by low bone density and loss of structural elements within the bone architecture . The combination of low bone density and loss of structural elements results in a situation where bone may no longer provide adequate mechanical support hormone replacement and bisphosphonates. Besides, recent studies have suggested statins to influence bone turnover by stimulating bone formation (Baba et al., 2013 and Lazzerini et al., 2013). Such conventional drugs have many adverse effects. Therefore, the new strategy to treat osteoporosis and to keep bone health is to use natural products. Diet play an important role in bone health. Serum osteocalcin concentration, the most abundant noncollageous protein in bone, is determined by food intake, food deprivation decreased its level, meanwhile refeeding restored it. This evidence strongly suggests that bone metabolism may be sensitive to changes in food intake (Ndiaye et al., 1992). Dietary fat intake may have consequences on skeletal health (Gunnes and Lehmann, 1995). Diets with highly-saturated fat content can produce deleterious effects on bone mineralization in growing animals (Wohl et al., 1998).

Human studies showed that saturated fatty acid intake may significantly increase hip fracture risk in postmenopausal women (Orchard et al., 2010). Conversely, dietary n-3 long-

chain polyunsaturated fatty acids (PUFA) play an important role on body growth and bone metabolism. Some reports suggest a relation between the dietary ratio of n-6/n-3 PUFA and bone formation (Watkins et al., 2003). Specific dietary fatty acids were found to modulate prostanoid synthesis in bone tissue and improve bone formation rates in animal models (Mollard et al., 2005). Isoprenoids are ubiquitous in fruits, vegetables, and other plant foods. They have been shown to inhibit bone resorption and stimulate bone formation via their influences on guanosine triphosphate-binding proteins (GTPases) (Mo et al., 2012).

Dietary isoprenoids and bone health

Isoprenoids are ubiquitous in fruits, vegetable and other plant food**.** Literature has recorded bone protective actions of the pure isoprenoids, mainly the mono;sesqui- and diterpenes of the isoprenoid family consisting only of multiples of the five-carbon isoprene unit (Elson et al., 1999). The 10-carbon monoterpenes composed of two isoprene units are the main constituents of essential oils and are widely distributed in the plant kingdom .Monoterpenes including borneol, menthol, t-verbenol and perillic acid at physiologically attainable levels (1-100 Dmol/L) inhibit the formation of osteoclasts and their actin ring. Geranylgeraniol and a sesquiterpene farnesol potentiated the anti-osteoclastogenic effect of menthol and perillyl alcohol, broneol and menthol also induced alkaline phosphatase (ALP) expression in osteaoblasts (Dolder et al., 2006). Moreover, dietary essential oils of pine, eucalyptus, sage, juniper, rosemary, and thyme, in descending order of potency, inhibited bone resorption in rats (Muhlbauer et al., 2003). Their monoterpene constituents,when fed in diet individually and in a

blend, showed antiresorption activity as well. Owing to essential oil lipophilic properties, these compounds easily cross cell membranes, and affect bone cell function by stimulating or inhibiting specific molecular pathways. Essential oil isopreniods increase osteoblast proliferation by protein kinase activation and by down-regulation of pro-apototic molecules such as Bax and caspases (Sabbieti

et al., 2011).

Essential oil isoprenoids suppress the pool of mevalonate-derived products (Mo and Elson,2006) for the prenylation of the small guanosine triphosphate binding proteins (GTPases). GTPases regulate the balance between osteoclastogenesis and osteoblastogenesis. The activities of GTPases require post-translational modification with mevalonate-derived prenyl pyro-phosphates. Mevalonate deprivation induced by competitive inhibitors of 3-hyroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase like isoprenoids, prevents the activations of GTPases, suppresses the expression of the receptor for activation of nuclear factor ϐ Kappa ligand and the activation of NF-פB, consequently, inhibits osteoclast differentiation and induces osteoclast apoptosis. In contrast, inactivation of GTPases enhances alkaline phosphatase activity, and the expression of bone morphogenetic protein-2, vascular epithelial growth factor (VEGF) and osteocalcin in osteoblasts and induces osteoblast proliferation and differentiation (Mo et al.,2012). Those actions of isoprenoids resonate with the association between intake of fruits and vegetables and increased bone mineral density and reduced bone fracture (Lanham-New, 2006). Also, those data delineate a positive function of essential oils on osteoblast metabolism, suggesting its possible use as a dietetic integrator in the prevention or in the therapy of pathologies resulting from impaired bone remodeling.

Tocotrienols are isoprenoid subclass that have farnesyl moiety derived from the mevalonate pathway. Tocotrienol have a wide presence in plant foods including avocads , bananas, cabbage, onion, peaches, cereals, wheat and olive. Oils from barely, oats, palms and rice bran are good sources of tocotrienols (Nesaretnam, 2008). Tocotrienols strongly down regulate HMG-Co reductase. Thus protecting bone from resorption. Besides, they inhibit lipopolysaccharide (LPS) induced expression of cyclooxygenase (COX-2), PGE2, interleukin-6, and tumor necrosis factor Ŭ in rat cells (Yam et al., 2009). Similarly, tocotrienols suppress LPS-induced nitric oxide synthase, COX-2 and NF.əƀ expression in human cells (Wu et al., 2008). Furthermore , animal studies suggest that tocotrienols offer bone protection. They restore free radical induced reduction in the serum level of osteocalcin, the number of osteoblasts, and bone formation in rats while reducing the level of bone-resorbing cytokines (Ahmad et al., 2005). Tocotrienols counteracted nicotine effect on bone resorption in rats (Hermizi et al., 2009)

High fat diet and bone health

Macri et al. (2012) have tested the effects of high fat diet (20% W/W) containing either: soybean oil, corn oil (CO), linseed oil (LO) or beef tallow (BT) against control fed 7% W/W soybean oil on bone metabolism in growing rats. They documented that rats fed the BT diet had lower total skeleton body mineral content (BMC), similar BMC/W (BMC related to body weight), total skeleton body mineral density(BMD), and spine BMD but higher total-alkaline phosphatase (t-AP) as compared with those consuming high-fat vegetable oils diets. However, BT group had a similar bone volume % (BV%) as compared with the CO group. BT group showed significantly

diminished total skeleton BMC, BMC/W, spine BMD and the BV% as compared to control group (7% W/W soybean oil). BT appeared to impair bone health in growing animals. The bone mineral alterations may be the result of the formation of intestinal soaps with calcium that reduce its absorption (Moussavi et al., 2008). There may also be alterations of membrane fluidity that diminish calcium uptake by brush border membrane vesicles, reducing mineral content (Mailhot et al., 2010). Studies performed in vitro showed that saturated fatty acids promoted osteoclast survival by preventing apoptosis (Oh et al., 2010). Meanwhile, no significant differences among rats fed high-fat vegetable oil diets were found. The absence of differences of bone formation or resorption between those high-fat vegetable oil diets would be due to the fulfillments of the requirements of n-6 and n-3 fatty acids by each one of those diets. Healthy growing rats were not susceptible to n-6/n-3 fatty acids ratios, whereas the response would be different in animals with skeletal bone disorders (Watkins et al., 2001).

On contrast, Costa et al.(2011) have documented that feeding high-fat diet containing soybean oil (19% W/W) or canola oil (19% W/W) to growing rats extremely enhanced bone measurements. Both fats produced a higher femur mass and a higher lumbar vertebrae mass and length as compared to control. Canola group had more radiodensity in the proximal femoral epiphysis and lumbar vertebrae compared to control and high soybean oil groups.

On the other hand, Halade et al.(2010) chronically fed a high fat diet to aged mice and documented that mice exhibited increased body weight, total body fat mass, abdominal fat mass, and reduced bone mineral density in different skeletal sites which was accompanied by increased bone marrow (BM) adiposity, up regulation of peroxisome proliferator-activated receptor ɔ (PPAR- ɔ), the dominant regulator of adipogenesis, (Rosen and Bouxein, 2006) cathepsin K

(ctsk) and increased proinflammatory cytokines in bone marrow. It has been reported that interleukin-6 (IL-6 and) and tumor necrosis factor- Ŭ (TNF-Ŭ) stimulates osteoclastogenensis (Kitaura et al., 2004) and these are generally recognized as osteoresorptive factors. Also, ctsk is the most abundantly expressed cysteine protease in the osteoclasts (Saftig et al., 1998) and is believed to be a tool in bone matrix degradation necessary for bone resorption. This indicates that the observed bone loss in this model may be due to increased osteoclasts. Higher levels of ɤ -6 fatty acids in diets activate PPAR- ɔ expression in BM cells which contributes to fatty bone formation and inhibits osteogenesis. This effect is reasonable since adipocytes and osteoblasts originates from a common progenitor mesenchymal stem cells (MSCS) (Rosen and Bouxein, 2006).

ω3 polyunsaturated fatty acids (PUFAs) and bone health

Essential omega-3 fatty acids are polyunsaturated fatty acids including; Ŭ-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). There are several sources of omega 3 fatty acids including fish, eggs, walnuts, and flaxseed. ɤ 3 fatty acids are now generally recognized as potential key nutrients to prevent the pathological conditions associated with the aging process (Ubeda et al., 2012). Recently, ɤ 3 polyunsaturated fatty acids (PUFAs) and bone health have received considerable attention for their favorable role in some inflammatory diseases, including bone disorders. Orchard et al. (2013) have showed that higher red blood cell ALA, as well as, EPA and total n-3-PUFAs may predict lower hip fracture risk in postmenopausal women.

Flaxseed oil is rich in n3 Ŭ-ALA a metabolic precursor of EPA and DHA and contains only trace amounts legman. It has a low n6:n3 ratio of å 1:3.8. Soybean oil has a higher n-3 fatty acid content and is the only single fat source that gives an adequate amount and balance of n-3 and n-6 essential fatty acids (Reeves et al., 1993). Although both EPA and DHA suppress the immune system and the production of proinflammatory cytokines (Watkins et al., 2003), EPA but not DHA is a precursor for the production of anti-inflammatory eicosanoids (Watkins et al., 2001). Recently, in vivo study confirmed that bone is sensitive to changes in the omega-6 (n-6) to n-3 fatty acids dietary ratio (Li et al.,2003). A 50% reduction in the n-6:n-3 ratio from 9:1 to 4.5:1 using flaxseed oil does not alter growth or bone mass in piglets over 21 days (Weiler and Fitzapatrick-Wong, 2002). Therefore, addition of flaxseed or its oil appears to confer benefit to body composition without adverse effects on growth or bone mass in animals. Flaxseeds oil given to weanling rats, resulted in 5.1% higher BMC in males and 2.2 % higher BMC in females compared to the corn oil group. While, higher values of BMD (3.1%) were only observed for males. Femur BMD was also higher in females (Weiler et al., 2007). In healthy adult humans, ALA rich diets delivered by adding flaxseed oil (FO) and walnuts significantly decreased Ntelopeptides of type 1 collagen (NTx) levels (a bone resorption marker) and maintained bonespecific alkaline phosphatase activity (Griel et al., 2007). Lower linoleic acid (LA):ALA ratios to elderly developed by flaxseed oil (FO) supplementation were positively related to hip BMD (Weiss et al., 2005). During resistance training, older adults showed significantly higher hip BMD and BMC in both flaxseed oil and placebo groups indicating that flaxseed oil had no benefits compared with placebo (Cornish and Chilibeck, 2009). Meanwhile, feeding diets supplemented with ɤ-3 ALA significantly improved skeletal health in laying hens and

biochemical evidence suggests that increased bone turnover has enhanced the bone mechanical properties (Tarlton etal., 2013). In growing mice, feeding FO increased ɤ -3 PUFA and decreased ɤ -6 PUFA levels in plasma, but did not influence BMD, BMC, bone strength, and serum proinflammatory cytokines (Cohen and Ward, 2005). Similar results were observed in growing gilts (Farmer et al., 2007). While, in rapidly growing male piglets, diet high in FO resulted in higher DHA levels in the plasma and brain which highly correlated with lower uniary NTx levels indicating reduced bone resorption (Weiler and Fitzpatrick-Wong, 2002). Long term (42 wk) feeding of FO-rich diets (20% FO) increased bone strength and femoral ɤ -3PUFA levels in mature male rats (Lau et al., 2010). Adult female rats fed FO-rich diets during their perinatal period showed higher BMD than rats fed w-6 PUFA-rich diets, suggesting the influence of FO on bone early in life (Korotkova et al., 2004).Osteoporotic bone features may be partly mitigated by consuming diet rich in FO possibly by inhibiting bone resorption (Boulbaroud et al., 2008). In this context, in postmenopausal animal models, flaxseed supplementation consistently showed improved bone features so that it appeared to offer added benefits to bone over the estrogen therapy alone, implying a possible use of flaxseeds for postmenopausal women who were receiving estrogen (Sacco et al., 2009).

Inflammatory bowel disease (IBD) is characterized by uncontrolled production of the proinflammatory cytokines that stimulate osteoclastogenesis in adults (Habtezion et al., 2002) and children (Thearle et al., 2000). Dietary intervention with FO (10%) results in modest improvements in bone outcomes in mice with IBD (Cohen et al., 2005).

The impact of fish oil on bone metabolism has been investigated in numerous animal models including mice (Sun et al., 2003), rats (Trebble, 2005), chicks (Watkins et al., 1997), rabbits

(Judex et al., 2000) and piglets (Weiler and Fitzpatrick-Wong 2002). High consumption of fish Ó 3 servings/wk relative to lower intakes were associated with maintenance of BMD in men and women (Farina et al., 2011). Also, fish oil, a rich source of EPA, has been used to modulate the dietary omega 6: omega 3 ratio with the aim to reduce intestinal inflammation, treat IBD and subsequently improves bone alterations associated with this disease (Nieto et al., 2002). The intakes of soy isoflavone and/or fish oil might have ameliorating effects on bone loss due to ovariectomy (OVX) in mice (Uchida et al., 2011). Sun et al., (2004) reported that growing mice fed 5% fish oil for 3 months before being ovariectomized resulted in reduced OVX-induced BMD loss. By contrast, high dose (1gm/kg body weight) of EPA for ovariectomized -rats for 9 weeks, exacerbated the effects of ovariectomy on BMD. While low dose (0.1gm/kg body weight) showed non significant effects on bone (Poulsen and Kruger, 2006). Also, Judex et al. (2000) reported a detrimental effect of high-dose fish oil (10% of diet) on bone in growing rabbits. Therefore the quantity of either fish oil or its individual fatty acid must be adjusted.

Combination of conjugated linoleic acid (CLA) with fish oil prevented age-associated bone marrow adiposity, improved insulin sensitivity, reduced inflammation and oxidative stress, improved BMD, down-regulated genes involved in osteoclastogenesis, as well as, osteotropic factors (TNF-Ű, IL-6). Furthermore, CLA and fish oil induced the production of potent antiinflammatory, antisteatotic, insulin-sensitizing adipokine, adiponectin (Halade et al., 2011).Moreover, fish oil potentiates the positive influence of inulin-type fructans on mineral bioavailability in growing rats. Soybean oil failed to exert such effect (Lobo et al., 2009). Feeding growing rats with tuna oil diets (12% w/w) had a positive effect on the long bones (Lukas et al., 2011). Tuna oil is the richest fish oil source of DHA that may promote bone growth

by activating osteoblasts in the periosteum. In a human study, adolescent males showed positive correlations of serum DHA and ɤ-3 PUFA concentrations to total body BMD suggesting that consumption of ɤ -3 PUFAs, especially DHA, increased bone mass during growth (Hogstrom et al., 2007).

Reported mechanisms of action of dietary ɤ-3 PUFAs on bone include alterations in Ca absorption, osteoblast differentiation, lipid oxidation, eicosanoid production, inflammation (Salari et al., 2008) and gene expression (Rahman et al., 2008). Kruger and Schollum (2005) reported that young rats fed a diet supplement with 5% tuna oil had a higher Ca absorption, reduced urinary Ca excretion, and increased bone Ca. The enhanced Ca absorption may be due to ɤ-3 PUFAs increasing cell membrane unsaturation. In terms of human intervention studies, one investigation observed an increase in calcium clearance, serum calcium, and serum bone formation markers in older postmenopausal osteoporotic women who supplemented with fish oil for 16 weeks (vanPapendorp et al., 1995). Also, older osteoporotic women who were fed a gamma-linoleic acid (GLA) and EPA enriched diet for 36 months found a significant increase in lumbar BMD (Kruger et al., 1998). In vitro studies have shown a positive effect of EPA in promoting the accumulation of Ca in cultured osteoblasts. In vivo, EPA supplementation (0.15 g/kg) completely negated the reduction in bone weight resulting from ovariectomy in rats fed a low calcium diet but had no effect when administered in conjuction with a high calcium diet (Sakaguchi et al., 1994). EPA has previously been implicated as modulators of vitamin D levels and/or activity in humans (Baggio et al., 2000). Vitamin D levels become particularly important in determining the balance between bone formation and resorption when dietary calcium supply is limited as in the study of Sakaguchi et al. (1994). According to Poulsen et al.(2007), ɤ-3

PAUFs promotes bone formation by preventing formation of products that inhibit osteoblastogenesis such as lipid peroxidation. Peroxidation of membrane lipids results in decreased membrane fluidity and depolarization (Lu et al., 2001). Also, free radicals formed during lipid peroxidation have been shown to inhibit the function of membrane-associated proteins, such as Ca2+-ATPase (Xu et al., 1997).If intestinal Ca2+ATPase is inhibited, dietary calcium absorption will be decreased. Rats fed tuna oil or salmon oil showed reduced lipid oxidation compared to rats fed corn oil (Lukas et al., 2011). Increased oxidative stress has been suggested to be detrimental to bone by promoting the formation of pro-inflammatory prostaglandinge E2 (PGE2). High PGE2 leads to an uncoupling of bone remodeling in favor of bone resorption (McLean, 2009). Salmon oil is high in EPA that competes with the ɤ -6 PUFA,arachidonic acid(AA),for enzymes involved in PGE2 synthesis. This competitive inhibition of AA by EPA could benefit bone health by reducing PGE2 .

NF-KappaB is a transcriptional activator of many genes, including some that lead to bone resorption. ɤ -3 fatty acids decrease the activation of receptor activator of NF-Kappa B ligand on T cells (Fernandes et al., 2003), thus inhibiting bone resorption. DHA may be much more effective than EPA in alleviating RANKL-induced bone resorption (Rahman et al., 2008). Moreover, oxidized DHA, which is a putative metabolite of DHA, is a ligand for peroxisome proliferator activated receptor gamma (PPAR gamma). PPAR gamma regulates the expression of numerous genes including those for bones turnover (Itoh andYamamoto,2008).Furthermore, fish oil in combination with CLA down regulated ctsk gene which is abundant in osteoclast and plays a vital role in bone resorption (Halade et al., 2011). Moreover, EPA (along with other n-3 PUFAs) inhibits gene expression of the prostaglandin-synthesizing enzyme, COX-2 (Achard et

al., 1997). Low concentrations of prostaglandins promote bone formation, whilst at high levels they have a catabolic effect on bone (Raisz et al., 1993).

Conclusion

Skeleton health is dependent on various nutrients beyond calcium and vitamin D. The amount and source of fat in the diet have differential effects on bone. It is possible that a lower ratio of omega-6 to omega-3 fatty acids may be positively associated with bone health. It would be better to obtain these fatty acids from their dietary sources not as dietary supplements as overdose of those acids has detrimental effects. There is a number of metabolic pathways by which fatty acids can influence bone health including calcium absorption, hormonal changes, gene expression, lipid peroxidation and eicosanoid production. On the other hand, consumption of fruits, vegetables and some herbs is associated with greater bone mineral density and inhibited bone resorption. Such effects on bone are exerted, in part by isoprenoidsô content in these dietary components. Generally, nutrient rich diet with adequate fish oil, fruit, vegetable and herbs will improve bone health especially in children, postmenopausal women, aged persons and in various osteoporetic conditions. However, this dietary intervention will not replace medications .

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