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WHI Study Results

Calcium and Vitamin D Supplements Offer Modest Bone Improvements, No Benefits for Colorectal Cancer

Calcium and vitamin D supplements in healthy postmenopausal women provide a modest benefit in preserving bone mass and prevent hip fractures in certain groups including older women but do not prevent other types of fractures or colorectal cancer, according to the results of a major clinical trial, part of the Women's Health Initiative (WHI). While generally well tolerated, the supplements were associated with an increased risk of kidney stones.

The study results are published in the February 16 issue of *The New England Journal of Medicine*. The WHI is sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health.

“This important study provides guidance for women on the risks and benefits of supplementing their diets with calcium and vitamin D. The overall results suggest that women, particularly those over 60, should consider taking calcium and vitamin D for bone health but they should not expect these supplements to help prevent colorectal cancer,” said Elizabeth G. Nabel, M.D., NHLBI director and director of the Women's Health Initiative.

The WHI Calcium with Vitamin D (CaD) trial of 36,282 postmenopausal women ages 50 to 79 found a small but significant 1 percent higher hip bone density for those taking calcium combined with vitamin D compared to those taking placebo. During the trial, 374 women had hip fractures with a fracture rate of 14 per 10,000 cases per year in the supplemented group compared to 16 per 10,000 per year in the placebo group. This 12 percent reduction in hip fracture in those taking the calcium plus vitamin D supplement was not statistically significant; however, women who consistently took the full supplement dose experienced a significant 29 percent decrease in hip fracture. Women older than 60 had a significant 21 percent reduction in hip fracture. The supplements had no significant

effect on spine or total fractures.

Calcium/vitamin D supplements provided no detectable effect on the incidence of colorectal cancer. There were similar rates of cancer in both the calcium/vitamin D and placebo groups (13 cases per 10,000/year compared to 12 cases per 10,000/year respectively).

Overall, the supplements were well tolerated by participants and the only adverse effect found was a 17 percent increase in kidney stones. Kidney stones were reported by 449 women (34 cases per 10,000 per year) in the CaD group compared to 381 women (29 cases per 10,000 per year) in the placebo group.

The WHI Calcium with Vitamin D trial was primarily designed to study the effect of calcium/vitamin D supplementation on preventing hip fracture with secondary study objectives testing the effect of CaD on spine and other types of fracture and on colorectal cancer. Participants in this study had previously enrolled in one or both of the WHI trials of hormone therapy or dietary modification.

Half of the over 36,000 participants in the CaD trial received a daily dose of 1000 milligrams of calcium carbonate combined with 400 IUs of vitamin D3. The other half of the study group received placebo pills in similarly marked bottles. Participants could choose between chewable or swallowable pills. During the study, a sub-set of participants had regular bone density scans. Study participants were followed for an average of 7 years with three-quarters of them still taking their pills by the end of the study.

Osteoporosis, a skeletal disorder characterized by weakened bones leading to an increased risk of fracture is a major cause of disability, loss of independence, and death. It contributes to an estimated 300,000 hip fractures in the U.S. each year. Four out of 10 women over 50 will experience a fracture at the hip, spine, or wrist in their lifetime. Ten million people in the U.S. are estimated to have osteoporosis and 34 million more have low bone mass, placing them at greater risk for fracture.

“Given the serious public health burden of fractures associated with osteoporosis, it is important to learn as much as possible about ways to prevent and treat bone loss,” said Joan McGowan, Ph.D., of the NIH’s National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and a co-author on the paper.

According to the study’s authors, there are several possible reasons why despite improvements in hip bone density, the reduction in hip fractures was smaller than expected and only statistically significant in certain groups – those over 60 and women who took the full intended dose of combined supplements.

“Although 76 percent of women were still taking study pills at the end of the trial, only 59 percent were taking the intended number of pills,” said Rebecca D. Jackson, M.D., endocrinologist and the study’s lead investigator at Ohio State University in Columbus. “In a secondary analysis, we found a significant 29 percent decrease in hip fracture risk among women who took most of their study pills – that’s four fewer hip fractures for every 10,000 women per year,” she said.

The rate of hip fractures was about half of what was expected, and this decreased study power to show a significant finding, according to Dr. Jackson. “The low rates could be due to a number of factors, such as the high body mass index of participants (heavier people have stronger bones), the inclusion of relatively few women over age 70 years, and the fact that many participants were already using calcium and vitamin D supplements, or were on hormone therapy,” she said.

“If we look at all the findings together,” said McGowan, “for every 10,000 women treated for one year, two hip fractures would be prevented and five cases of kidney stones would be caused. The number of hip fractures prevented would climb to four for compliant patients and six for women over 60. Since hip fractures are considered to be more serious than kidney stones, on balance, the public health benefit of the supplements outweighs the risks.”

“The study’s findings of slowed bone loss and the reduction in hip fractures for some groups suggest a role for these supplements in preventing hip fracture in generally healthy postmenopausal women and support the current Surgeon General’s recommendations for these nutrients,” added McGowan, who is also the senior scientific editor of the Surgeon General’s report on bone health. She noted, however, that supplements may not be necessary for healthy women whose diet meets recommended levels of calcium and vitamin D.

The study found no evidence of benefit from calcium/vitamin D for the prevention of colorectal cancer, according to Jean Wactawski-Wende, Ph.D., epidemiologist and the study’s lead investigator at the University at Buffalo.

Over an average of 7 years, 322 women in the study were diagnosed with invasive colorectal cancer. There was no statistically significant difference between the two groups in number of cancer cases or in the characteristics or severity of tumors. There were also no differences between groups in the number of polyps reported by the participants. When the investigators analyzed only the data obtained from participants who were taking most of their study pills, there was still no benefit seen from calcium/vitamin D supplementation.

“As the third leading cause of cancer death and incidence for women in the United States, there is great interest in the prevention of colorectal cancer. Unfortunately, our findings do not validate some previous studies and polyp prevention trials which showed a benefit for

calcium/vitamin D,” said Wactawski-Wende.

She added, however, that study design and population issues may have limited the study’s ability to show a protective effect of calcium/vitamin D. Since participants were not restricted from taking personal calcium or vitamin D supplements, they had a relatively high calcium and vitamin D intake at enrollment and intake rose even higher during the trial so the impact of study supplementation may have been muted.

Duration may have also been a factor, said Wactawski-Wende. “If the benefit of CaD is for prevention of cancer at its early stages and colorectal cancer takes 10 to 20 years to develop, 7 years of supplementation and follow-up may not be enough time to show a benefit. Still, we found no trend toward protection in the later years of follow-up,” she said. She added that the ongoing 5-year WHI extension study will continue to track occurrences of colorectal cancer – as well as other diseases – and may provide answers on later effects of the WHI CaD supplementation.

“The WHI will continue to provide us with answers about the major health conditions affecting women for years to come,” said Nabel, “The study’s participants and investigators have made major contributions to disease prevention in postmenopausal women.”

Resources:

- For a summary of health recommendations for postmenopausal women based on the WHI results and other studies, see <http://www.nhlbi.nih.gov/whi/recommend.htm>
- For information on bone health and osteoporosis, see www.niams.nih.gov and <http://www.niapublications.org/agepages/osteo.asp>.
- For information on eating for general health, see www.health.gov/dietaryguidelines/dga2005/recommendations.htm
- For information on dietary supplements, see <http://dietary-supplements.info.nih.gov/index.aspx>
- For more on the Women's Health Initiative, see <http://www.nhlbi.nih.gov/whi/>

To interview Dr. Nabel or WHI project officer Jacques Rossouw, M.D. of NHLBI, contact the NHLBI Communications Office at 301-496-4236. To interview Dr. Donna Griebel of NCI’s Division of Cancer Prevention, contact the NCI Press Office at 301-496-6641; to interview Dr. McGowan, contact the National Institute of Arthritis and Musculoskeletal and Skin Diseases Office of Communications at 301-496-8190. To interview Dr. Jackson, contact Michelle Gailiun at Ohio State University at 614-293-6054; to interview Dr. Wactawski-Wende, contact Lois Baker at the University at Buffalo Office of News Services at 716-645-5000, ext. 1417.

WHI—a Legacy to Future Generations, a conference on the past, present, and future of WHI (including synthesis of findings generated from the WHI observational study and all four clinical trials -- estrogen plus progestin, estrogen alone, dietary modification, and calcium/vitamin D --will be held February 28-March 1, 2006 on the NIH campus. For more information and a conference agenda, go to: <http://www.nhlbi.nih.gov/whi/references.htm>. For more information on the Women's Health Initiative, see <http://www.nhlbi.nih.gov/whi>.

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