Gene Variants Linked To Bone Density, Likelihood of Fracture

BY MARY ANN MOON
Contributing Writer

Variants in the LRP5 gene are associated with both bone mineral density and fracture risk, researchers in the Genetic Markers for Osteoporosis (GENOMOS) consortium reported.

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.

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 genotyping 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.

Patients With HIV Are Now Living Long Enough to Face Osteoporosis

BY NANCY WALSH
New York Bureau

BOSTON — An increased risk for osteoporosis or osteopenia is among the age-related complications faced by patients surviving long term with HIV disease.

Cross-sectional studies have shown that patients with HIV have a greater prevalence of reduced bone mineral density, compared with healthy controls, but longitudinal data that would demonstrate the significance of this increased risk are lacking, said Dr. William G. Powderly of University College Dublin.

To meet this need for data, the Centers for Disease Control and Prevention is prospectively following a cohort of more than 500 HIV-infected patients in the Study to Understand the Natural History of HIV and AIDS (SUN), Dr. Powderly said at the 15th Conference on Retroviruses and Opportunistic Infections.

The routine care of older patients with HIV should include baseline measurement and regular monitoring of biomarkers of bone turnover.

On enrollment in SUN, patients had baseline bone densitometry and body composition measurements, clinical data, and fasting laboratory data collected, and were matched for age, race, sex, and body mass index with controls from the National Health and Nutrition Examination Study III.

Among the SUN patients (mean age 41 years), 52% had osteopenia and 10% had frank osteoporosis, Dr. Powderly said.

A total of 78% were men, 25% were black, and almost 80% were receiving antiretroviral therapy.

Analysis revealed that factors associated with an increased risk of low bone mineral density included age over 45 years (odds ratio 2.35) and CD4 count below 300 cells/mm^3 (OR 2.10), Dr. Powderly said.

Duration of HIV infection longer than 98 months also was associated with an increased risk (OR 1.56).

Determining whether bone mineral loss will continue over time and translate into increased risk for fractures is a "critically important" area of HIV research, Dr. Powderly said at the meeting, which was sponsored by the Foundation for Retrovirology and Human Health and the CDC.

Further information also is needed on HIV-associated risk factors. Aside from risk factors also present in the general population such as smoking, alcohol use, low body mass index, and lack of physical activity, the aging HIV patient also might have renal dysfunction and inadequate nutrition, which can further contribute to bone loss. HIV disease itself might alter the processes involved in bone mineralization and turnover, according to Dr. Powderly. In a study he and his colleagues performed, human osteoblast and mesenchymal stem cell lines were treated in vitro with several HIV proteins, including HIV p55-gag and HIV gp120.

Exposure to these proteins reduced calcium deposition, alkaline phosphatase activity, and mRNA levels of osteogenic transcription factors in osteoblasts, and the ability of stem cells to develop into osteoblasts was modulated (AIDS Res. Hum. Retroviruses 2007;23:1521-30).

There is also some evidence implicating potent antiretroviral medications in bone loss. In a meta-analysis of 20 studies that included 884 patients, 67% had reduced bone mineral density and 15% had osteoporosis. Those receiving antiretroviral therapy had a 2.5-fold increased risk of having reduced bone mineral density, compared with those who were treatment naive (AIDS 2006;20:2165-74).

The dynamic process of bone mineralization is another factor. "We reach the peak of bone mineralization at around 30 years, and then both men and women lose bone at a rate of approximately 0.5%-1% per year," according to Dr. Powderly.

Because women have lower peak bone mass than do men, they have higher rates of osteoporosis as they age. Until the relative contributions to bone loss of the various factors can be more fully clarified, the routine care of older patients with HIV should include baseline and routine monitoring of markers of bone turnover, according to Dr. Powderly.

Calcium Increased MI Risk in Healthy Menopausal Women

BY DAMIAN McNAMARA
Miami Bureau

Calcium supplementation significantly increased the risk of a myocardial infarction among healthy, postmenopausal women, compared with those taking placebo, in a secondary analysis of an osteoporosis study.

"I would not recommend calcium supplementation based on this finding," Dr. Rita F. Redberg, who was not involved in the study, said in an interview.

The HDL:LDL cholesterol ratios improved among the 732 women who took daily calcium supplementation, compared with the 739 participants who took placebo. This suggests that a different mechanism spurred the increase in myocardial infarction.

"This is an interesting point. It shows that just improving cholesterol does not reduce the risk of a heart attack," said Dr. Redberg, a Robert Wood Johnson Foundation health policy fellow and director of women's cardiovascular services at the University of California, San Francisco. "It was the same finding with estrogen: It lowered LDL, increased HDL, but did not reduce the number of heart attacks in studies."

The current findings contrast with previous suggestions of cardiovascular benefit from calcium supplementation. One study found that calcium increases the HDL:LDL cholesterol ratio by almost 20% (Am. J. Med. 2002;112:343-7).

Moreoover, there was a one-third decrease in deaths from cardiovascular events observed among women who had the greatest intake of calcium from either diet or supplements in the Iowa Women's Health Study (Am. J. Epidemiol. 1999;149:151-61).

Following completion of a 5-year osteoporosis study (Am. J. Med. 2006;1119:777-85), Dr. Mark J. Bolland and his associates at the University of Auckland (New Zealand) reassessed their data to compare cardiovascular events. Women were randomized to 1 g/day of elemental calcium (Citracal) or placebo. All of the 1,471 participants were postmenopausal for at least 5 years and older than age 55 years at baseline, and 10% of those were older than age 80 at baseline.

There is a known paradox: The calcium women lose from their bones ends up in their arteries.

DR. REDBERG

Death, sudden death, myocardial infarction, angina, other chest pain, stroke, and transient ischemic attacks events were recorded every 6 months. In all, 336 women stopped taking the calcium and 296 stopped taking the placebo before the study end.

A total of 21 of the 732 women in the calcium group experienced 24 myocardial infarctions, a statistically significant difference compared with 10 of the 739 in the placebo group who had 10 such events. A composite end point of sudden death, myocardial infarction, angina, or chest pain was also higher in the calcium group (155 events among 87 women) compared with the placebo group (135 events among 93 women).

No significant differences were found in angina, chest pain, transient ischemic attack, stroke, or sudden death events between groups. There were 34 deaths in the calcium group and 29 in the placebo, a nonsignificant difference.

Dr. Redberg was not surprised by the elevated MI risk. She said research by Dr. Linda Demer, vice chair of medicine at the University of California, Los Angeles, has indicated increased cardiovascular risk associated with calcium.

"It's called the calcium paradox. Women lose calcium from their bones as they get older and it ends up in their arteries and the lining of their vessel walls, leading to accelerated atherosclerosis," Dr. Redberg said.

"This study is a confirmation of that hypothesis, that calcium can end up in the walls of your arteries." Dr. Redberg is also a professor of medicine at the University of California, San Francisco.