Beneficial Effect of Omega-3 Fatty Acids on Bone Metabolism

To the Editor:

Over the past several years, interest has increased in the effect of consumption of dietary fish oil. Beneficial effects of omega-3 polyunsaturated fatty acids on bone metabolism have been described. A common recommendation for the general population is to consume at least 2 weekly portions of fatty fish.

Nutritionally important omega-3 fatty acids include alpha-linolenic acid, eicosapentaenoic acid, and docosahexaenoic acid, all of which are polyunsaturated. The human body cannot synthesize omega-3 fatty acids de novo, but it can form eicosapentaenoic acid and docosahexaenoic acid from alpha-linolenic acid. These conversions occur competitively with omega-6 fatty acids, which are closely related chemical analogues derived from alpha-linolenic acid. The synthesis of omega-3 fatty acids from alpha-linolenic acid within the body is slowed by the omega-6 analogues.

Modern Western diets typically have ratios of omega-6 to omega-3 in excess of 10 to 1; the optimal ratio is thought to be 4 to 1 or lower. The higher omega-6/omega-3 ratio in dietary oils has been implicated in causing osteoporosis.

Studies have shown a beneficial effect of omega-3 fatty acids on bone mineral density. Sham and ovariectomized mice were fed diets containing 5% corn oil or 5% fish oil. Significantly increased bone mineral density loss was observed in the ovariectomized mice fed corn oil, whereas mice fed fish oil were significantly less osteoporotic. Omega-3 fatty acids added in vitro caused a significant decrease in osteoclastic tartrate-resistant acid phosphatase activity in bone marrow cells compared with omega-6 fatty acids. Omega-3 fatty acids also inhibited bone marrow macrophage nuclear factor kappa B activation induced by the receptor activator of nuclear factor kappa B ligand in vivo.

In regard to bone formation, supplementing the diets of growing rats with omega-3 fatty acids results in greater bone formation in rats. Omega-3 fatty acids also increased alkaline phosphatase activity in osteoblastic cells in culture.

An additional study used the fat-1 mouse, a transgenic model that synthesizes omega-3 fatty acids from omega-6 fatty acids to directly determine whether the outcome of bone health was correlated with omega-3 fatty acids. Fat-1 ovariectomized mice exhibited significantly lower levels of receptor activator of nuclear factor kappa B ligand and tartrate-resistant acid phosphatase in their serum and higher bone mineral density than ovariectomized controls.

The fat-1 mouse was also used in a study to determine whether the fat-1 gene modulates the fatty acid composition of bone phospholipids. The authors concluded that dietary fatty acid incorporation into bone alters its metabolism through changes in the fatty acid composition of membrane phospholipids. Alteration of the membrane phospholipid fatty acid composition was thought to influence bone cell signaling and bone mineralization.

A more recent study evaluated whether a diet enriched in eicosapentaenoic or docosahexaenoic acid for the entire adult life of mice could improve bone microstructure and strength. Eicosapentaenoic acid reduced the age-related decline in osteocalcin and increased leptin and insulin-like growth factor-1 levels. These data indicate that the long-term intake of omega-3 fatty acids may improve cortical bone properties by an increase in leptin and insulin-like growth factor-1 levels.

Several studies have been performed on humans. One evaluated the effect of omega-3 fatty acids on bone biomarkers in osteoporotic postmenopausal women ingesting 900 mg of omega-3 fatty acids per day for 6 months. Although omega-3 fatty acids decreased bone resorption, they did not significantly affect bone formation. In another study, 39 patients received docosahexaenoic and eicosapentaenoic acid supplements for 1 year. Bone formation biomarkers improved significantly.

The fracture rate in postmenopausal women enrolled in the Women’s Health Initiative (N=137,486) was recently measured. Fatty acid intake was estimated from baseline food-frequency questionnaires and analyzed statistically. Although saturated fatty acid intake was significantly increased hip fracture risk, higher consumption of marine omega-3 fatty acids was, unexpectedly, also associated with a greater total fracture rate.

Omega-3 fatty acids have also been observed to suppress breast cancer cell metastasis to bone in mice by preventing the formation of osteolytic lesions. Docosahexaenoic and eicosapentaenoic acid significantly inhibited the expression of prometastatic protein and mRNA by a transcriptional mechanism.

Together, the available evidence shows that increased daily intake of dietary omega-3 fatty acids protects against postmenopausal bone loss. A higher dietary omega-3/omega-6 fatty acid ratio is associated with beneficial effects on bone health.
Association of Low-energy Femoral Shaft Fractures and Bisphosphonate Use

To the Editor:

I read the article “Association of Low-energy Femoral Shaft Fractures and Bisphosphonate Use” by Fowler and Craig published in January 2012 with great interest. I congratulate the authors on performing a well-designed study and would like to clarify a few points in the study.

Two different groups of femoral shaft fractures, the bisphosphonates group and the nonbisphosphonate group, were compared. The authors observed the radiographic finding of simple, transverse shaft fractures with lateral cortical thickening in patients on chronic bisphosphonates therapy (bisphosphonate group). However this finding is typical to the atypical femoral fracture defined by Shane et al. They described 2 groups in atypical femoral fracture or low-energy femoral shaft fracture: the bisphosphonates use atypical femora fracture group and the nonbisphosphonates use atypical fracture group. Therefore, the radiographic findings of nonbisphosphonates use atypical fracture are the same. The fracture patterns in 3 of 66 patients in the nonbisphosphate group were simple and transverse in nature, but the authors did not describe the lateral cortical thickening. I think that Shane et al might have observed that thickening in these 3 patients consistent with atypical fractures. Also, it would be interesting to see whether a difference exists in the clinical course between the bisphosphonates use atypical femoral fracture group and the nonbisphosphonate use atypical femoral fracture group.

REFERENCES


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Role of Endostatin in Orthopedics

To the Editor:

Endostatin is a C-terminal proteolytic fragment of collagen XVIII that is localized in the vascular and epithelial basement membrane zones of various organs. Endostatin is an endogenous inhibitor of angiogenesis. The antiangiogenic activity of endostatin results from the localized inhibition of vascular tube formation at areas of neoangiogenesis, with subsequent regression of vessels. Proteolytic degradation of the subendothelial basement membrane releases antiangiogenic fragments of basement membrane.
membrane components, such as endostatin, in areas of induced angiogenesis that would oppose the induced vascular outgrowth via a negative effect on vessel growth.\textsuperscript{3} The C-terminal portion of collagen XVIII’s protease-sensitive hinge region evolved as a sensor of proteolytic activity, such as what occurs during tumor invasion.\textsuperscript{4}

The most promising orthopedic indications over the next 5 to 10 years pertain to endostatin’s use as an anticancer agent. Unlike chemotherapy drugs, endostatin has virtually no toxicity because it acts only on the endothelial cells that line blood vessels without harming other cells. Moreover, cancers do not become resistant to endostatin, a common problem with chemotherapy, because endothelial cells divide slowly, making them unlikely to acquire mutations that confer resistance. However, endostatin is expensive to manufacture.

Endostatin has undergone phase I, II, and III clinical trials. Phase I trials showed that the drug was safe and well tolerated.\textsuperscript{5} In a phase II clinical trial of endostatin, 42 patients with pancreatic endocrine tumors or carcinoid were treated.\textsuperscript{6} In a phase III clinical trial, the addition of endostatin to the standard chemotherapeutic regimen in patients with lung cancer resulted in significant and clinically meaningful improvement in response rate, median time to progression, and clinical benefit rate compared with the chemotherapeutic regimen alone.\textsuperscript{7}

Unlike cytotoxic treatments, which offer measurable effects on tumor kill, endostatin affects cancer in ways that are hard to determine in patients with advanced cancers (who are the most frequent candidates for clinical trials). This makes it hard to show that endostatin may be best used in early disease, perhaps as a long-term maintenance therapy.

**Osteosarcoma**

Endostatin has prevented the postoperative progression of pulmonary metastases in osteosarcoma.\textsuperscript{8} Patients with osteosarcoma who have progression of pulmonary metastases experience an up-regulation of systemic angiogenic activity. The number and size of pulmonary metastases was smaller in mice injected with endostatin than in controls.\textsuperscript{9} Although this therapeutic strategy cannot provide a cure for osteosarcoma, it should enable osteosarcoma patients to coexist with dormant pulmonary metastases and lead to an improvement in their prognosis.\textsuperscript{8}

**Multiple Myeloma**

Disease progression in multiple myeloma is characterized by increasing bone marrow neovascularization.\textsuperscript{9} Targeting the mechanisms that control angiogenesis could represent an innovative therapeutic approach to multiple myeloma and has had a synergistic effect when combined with conventional chemotherapy.\textsuperscript{9}

**Rheumatoid Arthritis**

Rheumatoid arthritis (RA) is closely linked to angiogenesis.\textsuperscript{10} The neoangiogenesis condition of cancer is essentially identical to that of RA; therefore, endostatin is a potential treatment for RA. The formation of new blood vessels permits a supply of nutrients and oxygen to the proliferating synovial cells and augmented inflammatory cell mass in RA.\textsuperscript{11} The rheumatoid pannus, the site of inflammation and joint destruction in the rheumatoid synovium, relies on the development of new vasculature to sustain its growth.\textsuperscript{12} Angiogenesis is an attractive target in treating RA.

The number of inflammatory cells and synovial volume was significantly decreased by endostatin administration into mice with RA.\textsuperscript{13} In another study, endostatin inhibited pannus formation and bone destruction in mice with RA.\textsuperscript{14} In a further study, the number of new blood vessels in synovial tissue in rats with RA was reduced after treatment with endostatin.\textsuperscript{11}

**Osteoarthritis**

The effect of endostatin on articular chondrocytes has also been studied.\textsuperscript{15} Endostatin promoted chondrocyte adhesion, spreading, and proliferation in rabbits. In cultured chondrocytes, endostatin was observed to up-regulate collagen II and XVIII, while down-regulating collagen I and MMP9, markers of osteoarthritis. These findings indicate that endostatin is a homeostatic factor in cartilage metabolism. Endostatin is involved in the maintenance of the avascular tissue of the skeletal system.\textsuperscript{16}

**Growth and Deformity**

Endostatin inhibits endochondral ossification.\textsuperscript{17} Angiogenesis is essential for the replacement of cartilage by bone during skeletal growth and regeneration. Endostatin has prevented the formation of cartilage resorbing osteoclasts in mice.\textsuperscript{18} Endostatin reduces bone formation by retarding the cartilage phase of endochondral ossification. Bone growth and healing are regulated by endostatin.\textsuperscript{17}

Therefore, endostatin may be useful in controlling bone overgrowth or deformity. Bioengineers consider the use of endostatin a promising strategy of bone growth management, such as in the case of condylar overgrowth in temporomandibular deformity and dysfunction.\textsuperscript{18} Perhaps endostatin could play a role in the treatment of conditions such as hemihypertrophy or gigantism.

**Flexor Tendon Laceration**

Range of motion after flexor tendon repair is often diminished by the ingrowth of new blood vessels from the sheath on the repair site, which interfere with gliding. The use of endostatin may diminish neovascularization in this setting and contribute to improved outcomes.
Osteoporosis

Endostatin has reduced osteoclastic bone resorption. In addition, endostatin inhibited osteoclastogenesis and osteoclast differentiation in rats.

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