Effects of Low-Dose Thiazide on Bone Mass

LaCroix AZ, Ott SM, Ichikawa L, et al. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2000;133:516–26.

Study Overview

Objective. To determine whether hydrochlorothiazide, a thiazide diuretic, has beneficial effects on bone mineral density (BMD) in older adults.

Design. Randomized, double-blind, placebo-controlled trial. Analysis was by intention to treat.

Setting and participants. 3520 healthy normotensive enrollees of a staff-model health maintenance organization in Seattle, Washington, responded to direct mailings and a local media campaign targeting adults between 60 and 79 years of age. Respondents were prescreened over the telephone to yield 320 subjects. Among this cohort, more subjects were women (64%) and most were white (95%), with a mean age of 68 years. Potential participants were excluded if they had any of the following: contraindications to thiazide therapy (including allergies, certain renal disease or electrolyte abnormalities, gout, or a low-density lipoprotein level greater than 190 mg/dL), conditions that would complicate thiazide treatment (including alcohol abuse, serious cardiac problems, use of any diuretics or antihypertensive medications, or hypotension), conditions known to affect BMD (including lifestyle factors, use of certain medications, metabolic disorders, or hepatic or gastrointestinal disorders), or conditions that made trial completion unlikely (life-threatening disease, dementia, or the possibility of a change in residence.)

Intervention. Patients were randomized to receive either 12.5 mg of hydrochlorothiazide per day, 25 mg of hydrochlorothiazide per day, or identical-appearing placebo once daily for 36 months. All participants were given brochures that encouraged adequate intake of potassium (not defined in the article) and calcium (1000 to 1500 mg daily). Calcium levels were assessed at baseline and at 36 months with the Fred Hutchinson Cancer Research Center Food Frequency Questionnaire [1].

Main outcome measures. The primary outcome was BMD of the total hip. BMD of the lumbar spine and total body were secondary outcomes. BMD was measured at 6-month intervals for the 3 years of the study.

Main results. 97% of study participants completed the 36-month visit, and 90% completed all 6 follow-up visits. At 36 months, 88% percent of women patients were taking the study medication, with no difference among study groups. The percentages of men taking the medication at 36 months were 81.6% in the placebo group, 89.7% in the 12.5-mg group, and 60.5% in the 25-mg group ($P = 0.007$).

At 36 months' follow-up, the difference in change from baseline in total-hip BMD was 0.79 percentage point (95% confidence interval [CI], –0.12 to 7.71) in the 12.5-mg group and 0.92 percentage point (95% CI, –0.001 to 1.85) in the 25-mg group compared with the placebo group (dose-response relationship, $P = 0.03$). For the spine BMD measure at 6 months, the corresponding comparisons with placebo were 0.59 (95% CI, –0.22 to 1.41) in the 12.5-mg group and 1.04 (95% CI, 0.22 to 1.86) in the 25-mg group; again, the dose-response relationship was statistically significant ($P = 0.005$). A similar pattern was observed at 36 months, although the result did not reach statistical significance ($P = 0.12$). The only direct comparisons that reached statistical significance were for women in the 25-mg group (versus placebo) at 6 months' follow-up for all outcome measures and for all participants in the 12.5-mg group (versus placebo) at 6 months' follow-up for total-hip measurements.

Conclusion

Hydrochlorothiazide appears to confer modest benefits in BMD preservation among healthy, normotensive, older white women. Potential benefits gained by their male counterparts are less clear.

Commentary

This study had an excellent design and execution except for poor adherence among men in the 25-mg group. Unfortunately, this poor adherence clouds the results. The authors claim that adherence problems resulted in the lack of a dose-response relationship in male groups; however, unless there was some unusual circumstance, the poor compliance in this study does not bode well for clinicians who would translate the study results into clinical practice. Indeed, these findings demonstrate the difference between efficacy and effectiveness: while the study drug was clearly both efficacious and effective among women (although modestly so),

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among men one can argue only for the agent's efficacy. In the clinical world, however, only effectiveness matters.

Despite such problems, this study adds strong support to literature suggesting that thiazides may be useful in preserving BMD [2–4]. Of interest, though not discussed in the article, was the fact that the effects of thiazides appeared to diminish after the 6-month follow-up. This result is consistent with 1 of the 2 smaller randomized controlled trials that showed some benefit with thiazide treatment [4]. A smaller randomized trial published in October 2000 found a comparable benefit for normal postmenopausal women taking a 50-mg daily dose of hydrochlorothiazide who were followed for up to 2 years [5].

Applications for Clinical Practice

These data do not support the use of thiazides solely for the preservation of BMD. However, they do supply important evidence that should be considered when treating patients, especially women, for hypertension. As LaCroix and colleagues note, thiazides are generally underused. This study provides another reason to make greater use of this well-studied therapy for hypertension.

References

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