

# Bisphosphonates May Spur AF via Inflammation

BY NANCY WALSH  
New York Bureau

MONT TREMBLANT, QUE. — An inflammatory mechanism may be responsible for the atrial fibrillation that occurs in some patients following the intravenous administration of potent bisphosphonates, Dr. Jason Roberts reported in a poster session at the annual meeting of the Canadian Rheumatology Association.

In a pivotal trial of once-yearly zoledronic acid for the prevention of postmenopausal osteoporosis that randomized 7,765 women to annual infusions of active drug or placebo for 3 years, serious atrial fibrillation (AF) was seen in 1.3% of women in the zoledronic acid group compared with 0.5% of those in the placebo group.

This difference was statistically significant (N. Engl. J. Med. 2007;356:1809-22).

A letter accompanying the published study noted that a similar but nonsignificant trend had been observed in an earlier trial of alendronate. The letter stated, "Parenteral administration of bisphosphonates stimulates the release of inflammatory cytokines and increased levels of inflammatory cytokines have been associated with an increased risk of

atrial fibrillation" (N. Engl. J. Med. 2007; 356:1895-6).

To explore a potential connection between bisphosphonate administration and AF, a comprehensive literature review was undertaken and yielded certain mechanistic insights, according to Dr. Roberts of the University of Toronto.

"AF, once thought to be an electrical problem, is increasingly being viewed as an inflammatory condition associated with important structural changes," Dr. Roberts wrote.

Patients with AF have increased levels of inflammatory markers including interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and C-reactive protein. Atrial biopsies consistently show inflammatory changes, including myocyte necrosis and fibrosis.

The principal action of bisphosphonates is inhibition of osteoclastic bone resorption, but the potent nitrogen-containing aminobisphosphonates such as zoledronic acid, alendronate, pamidronate, risedronate, and ibandronate also have proinflammatory effects, with an acute phase reaction characterized by fever and flulike symptoms occurring following a first treatment with these drugs in more than one-third of patients (Clin. Exp. Immunol. 2005;139:101-11).

This response reflects the activation and proliferation of a subset of T cells referred to as gamma-delta T cells, according to Dr. Roberts.

Another effect of aminobisphosphonates is the inhibition of farnesyl pyrophosphate synthase (FPPS), a key enzyme in the mevalonate pathway, which is the biosynthetic route for the production of cholesterol (Ann. N.Y. Acad. Sci. 2006;1068:367-401).

Inhibition of FPPS results in accumulation of upstream metabolites including isopentenyl-5-pyrophosphate, which, like the aminobisphosphonates, directly activate gamma-delta T cells.

"Interestingly, statins, which inhibit an enzyme further upstream of IPP in the mevalonate pathway, have been shown to negate the proinflammatory effects of aminobisphosphonates," Dr. Roberts wrote.

Given the observations that aminobisphosphonates have proinflammatory effects and that AF is an inflammatory condition, it is "reasonable" to postulate that aminobisphosphonates may increase the risk of AF through an inflammatory mechanism mediated via the mevalonate pathway, he noted.

If this turns out to be the case, the proinflammatory state associated with AF

potentially could be prevented by statin therapy, he wrote.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers also have shown promise in modulating these inflammatory effects, although neither of these drugs nor any of the statins are currently recommended for the sole purpose of preventing AF (J. Am. Coll. Cardiol. 2007;50:2021-8).

## Atrial Fibrillation May Be Linked With Bisphosphonates



Note: Based on a randomized 3-year study of 7,765 women.  
Source: Dr. Roberts

ELSEVIER GLOBAL MEDICAL NEWS

## Ultrasound Helps Define Bone Defects In Women With Type 2 Diabetes

BY JOHN R. BELL  
Associate Editor

Ultrasound findings from a cross-sectional study of 162 postmenopausal women might help explain the paradox that women with type 2 diabetes can have higher bone mineral density than nondiabetic women and yet have a greater risk of fractures.

The study confirmed previous reports that bone mineral density (BMD) as measured by dual x-ray absorptiometry (DXA) is higher in women with type 2 diabetes than in women without diabetes. Yet a new diagnostic tool, quantitative ultrasound, revealed that the speed of sound through bone was lower in diabetic women.

This may indicate that their denser bone is in some

way of lesser quality, compared with the bone of women without type 2 diabetes.

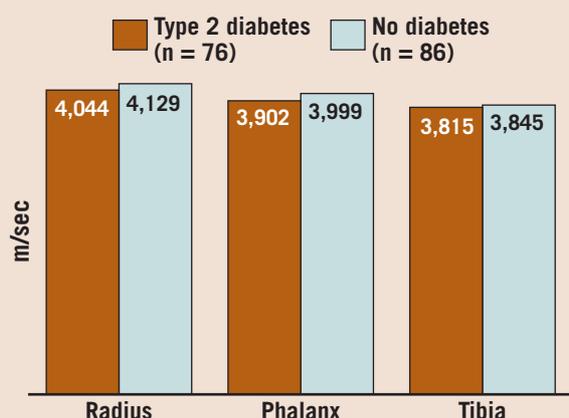
The findings suggest that quantitative ultrasound is a useful tool in detecting impaired bone quality in postmenopausal women with type 2 diabetes, and that it might have greater promise than DXA in detecting bone defects in diabetic patients, the authors wrote.

Dr. Bei Tao of Shanghai (China) Jiao-tong University School of Medicine and colleagues enrolled 76 postmenopausal women with type 2 diabetes and 86 nondiabetic postmenopausal women. In the diabetic women, mean BMD as measured by DXA was 1.06 g/m<sup>2</sup> in the lumbar spine, 0.80 g/m<sup>2</sup> in the femoral neck, and 0.74 g/m<sup>2</sup> in the total hip, compared with 0.90 g/m<sup>2</sup>, 0.80 g/m<sup>2</sup>, and 0.74 g/m<sup>2</sup>, respectively, in the nondiabetic women.

Quantitative ultrasound was used to assess the axial speed of sound along the distal third of the radius, the proximal phalanx of the third finger, and the midshaft of the tibia. The speed of sound was higher at all three locations in the nondiabetic women, compared with the diabetic women (see bar chart), the investigators reported online in the Journal of Clinical Endocrine Metabolism (2008 Mar. 4 [doi:10.1210/jc.2007-1760]).

Among the nondiabetic women, BMD at each site correlated significantly with the speed-of-sound measurements. But among the diabetic women, only the speed of sound at the phalangeal site correlated significantly with all three BMD values; the speed of sound in the tibia correlated with none of the BMD values, and the speed of sound in the radius correlated with only the BMD of the femoral neck.

### Speed of Sound in Bones Lower In Women With Type 2 Diabetes



Source: Journal of Clinical Endocrinology and Metabolism

ELSEVIER GLOBAL MEDICAL NEWS

## LRP5 Gene Variants Linked To BMD and Fracture Risk

BY MARY ANN MOON  
Contributing Writer

Variants in the LRP5 gene are associated with both bone mineral density and fracture risk, researchers reported in JAMA.

Two LRP5 variants were found to have "modest" effects that were very consistent across different populations and independent of subject sex or age. Based on these findings, carriers of these polymorphisms may have a fracture risk that is 15%-20% higher than that for noncarriers, wrote Joyce van Meurs, Ph.D., of Erasmus Medical Center, Rotterdam, the Netherlands, and her associates in the Genetic Markers for Osteoporosis (GENOMOS) consortium.

The study involved 37,534 subjects who underwent genotyping and assessment of bone mineral density. A total of 8,932 subjects had fractures, including 2,146 vertebral fractures (JAMA 2008;299:1277-90).

Members of the GENOMOS consortium—18 research teams in Europe and North America—performed prospective geno-

typing for several polymorphisms of the LRP5 gene that are thought to be related to osteoporosis. "Some scattered studies have tested this association, but results have not been conclusive due to limited sample size," the researchers wrote.

"The current collaborative study has the potential to answer this question more definitively because of its large sample size and therefore large power to observe the expected modest associations," Dr. van Meurs and her associates explained.

"Although any single marker explains only a small portion of the phenotype risk, identification of several such osteoporosis risk variants may eventually help in improving clinical prediction," they wrote. "Single genetic risk variants may also offer useful insights about mechanisms and pathways that may be useful in drug development."

The investigators cautioned that their results may not apply to Asian or African populations, since the study subjects were predominantly whites of European descent.