Ups Cardiac, All-Cause Mortality

Thyroid Dysfunction *from page 1*

dysfunction," the endocrinologist said at the annual meeting of the American Thyroid Association.

He reported on 1,100 adult participants in the longitudinal Japanese-Brazilian Thyroid Study. None were on thyroid medications at baseline.

At baseline, subclinical hypothyroidism—defined as an abnormally low serum TSH level in the presence of normal serum free T4 and total or free T3—was identified in 6.2% of the study population. Subclinical hyperthyroidism was detected in 8.9%. Overt hyperthyroidism was found in 1.8%, while 0.8% had overt hypothyroidism. The remaining subjects were euthyroid.

During a mean 7 years of follow-up, 76 participants died. The overall mortality rate was 5.1% in euthyroid individuals and significantly higher at 12.1% in those with subclinical hypothyroidism and 21.7% in participants with subclinical hyperthyroidism.

All-cause and cardiovascular mortality were higher in subjects with more pronounced subclinical thyroid dysfunction than in those with milder abnormalities. For example, the cardiovascular mortality rate was 2.8% in euthyroid subjects, 8.6% in those with relatively mild subclinical hyperthyroidism as defined by a TSH of 0.1-0.44 mU/L, and more than 27% in participants with a TSH below 0.1 mU/L. But even in individuals with only mildly increased or decreased TSH the increase in mortality was statistically significant.

Subjects with subclinical thyroid dysfunction tended to be older than euthyroid individuals. However, the populations had similar baseline rates of dyslipidemia, diabetes, hypertension, metabolic syndrome, smoking, and macrovascular disease.

In a multivariate Cox regression analysis that controlled for age and other potential confounders, subclinical hyperthyroidism was independently associated with a 3.4-fold increased risk of all-cause mortality compared with euthyroid status. Subclinical hypothyroidism conferred a 2.4-fold increased risk.

These data highlight the need to identify and treat individuals with subclinical thyroid dysfunction.

DR. SGARBI

Individuals with subclinical hyperthyroidism were at 5.5-fold increased risk for cardiovascular mortality. The 1.9-fold increase in subclinically hypothyroid subjects was not statistically significant. The elevated all-cause mortality in this group was attributed to a combination of cardiovascular, cancer, and infectious disease deaths.

In the subclinically hyperthyroid group, all-cause and cardiovascular mortality rates were significantly increased among both men and women. In those with subclinical hypothyroidism, however, the elevated mortality risk was present only in men.

The increased mortality associated with subclinical thyroid dysfunction was confined to patients aged older than 60 years.

Dr. Orlo H. Clark, an audience member, wondered if the Brazilian findings could be extrapolated to patients who have had surgery for thyroid cancer.

"Are we hurting patients when we purposely suppress their TSH once they've had thyroid cancer surgery? Do you think that has an adverse effect on their survival?" asked Dr. Clark, professor and chair of the department of surgery at the University of California, San Francisco, Medical Center at Mount Zion.

Dr. Sgarbi replied that he believes that's a reasonable implication, although the study didn't address that issue.

The Japanese-Brazilian Thyroid Study was funded by a federal agency. ■

High Vitamin C Intake May Reduce Hip Fracture Risk

BY JEFF EVANS
Senior Writer

Montreal — Consumption of vitamin C at sufficiently high levels is associated with nearly a 50% decrease in the risk of hip and nonvertebral osteoporotic fractures in elderly men and women, according to a 15- to 17-year follow-up of participants in the Framingham Osteoporosis Study.

Previous studies of menopausal and postmenopausal women have shown that dietary intake of vitamin C is associated with increased bone mineral density (BMD), and that a high vitamin C serum level is associated with a decreased prevalence of fracture. Poor dietary intake of vitamin C also has been associated with an increased risk of hip fracture, Marian T. Hannan, D.Sc., said at the annual meeting of the American Society for Bone and Mineral Research.

Vitamin C, an antioxidant, plays an important role in the formation of collagen, which is a major component of connective tissue. Published evidence suggests that oxidative stress may result in increased osteoclast formation, resulting in greater bone resorption, said Dr. Hannan, who presented the study on behalf of Shivani Sahni of Tufts University, Boston. (Ms. Sahni performed the research as a part of her thesis but could not attend the meeting.)

Of 5,209 men and women in the original Framingham Heart Study cohort, the investigators identified 958 individuals who had participated in the beginning of the osteoporosis study in 1988-1989, had answered a food-frequency questionnaire, and had no history of a hip fracture. These individuals had a mean age of 75 years and experienced 100 hip fractures and 180 nonvertebral osteoporotic fractures during the follow-up period, Dr. Hannan reported.

For the study, participants were divided into three groups based on their intake of vitamin C. The relative risk of hip fracture was significantly lower for individuals who had the highest total intake of both dietary and supplemental vitamin C (a median of 305 mg/day) than it was for people with the lowest total intake (median of 97 mg/day). This translated into a 44% decrease in relative risk of hip fracture, according to Dr. Hannan of Harvard Medical School's Institute for Aging Research, Boston.

Those with the highest total intake of vitamin C also had a 36% lower relative risk of having a nonvertebral osteoporotic fracture than did individuals with the lowest total intake.

When the investigators looked at supplemental vitamin C intake alone, the highest users (median of 260 mg/day) had a 70% lower relative risk of hip fracture than did nonusers. Supplements accounted for about 28% of the individuals' total vitamin C intake, she said.

The investigators found no effect for dietary intake of vitamin C alone.

All of the comparisons were adjusted for age, sex, body mass index, height, smoking status, estrogen use in women, physical activity, alcohol use, multivitamin use, femoral neck BMD, and total intake of energy, calcium, vitamin D, and potassium.

One audience member suggested that the discrepancy between the effects of supplemental and dietary vitamin C intake could mean that there are residual confounding effects from factors that were not accounted for in the study, such that supplemental use of vitamin C may be a marker for people who care more about their health and take better care of themselves. This is a problem that can only be answered with a randomized, controlled trial, Dr. Hannan noted.

"We were intrigued by the lack of a BMD effect on [the association between] vitamin C and fracture, and we believe that it implies that vitamin C may affect a different pathway or other fracture risk factors, for example, fall risk factors or mobility risk factors," Dr. Hannan said. ■

Sitagliptin Plus Metformin Shows 2-Year Benefit for Glucose

BY SARA FREEMAN
Contributing Writer

Rome — A 1.7% reduction in hemoglobin A_{1c} was achieved in patients with type 2 diabetes given the combination of sitagliptin plus metformin in a 1-year extension of a 54-week phase III trial.

This reduction, seen after 104 weeks of total follow-up, was significantly better than the reductions achieved with either drug alone or placebo, and was associated with no more adverse events than metformin monotherapy.

Dr. Debora Williams-Herman of Merck Research Laboratories in Rahway, N.J., presented the data at the annual meeting of the European Association for the Study of Diabetes.

The extension trial involved 454 patients who had already completed 1 year of treatment with the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin alone at a dose of 100 mg/day; twice-daily treatment with metformin alone at a dose of 500 mg or 1,000 mg; both drugs in combination (50 mg sitagliptin plus either 500 or 1,000 mg of metformin); or placebo and 100 mg metformin. The results of this investigation were published last year and showed that, at 54 weeks' follow-up, the mean change from baseline in hemoglobin A_{1c} (HbA_{1c}) level was –1.8% in patients given the 50-mg sitagliptin/1,000 mg metformin combination (Diabetes Care 2007;30:1979-87).

Now, at 2 years, the results show a similar and sustained reduction in HbA_{1c}, compared with the original baseline values, with a –1.7% mean change in HbA_{1c} in the 105 patients who were treated with the sitagliptin and higher-dose metformin combination. A mean change of –1.4% in HbA_{1c} was reported in the 96 patients who were given the sitagliptin plus lower-dose metformin combination, with mean changes in HbA_{1c} of –1.3%, –1.1%, and –1.1% in the metformin 1,000 mg/day, metformin 500 mg/day, and sitagliptin 100 mg/day groups, respectively.

Almost two-thirds (60%) of patients given the sitagliptin plus higher-dose metformin combination achieved an HbA_{1c} below 7%, compared with 45% each for patients given the sitagliptin plus lower-dose metformin combination and those given 1,000 mg metformin. Approximately one-third (32%) of patients given sitagliptin monotherapy and 28% of those treated with metformin 500 mg achieved an HbA_{1c} of less than 7%.

As expected, patients who had a higher initial baseline HbA_{1c} achieved greater overall reductions in blood glucose over the course of the 2-year follow-up.

Dr. Williams-Herman reported that 5 of 107 patients (5%) given the sitagliptin plus higher-dose metformin combination experienced hypoglycemia during the extension study (i.e., between weeks 54 and 104). This can be compared with 2 of 100 patients (2%) given sitagliptin plus metformin 500 mg, 2 of 88 patients (2%) given metformin 1,000 mg, 1 of 85 patients (2%) given metformin 500 mg, and 1 of 42 patients (2%) given placebo and then 1,000 mg metformin. No patients given sitagliptin monotherapy developed hypoglycemia during the extension study.

"In patients with type 2 diabetes inadequately treated with diet and exercise, initial combination therapy with sitagliptin and metformin over 2 years showed substantial glycemic improvement," she said.

Commenting on these data at a press briefing organized by Merck Sharp & Dohme, which markets sitagliptin, Dr. Bernard Charbonnel of the University Hospital of Nantes, France, said sitagliptin and metformin used together produced "powerful glycemic improvements." He added: "Around 60% of patients achieved the HbA_{1c} goal of less than 7% at 2 years, which is rather impressive." ■