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Is Nitroglycerin a Novel and Inexpensive Treatment for Osteoporosis?

Sundeep Khosla, MD

College of Medicine, Mayo Clinic, Rochester, Minnesota

Current Food and Drug Administration–approved medications in the United States for prevention or treatment of osteoporosis fall into 1 of 2 categories. The first includes antiresorptive drugs, which inhibit bone resorption, with a subsequent reduction in coupled bone formation. These drugs increase bone mineral density (BMD), but this is due largely to refilling of bone remodeling cavities and an increase in mineralization density. There is no evidence that any of these agents lead to deposition of new bone. Antiresorptive drugs include the bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), a selective estrogen receptor modulator (raloxifene), estrogen, calcitonin, and a monoclonal antibody against receptor activator of nuclear factor- κ B ligand (denosumab). The second category includes formation-stimulating drugs, of which teriparatide is the only member.¹ Teriparatide stimulates new bone formation and thus has the potential to reverse (rather than just prevent) bone loss. However, with the exceptions of generic alendronate and estrogen, all of these therapies, particularly teriparatide, are relatively expensive.

Thus, the prospect of an inexpensive drug that both inhibits bone resorption and stimulates bone formation has tremendous appeal. Previous research, along with the findings reported by Jamal and colleagues² in this issue of *JAMA*, suggest that nitroglycerin may be just such a drug and may have the potential to become a novel therapeutic option for the treatment of osteoporosis.

Organic nitrates, such as nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate, are known donors of nitric oxide, which causes vasodilatation of coronary vessels and reduces cardiac workload.³ In addition, in vitro and animal data have demonstrated that nitric oxide has beneficial effects on bone metabolism.⁴ Nitric oxide donors have been shown to decrease bone resorption in vitro by reducing osteoclast numbers and activity,⁵ and also have been shown to increase osteoblast cell proliferation, osteocalcin synthesis, and in vitro mineralization by osteoblastic cells.⁴ The effects of nitric oxide on bone appear to be dose-dependent—high concentrations are detrimental to bone by enhancing osteoclastic bone resorption, inhibiting osteoblast proliferation, and increasing osteoblast apoptosis.⁴

At least part of the protective skeletal effect of estrogen appears to be mediated by the nitric oxide pathway.⁴ Consistent with this, Wimalawansa et al⁶ demonstrated that dermal application of nitroglycerin ointment was able to prevent ovariectomy-induced bone loss in rats. These investigators subsequently found that, as suggested by the in vitro data indicating possible biphasic effects of nitroglycerin on bone, once-daily administration of nitroglycerin

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Corresponding Author: Sundeep Khosla, MD, Endocrine Research Unit, Guggenheim 7-11, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (khosla.sundeep@mayo.edu).

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ointment prevented ovariectomy-induced bone loss, whereas more frequent administration (2 or 3 times daily) was less effective.⁷

Consistent with the in vitro and animal findings, several epidemiological studies have provided evidence for a protective association between nitrates and bone.^{8,9} In the largest of these studies, Rejnmark et al⁹ examined nitrate use in 124 655 individuals who sustained a fracture vs 373 963 age- and sex-matched controls. After adjustment for possible confounders, the use of nitrates was associated with an 11% reduction in the risk of any fracture (odds ratio [OR], 0.89; 95% confidence interval [CI], 0.86–0.92) and a 15% reduction in the risk of hip fracture (OR, 0.85; 95% CI, 0.79–0.92).

Despite the compelling in vitro and animal data as well as supportive epidemiological data, direct evidence for a beneficial effect of nitric oxide donors for preventing bone loss has been conflicting. In an open-label pilot study, Wimalawansa¹⁰ randomized young premenopausal women undergoing oophorectomy to receive either standard hormone therapy (0.625 mg/d of conjugated equine estrogens) or 15 mg/d of nitroglycerin ointment for 12 months (n=8 per group). The primary outcome measures of BMD by dual-energy radiograph absorptiometry at the spine and hip were no different between groups, suggesting that nitroglycerin therapy was as effective as estrogen in preventing bone loss. Although levels of the bone resorption marker, urine *N*-telopeptide of type 1 collagen, decreased following both estrogen and nitroglycerin treatment, levels of the bone formation markers, serum osteocalcin and bone-specific alkaline phosphatase, decreased following estrogen therapy but increased following nitroglycerin treatment. These findings demonstrated possible beneficial effects of nitroglycerin on bone in humans and suggested, consistent with in vitro findings, nitric oxide donors may have dual beneficial effects on bone by inhibiting bone resorption and stimulating bone formation.

In contrast with these findings, a subsequent, larger study by the same group of investigators showed no benefit of transdermal nitroglycerin in preventing bone loss in early postmenopausal women.¹¹ In this 3-year, randomized, double-blind, placebo-controlled clinical trial, 186 postmenopausal women (mean age, 56 years) were randomized to receive placebo or nitroglycerin ointment (22.5 mg/d). After 36 months of therapy, changes in BMD at multiple sites did not differ between the groups. Due to the significant incidence of headaches related to nitroglycerin treatment, adherence was suboptimal in this study (estimated at approximately 70%), perhaps contributing to the negative findings.

The study by Jamal et al² in this issue of *JAMA* provides additional data suggesting modest beneficial effects of nitrates on bone in postmenopausal women. This study enrolled 243 postmenopausal women (mean age, 62 years) with lumbar spine T scores between 0 and –2.0 who completed a 1-week run-in period using nitroglycerin ointment (15 mg/d). At 24 months, 118 of 126 women in the nitroglycerin group and 111 of 117 women in the placebo group completed all of the assessments. Adherence, judged by monthly telephone calls, was high among women who completed the trial.

At 24 months, spine and femoral neck BMD by dual-energy radiograph absorptiometry increased by approximately 7% in the nitroglycerin-treated group compared with the placebo group (ie, an absolute BMD increase at the spine from 1.05 g/cm² at baseline to 1.14 g/cm² at 24 months in the nitroglycerin group vs an increase in BMD from 1.06 g/cm² to 1.08 g/cm² in the placebo group). Cortical bone parameters at the radius and tibia, assessed using peripheral quantitative computed tomography, also showed improvements in women treated with nitroglycerin (eg, 14% and 25% increases relative to placebo in cortical thickness at the radius and tibia, respectively). These changes in cortical bone parameters are greater than those observed with the current antiresorptive medications or teriparatide.

Consistent with the earlier work of Wimalawansa,¹⁰ Jamal et al also reported that the bone resorption marker, urine *N*-telopeptide, decreased by 54%, whereas the bone formation marker, bone-specific alkaline phosphatase, increased by 35% in women treated with nitroglycerin.

Although these data suggest that nitroglycerin therapy may have the potential to reduce fractures (largely dependent on the effects on cortical bone),¹² the study by Jamal et al² was underpowered to assess fracture risk, with only 2 fractures in both the nitroglycerin and placebo groups. In addition, headaches were more frequent among women receiving nitroglycerin, although the incidence of this adverse reaction decreased significantly over time. There was 1 death in the nitroglycerin group due to stroke, with the authors reporting that other serious adverse effects were comparable between the 2 treatment groups. However, the authors did not report data on blood pressure changes associated with nitroglycerin treatment.

Despite the differences in the results of the study by Jamal et al² compared with the largely negative study by Wimalawansa et al,¹¹ the findings reported by Jamal et al² should set the stage for an adequately powered, larger study using nitroglycerin ointment with fracture as an outcome. If such a study demonstrates efficacy for reducing fractures, clinicians would have a novel and inexpensive therapy for osteoporosis. The findings of the current study also should prompt development of additional nitric oxide donors with greater skeletal efficacy and a better adverse effect profile, particularly with regard to headaches.

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