Thiazide Diuretics and the Risk for Hip Fracture

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Background: **Since most hip fractures are related to osteoporosis, treating accelerated bone loss can be an important strategy to prevent hip fractures. Thiazides have been associated with reduced age-related bone loss by decreasing urinary calcium excretion.**

Objective: **To examine the association between dose and duration of thiazide diuretic use and the risk for hip fracture and to study the consequences of discontinuing use.**

Design: **Prospective population-based cohort study.**

Setting: **The Rotterdam Study.**

Participants: **7891 individuals 55 years of age and older.**

Measurements: **Hip fractures were reported by the general practitioners and verified by trained research assistants. Details of all dispensed drugs were available on a day-to-day basis. Exposure to thiazides was divided into 7 mutually exclusive categories: never use, current use for 1 to 42 days, current use for 43 to 365 days, current use for more than 365 days, discontinuation of use since 1 to 60 days, discontinuation of use since 61 to 120 days, and discontinuation of use since more than 120 days.**

Results: **281 hip fractures occurred. Relative to nonuse, current use of thiazides for more than 365 days was statistically significantly associated with a lower risk for hip fracture (hazard ratio, 0.46 [95% CI, 0.21 to 0.96]). There was no clear dose dependency. This lower risk disappeared approximately 4 months after thiazide use was discontinued.**

Conclusions: **Thiazide diuretics protect against hip fracture, but this protective effect disappears within 4 months after use is discontinued.**

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Hip fractures are associated with substantial morbidity and mortality. The costs of surgery and rehabilitation are a burden on public health resources, especially because the incidence of hip fracture increases as the population ages (1, 2). Most hip fractures are related to osteoporosis, and treating accelerated bone loss may therefore be an important strategy to prevent hip fractures (3).

Thiazide diuretics are widely used as antihypertensive agents. They are inexpensive and effective and have few important adverse effects (4). Thiazides are thought to protect against age-related bone loss by reducing urinary calcium excretion (5). This bone-sparing effect could lead to reduced fracture incidence in patients treated for hypertension. Several epidemiologic studies have examined the effect of thiazides on bone mineral density and fracture incidence. Although bone mineral density was found to be increased in thiazide users, the difference was often small (6–12). Thiazides were found to have a protective effect on hip fracture in most studies (9, 12–17), but occasionally an increased risk was found (18). Most of the studies, however, had limitations. Some studies included detailed drug-dispensing data but limited information on potential confounders and effect modifiers (15, 18, 19). Other studies had small patient samples or used only baseline interview data on thiazide use (9, 12, 16, 20) without accounting for timing of thiazide use (14, 20, 21). Detailed information on thiazide dose and duration of use was often absent or unreliable because no data on day-to-day use were available. Because of these limitations, it is still unclear how long thiazides have to be taken to affect fracture incidence and how long this effect persists after thiazide use is discontinued.

We conducted a prospective, population-based cohort study using detailed drug-dispensing information, as well as extensive information on potential risk factors, to examine the association between current and past use of thiazides and the incidence of hip fractures in men and women 55 years of age and older. We also studied the effect of discontinuing thiazide use on fracture risk.

METHODS

Study Sample

This study was conducted as part of the Rotterdam Study, a prospective, population-based cohort study on the occurrence and determinants of disease and disability in elderly persons (22). In 1990, all inhabitants of Ommoord, a suburb of Rotterdam in the Netherlands, who were 55 years of age or older and had lived in the district for at least 1 year were invited to participate in the study. Of the 10 275 eligible persons, 7983 (78%) participated. Participants gave informed consent and permission to retrieve information from medical records. At baseline, between 1990 and 1993, trained interviewers administered an extensive questionnaire covering socioeconomic background and medical history, among other topics, during a home interview. During subsequent visits to the study center, additional interviewing, laboratory assessments, and clinical examinations were performed. Information on vital status is obtained at regular time intervals from the municipal authorities in Rotterdam. The Medical Ethics Committee of the Erasmus MC, Rotterdam, the Netherlands, approved the study.

For the present study, all participants were followed from 1 June 1991 until they had an incident hip fracture,

died, or reached the end of the study at 31 December 1999, whichever came first.

Exposure Definition

In the research area, there are 7 fully computerized pharmacies that are linked to 1 network. During the study, all participants filled their prescriptions in 1 of these 7 pharmacies. Data on all dispensed drugs since 1 January 1991 are available in computerized format on a day-to-day basis. The data include the date of prescribing, the total amount of drug units per prescription, the prescribed daily number of units, product name, and the Anatomical Therapeutic Chemical (ATC) code (23).

The exposure of interest included plain thiazides and thiazides combined with potassium and potassium-sparing agents. Although formally not a thiazide, chlorthalidone was included because it has a similar effect on calcium excretion. In a previous study, these 2 diuretics did not differ (12). Therefore, we did not distinguish between them.

When a hip fracture occurred, the date was defined as the index date and the cumulative duration of use of thiazides on that date was calculated for each participant. Current use was defined as use of thiazides at the index date and was expressed as the number of consecutive days of use. Past use was defined as use of thiazides after baseline and before but not on the index date itself. Past use was expressed as the number of days since discontinuing use. To study the effect of duration of thiazide use, exposure at the index date was divided into 7 mutually exclusive categories, defined a priori: never use, current use for 1 to 42 days, current use for 43 to 365 days, current use for more than 365 days, discontinuation of use since 1 to 60 days, discontinuation of use since 61 to 120 days, and discontinuation of use since more than 120 days. We selected the first duration of 42 days because in the first 6 weeks of thiazide use, the decrease in circulating volume can cause dizziness and relative cerebral ischemia. We anticipated that this might be associated with a transiently increased risk for falls that should be distinguished from a potentially protective effect after prolonged use. After 42 days, the circulating volume in most patients is within normal limits (24). The duration of more than 365 days was chosen because trials on incidence of nonvertebral fractures with use of antiosteoporotic agents, such as bisphosphonates, all had at least 1 year of follow-up as well. Finally, the duration of 60 days after discontinuing use was chosen because it was used in an earlier study (15).

We expressed the prescribed daily dosage during current use at the index date as a proportion of the defined daily dosage (25). The defined daily dosage of thiazide diuretics is the standard recommended adult daily dosage for treating patients with hypertension in the Netherlands.

To avoid potential misclassification of exposure at baseline, we ensured that all participants had potential pharmacy data for at least 5 months before baseline.

Context

Thiazide diuretics reduce urinary calcium excretion and increase bone mineral density, but do they prevent bone fractures?

Contribution

In this population-based cohort study of 7891 older adults, patients taking thiazides for more than 1 year had a lower risk for hip fracture than those not taking thiazides (hazard ratio, 0.46 [95% CI, 0.21 to 0.96]). Within 4 months of stopping thiazides, the risk for hip fracture returned to its pretreatment value.

Implications

Thiazide diuretics may reduce hip fractures. Whether they have effects similar or additive to those of other bone protective agents merits study.

–The Editors

Outcome Definition

The study participants' general practitioners report all fatal and nonfatal events, such as fractures, through a computerized system. These data cover about 80% of the study sample. For participants who were not covered in this system, research physicians performed annual checks on the complete medical records of all general practitioners in the Rotterdam Study.

Two research physicians independently coded all fractures that occurred during the study period using the International Classification of Diseases, 10th revision (ICD-10) (26). A medical expert in the field who was unaware of patients' history and medication use (including thiazides) reviewed all coded events for a final classification. Fractures with ICD-10 codes S72.0, S72.1, and S72.2 were included, but pathologic hip fractures (M84.4) and fractures in prosthetic hips (M96.6) were excluded.

Cofactors

The following baseline patient characteristics, all determined by interview, were individually assessed as potential confounders: age, sex, score on the Mini-Mental State Examination (<26 points) (27), use of a walking aid, any fracture in the past 5 years, history of hysterectomy, thyroid disease, frequency of falling (≥once per month), current smoking, intake of alcohol (>2 g/d), and dizziness. Participants were interviewed about a previous diagnosis of Parkinson disease or use of antiparkinsonian drugs and were screened for symptoms of Parkinson disease by study physicians at the research center. Diabetes mellitus was defined as the use of glucose-lowering medication or a random or postload serum glucose level of 11.1 mmol/L (200 mg/dL) or greater. Hypertension (systolic blood pressure > 160 mm Hg, diastolic blood pressure > 95 mm Hg, or use of any antihypertensive drug), visual impairment in 1 or both eyes, and body mass index (kg/m^2) were

Table 1. **Baseline Characteristics of Participants with Hip Fracture and the Total Study Sample***

Characteristic	Participants with Hip Fracture (n = 281)	Total Participants (n = 7891)	Participants with Missing Values
Sex, *n*			(0)
Men	60	3071	
Women	221	4820	
Age, *y*	78.24 ± 8.61	68.93 ± 9.90	(0)
Subgroups, *n*			
55–64 y	21	3022	
65–74 y	66	2592	
75–84 y	121	1658	
≥85 y	73	619	
Femoral neck BMD, g/cm^2	0.71 ± 0.124	0.84 ± 0.137	(26)
Subgroups, *n*			
>0.89 g/cm^2	11	1845	
0.78–0.89 g/cm^2	36	1993	
<0.78 g/cm^2	106	1972	
Mean BMI, kg/m^2	25.74 ± 3.60	26.28 ± 3.74	(13)
Mean weight, *kg*	68.39 ± 11.12	72.99 ± 11.96	(12)
Lower-limb disability, *n*			(3)
None	47	3584	
Mild	109	2850	
Severe	109	1207	
MMSE score < 26, *n*	89	1102	(10)
Hypertension, *n*	102	2612	(10)
Parkinson disease, *n*	6	75	(3)
Thyroid disease, *n*	31	691	(8)
Diabetes mellitus, *n*	39	802	(15)
Visual impairment, *n*	40	523	(19)
Peripheral arterial disease, *n*	74	1210	(19)
History of fracture, *n*	58	1074	(7)
History of hysterectomy, *n*	16	456	(6)
Use of a walking aid, *n*	82	839	(8)
Dizziness, *n*	56	1261	(13)
Current smoking, *n*	58	1725	(4)
Recent falling, *n*	78	1336	(3)
Estrogen use at baseline, *n*	2	101	(27)
Calcium intake, *n*			(31)
Upper two tertiles (>958 mg/d)	82	3618	
Lower tertile (≤958 mg/d)	44	1804	
Mean alcohol intake, *g/d*	8.2 ± 12.5	10.3 ± 15.2	(31)

* Values in parentheses are percentages; values expressed with plus/minus signs are means ± SD. BMD = bone mineral density; BMI = body mass index; MMSE = Mini-Mental State Examination.

measured at the research center. Presence of peripheral arterial disease was measured (as described elsewhere [28]) by using a single measurement of systolic blood pressure taken at both the left and the right posterior tibial artery. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm was calculated for each leg. Peripheral arterial disease was considered present when the blood pressure at the arm was lower than 0.9 mm Hg on at least 1 side. Lower-limb disability was assessed by using a modified version of the Stanford Health Assessment Questionnaire (29) and by calculating the mean score of answers to questions about rising, walking, bending, and getting in and out of a car (30). A score of 0 indicates no disability, a score between 0 and 1 indicates mild disability, and a score of more than 1 indicates severe disability. Intake of calcium was adjusted for the total caloric intake according to the method of Willett and associates (31). Bone mineral density of the femoral neck was measured by using dual-energy x-ray absorptiometry (DPX-L densitometer, Lunar Corp., Madison, Wisconsin), as described elsewhere (32). Bone mineral density was stratified by dividing the study sample at the median observation (0.71 g/cm^2).

Use of other medications, such as corticosteroids, benzodiazepines, antidepressants, antihistamines, opioids, antacids, antipsychotics, statins, and estrogens, was analyzed as a potential confounder.

Statistical Analysis

Since exposure to thiazides may vary over time, we calculated risks for hip fracture with a Cox proportional hazards model (33), with the exposure represented by time-varying covariates. The model compared the exposure to thiazides on the index date of each participant with an incident hip fracture with all other participants in the cohort who were alive and at risk for hip fracture at the index date. We also used time-dependent categorical variables to compare duration of current use with time since last use. The 7 exposure categories of continuous use in days are represented in the model by 6 dummy variables with "never use" as a reference category. Use of other prescribed

drugs was also analyzed as a time-dependent categorical variable. We did a trend analysis on the exposure categories for current use.

To adjust for potential confounders, cofactors associated with the occurrence of hip fracture were included in the age- and sex-adjusted model if doing so caused a change in the point estimate of more than 5%. Because bone mineral density is a potential intermediate factor in the cause–effect relationship of thiazides and hip fractures, we selected only participants who did not use thiazides at baseline to study effect modification by femoral neck bone mineral density. To study whether there was a daily dose–effect relationship for current users, we divided daily dosage into equal to or less than 1.0 defined daily dosage and higher than 1.0 defined daily dosage and tested the effect of low-dosage use and high-dosage use against no use in separate regression analyses. To test an earlier suggestion of effect modification by low calcium intake (13), we also ran separate regression analyses for participants with the lowest tertile of calcium intake at baseline (≤958 mg/d) versus participants with higher intake.

Multiple imputation was used to impute missing information for confounding variables. Five imputation values were calculated on the basis of the posterior predictive distribution of the missing values, and 5 complete data sets were created. On each complete set, the statistical analyses were performed and the point estimates of the 5 data sets were combined to form 1 average summary statistic. The variance of the summary statistic is calculated from the within-imputation variance and the between-imputation variance. The combined variance accounts for the uncertainty introduced by estimating the missing values (34). All analyses were performed with SAS software, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Eighty-four participants died and 8 participants had an incident hip fracture before 1 June 1991. Therefore, the study sample included 7891 participants. During a total follow-up of 58 009 person-years, 281 hip fractures occurred. **Table 1** shows baseline characteristics for the participants with hip fractures and the entire study sample, as well as the percentage of missing values for the variables. When included in a Cox proportional hazards model with age and sex, body mass index, lower-limb disability, current smoking, and estrogen use caused a change in the point estimate of 5% or more. These variables were therefore included in the final model. At baseline, thiazide users were more likely to be disabled; have a history of dizziness, diabetes mellitus, and frequent falling; and have had previous fractures in the past 5 years, but these factors did not change the point estimate by 5% or more.

The risk for hip fracture for ever use of thiazides (yes or no) was decreased but did not reach statistical significance (hazard ratio, 0.94 [95% CI, 0.72 to 1.24]). The risk for hip fracture with current use of thiazides, regardless of duration of use, was also not statistically significant (hazard ratio, 0.71 [CI, 0.47 to 1.06]). When duration of current thiazide use (in months) was used as a continuous variable, there was a statistically significant inverse association between increased duration and risk for hip fracture (hazard ratio, 0.99 [CI, 0.97 to 0.99]). **Table 2** shows that with increasing duration of consecutive use among current users, the adjusted risk for hip fracture was statistically significantly reduced to 0.46 for persons exposed to thiazides for more than 1 year. Although the risk was lower among persons taking the lowest dose, the difference was not significant. We assessed whether the protective effect of thiazides persisted after discontinuing thiazide use and found a nonstatistically significant risk reduction up to 120 days, after which the hazard ratio returned to 1.0 (**Figure**).

Table 2. **Hazard Ratios of Thiazide Use on Hip Fracture**

Thiazide Use	Participants with Hip Fracture, *n*	Hazard Ratio (95% CI)*
Never use	202	1.00 (reference)
Ever use	79	0.94 (0.72–1.24)
Current use	26	0.71 (0.47–1.06)
Duration of current use		
1–42 d	6	1.17 (0.52–2.63)
43–365 d	13	0.81 (0.46–1.42)
>365 d	7	0.46 (0.21–0.96)
Daily dosage†		
≤1.0 DDD	3	0.29 (0.09–0.90)
>1.0 DDD	4	0.85 (0.32–2.32)

* Adjusted for age, sex, lower-limb disability, body mass index, estrogen use, and current smoking. DDD = defined daily dosage.
† DDD in current users with >365 days of thiazide use.

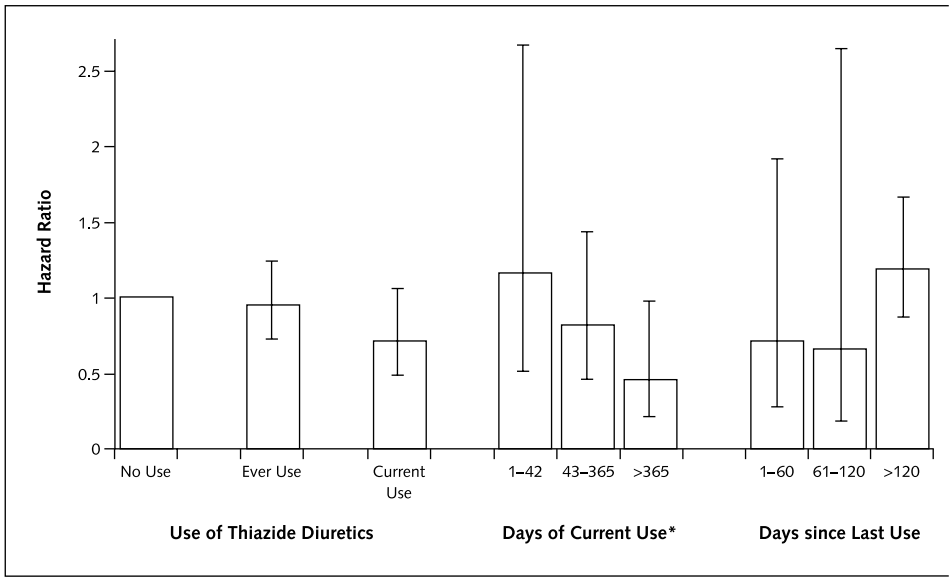
The strongest protective effect was found in participants older than 80 years of age, but the difference between this group and participants younger than 80 years of age was not statistically significant. The effect of long-term thiazide use did not differ in participants with lower or higher bone mineral density. Participants with a higher intake of calcium had a somewhat larger risk reduction (**Table 3**). Because the study included few men with hip fracture, there was insufficient power to study effect modification by sex.

To adjust for potential misclassification of duration of thiazide use at the start of the study, we also did an analysis in which we excluded all participants (35 case-patients, 849 controls) who used thiazides at baseline (self-reported users and pharmacy data–derived users) and participants with less than 365 days of follow-up. We still found a 30% reduction in incident hip fractures, but because of smaller numbers of participants, this was no longer statistically significant (hazard ratio, 0.72 [CI, 0.29 to 2.15]).

DISCUSSION

In this study, long-term use of thiazides was associated with a lower risk for hip fractures. Although this associa-

Figure. **Hazard ratios and 95% CIs for hip fracture with use of thiazide diuretics.**



All estimates were adjusted for age, sex, body mass index, lower-limb disability, current smoking, and estrogen use. *$P = 0.05$ for trend of current use.

tion was already visible after short-term use, the risk reduction reached statistical significance only after 1 year of continuous use. This protective effect occurred independently of thiazide dose. After discontinuation of thiazide treatment, the protective effect disappeared after 4 months. Because our study sample was predominantly female, we could not study effect modification by sex.

With the exception of 1 case–control study in which thiazides were associated with an increased risk for hip fracture (18), several other observational studies found that thiazide use is associated with a lower incidence of hip fractures (12, 13, 15, 16, 19). Few studies have investigated the duration of the protective effect of thiazides. A previous study (15) found a decreased risk for fracture for up to 2 months after discontinuing use, and a case–control study found an increased risk for hip fracture for any past use (13). We more precisely assessed the duration of the protective effect of thiazides after discontinuation of use and found a risk reduction for up to 4 months after discontinuation.

Several studies published over the past decades have discussed the mechanisms by which thiazides might protect against hip fracture. First, thiazides can reduce renal calcium excretion, thereby creating a positive calcium balance (5, 35). Second, by inducing a metabolic alkalosis, thiazides can inhibit bone resorption (36, 37). Furthermore, in vitro studies showed that thiazides directly inhibit osteocalcin secretion of osteoblast-like cells (38, 39). Transbøl and colleagues (21) found an effect of thiazides on bone mineral density only in the first 6 months of use, after which the bone mineral density of thiazide users and placebo users did not differ statistically significantly. Other studies, including a randomized, controlled trial, found protective effects of thiazides on bone mineral density (8, 9, 11), but these effects were often small. We could not study the effect of thiazides on bone mineral density because we had only cross-sectional data. However, if we adjusted for cross-sectionally measured bone mineral density in 1993, 2 years after the study began, the effect remained. When we investigated effect modification by calcium intake, we observed a trend toward a larger thiazide effect for participants with a higher calcium intake. This might suggest that creating a positive calcium balance is not the only mechanism by which thiazides affect hip fracture risk, because participants with moderate to high calcium intake also benefit from thiazides.

Several aspects of validity need to be discussed. Selection bias is unlikely to have occurred because our study was prospective and population-based. Although nonparticipants of the Rotterdam Study were slightly older (on aver-

Table 3. **Risk for Hip Fracture in Participants with More Than 365 Days of Current Thiazide Use: Effect Modification of Age, Bone Mineral Density, and Calcium Intake**

Variable	Participants with Hip Fracture, *n/n*	Hazard Ratio (95% CI)*
Age		
≤80 y	4/158	0.53 (0.19–1.43)
>80 y	3/123	0.38 (0.12–1.21)
Bone mineral density†		
≤0.71 g/cm^2	2/82	0.67 (0.09–4.87)
>0.71 g/cm^2	2/71	0.62 (0.09–4.55)
Calcium intake‡		
≤958 mg/d	6/199	0.57 (0.13–2.45)
>958 mg/d	1/82	0.21 (0.03–1.50)

* The estimates were adjusted for age (*d*), sex, lower-limb disability, current smoking, body mass index, and estrogen use.
† For investigation of effect modification of bone mineral density, participants with thiazide use at baseline were excluded.
‡ The calcium intake was adjusted for total caloric intake.

age, 73 vs. 70 years of age), it is very unlikely that participation was conditional on exposure to thiazides. Information bias is also unlikely, since exposure data were gathered before disease onset. We used pharmacy records to avoid potential misclassification of exposure, which was the main concern in earlier studies that defined exposure as use of thiazides at a baseline interview. Because we had access to independent and reliable information about drug exposure, in particular duration of use and past use, we could investigate the effect of thiazides for different periods of use. It is also unlikely that confounding explains our results, because we adjusted for many known confounders. It is well known that thiazides can enhance calcium metabolism, but it is unlikely that general practitioners prescribed thiazides preferentially to patients to lower their hip fracture risk during the study period. Confounding by indication cannot explain our results, because thiazides were prescribed somewhat more frequently to patients at a higher risk for hip fracture. This would tend to negate the protective effect and even indicate a spurious risk increase. Because there were few men in our study, the effects of thiazides on hip fracture risk in women probably dominate our results. Therefore, it is possible that these effects are somewhat different in men.

Hypertension is a very common medical problem that often requires long-term treatment. Thiazides are still recommended as first-choice antihypertensive agents, but the prescription rate for these drugs has decreased over the past decade (40). Recently, a randomized trial showed that thiazide-type diuretics are superior in preventing major forms of cardiovascular disease compared with angiotensin-converting enzyme inhibitors and calcium-channel blockers (41). Thiazides are inexpensive and have few adverse effects (42). Our results demonstrate that with long-term thiazide use, incidence of hip fracture can be statistically significantly reduced.

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References

1. **Cummings SR, Melton LJ.** Epidemiology and outcomes of osteoporotic fractures. Lancet. 2002;359:1761-7. [PMID: 12049882]

2. **Melton LJ 3rd.** Hip fractures: a worldwide problem today and tomorrow. Bone. 1993;14 Suppl 1:S1-8. [PMID: 8110512]

3. **Cummings SR, Kelsey JL, Nevitt MC, O'Dowd KJ.** Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev. 1985;7:178-208. [PMID: 3902494]

4. **Moser M.** Why are physicians not prescribing diuretics more frequently in the management of hypertension? JAMA. 1998;279:1813-6. [PMID: 9628713]

5. **Duarte CG, Winnacker JL, Becker KL, Pace A.** Thiazide-induced hypercalcemia. N Engl J Med. 1971;284:828-30. [PMID: 5549805]

6. **Morton DJ, Barrett-Connor EL, Edelstein SL.** Thiazides and bone mineral density in elderly men and women. Am J Epidemiol. 1994;139:1107-15. [PMID: 8192143]

7. **Reid IR, Ames RW, Orr-Walker BJ, Clearwater JM, Horne AM, Evans MC, et al.** Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. Am J Med. 2000;109:362-70. [PMID: 11020392]

8. **Wasnich RD, Benfante RJ, Yano K, Heilbrun L, Vogel JM.** Thiazide effect on the mineral content of bone. N Engl J Med. 1983;309:344-7. [PMID: 6866070]

9. **Wasnich RD, Ross PD, Heilbrun LK, Vogel JM, Yano K, Benfante RJ.** Differential effects of thiazide and estrogen upon bone mineral content and fracture prevalence. Obstet Gynecol. 1986;67:457-62. [PMID: 3960416]

10. **LaCroix AZ, Ott SM, Ichikawa L, Scholes D, Barlow WE.** 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. [PMID: 11015164]

11. **Sigurdsson G, Franzson L.** Increased bone mineral density in a population-based group of 70-year-old women on thiazide diuretics, independent of parathyroid hormone levels. J Intern Med. 2001;250:51-6. [PMID: 11454142]

12. **Cauley JA, Cummings SR, Seeley DG, Black D, Browner W, Kuller LH, et al.** Effects of thiazide diuretic therapy on bone mass, fractures, and falls. The Study of Osteoporotic Fractures Research Group. Ann Intern Med. 1993;118:666-73. [PMID: 8489642]

13. **Felson DT, Sloutskis D, Anderson JJ, Anthony JM, Kiel DP.** Thiazide diuretics and the risk of hip fracture. Results from the Framingham Study. JAMA. 1991;265:370-3. [PMID: 1984536]

14. **Hale WE, Stewart RB, Marks RG.** Thiazide and fractures of bones [Letter]. N Engl J Med. 1984;310:926-7. [PMID: 6700685]

15. **Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F, Stergachis A.** Current use of thiazide diuretics and prevention of femur fractures. J Clin Epidemiol. 1996;49:115-9. [PMID: 8598504]

16. **LaCroix AZ, Wienpahl J, White LR, Wallace RB, Scherr PA, George LK, et al.** Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med. 1990;322:286-90. [PMID: 2296269]

17. **Rashiq S, Logan RF.** Role of drugs in fractures of the femoral neck. Br Med J (Clin Res Ed). 1986;292:861-3. [PMID: 3083912]

18. **Heidrich FE, Stergachis A, Gross KM.** Diuretic drug use and the risk for hip fracture. Ann Intern Med. 1991;115:1-6. [PMID: 2048857]

19. **Ray WA, Griffin MR, Downey W, Melton LJ 3rd.** Long-term use of thiazide diuretics and risk of hip fracture. Lancet. 1989;1:687-90. [PMID: 2564506]

20. **Adland-Davenport P, McKenzie MW, Notelovitz M, McKenzie LC, Pendergast JF.** Thiazide diuretics and bone mineral content in postmenopausal women. Am J Obstet Gynecol. 1985;152:630-4. [PMID: 4025422]

21. **Transbøl I, Christensen MS, Jensen GF, Christiansen C, McNair P.** Thiazide for the postponement of postmenopausal bone loss. Metabolism. 1982;31:383-6. [PMID: 7078423]

22. **Hofman A, Grobbee DE, de Jong PT, van den Ouweland FA.** Determinants of disease and disability in the elderly: the Rotterdam Elderly Study. Eur J Epidemiol. 1991;7:403-22. [PMID: 1833235]

23. Anatomical Therapeutic Chemical Index. Oslo, Norway: World Health Organization Collaborating Centre for Drug Statistics Methodology; 1993.

24. Tractus uropoeticus. In: van der Kuy A, ed. Farmacotherapeutisch Kompas.

Amstelveen: Commissie Farmaceutische Hulp of the College voor zorgverzekeringen; 2000:523.

25. Anatomical Therapeutic Chemical Index Including Defined Daily Doses for Plain Substances. Oslo, Norway: World Health Organization Collaborating Centre for Drug Statistics Methodology; 1992.

26. International Statistical Classification of Diseases and Related Health Problems, 10th revision. vol 1. Geneva, Switzerland: World Health Organization; 1992.

27. **Folstein MF, Folstein SE, McHugh PR.** "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12:189-98. [PMID: 1202204]

28. **Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE.** Peripheral arterial disease in the elderly: The Rotterdam Study. Arterioscler Thromb Vasc Biol. 1998;18:185-92. [PMID: 9484982]

29. **Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP.** Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. Arthritis Rheum. 1983;26:1346-53. [PMID: 6639693]

30. **Burger H, de Laet CE, van Daele PL, Weel AE, Witteman JC, Hofman A, et al.** Risk factors for increased bone loss in an elderly population: the Rotterdam Study. Am J Epidemiol. 1998;147:871-9. [PMID: 9583718]

31. **Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al.** Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985;122:51-65. [PMID: 4014201]

32. **Burger H, van Daele PL, Algra D, van den Ouweland FA, Grobbee DE, Hofman A, et al.** The association between age and bone mineral density in men and women aged 55 years and over: the Rotterdam Study. Bone Miner. 1994; 25:1-13. [PMID: 8061547]

33. **Cox DR.** Regression models in life tables. Journal of the Royal Statistical Society. Series B (Methodological). 1972;34:187-220.

34. **Twisk J, de Vente W.** Attrition in longitudinal studies. How to deal with missing data. J Clin Epidemiol. 2002;55:329-37. [PMID: 11927199]

35. **Adams JS, Song CF, Kantorovich V.** Rapid recovery of bone mass in hypercalciuric, osteoporotic men treated with hydrochlorothiazide. Ann Intern Med. 1999;130:658-60. [PMID: 10215562]

36. **Arnett TR, Spowage M.** Modulation of the resorptive activity of rat osteoclasts by small changes in extracellular pH near the physiological range. Bone. 1996;18:277-9. [PMID: 8703584]

37. **Peh CA, Horowitz M, Wishart JM, Need AG, Morris HA, Nordin BE.** The effect of chlorothiazide on bone-related biochemical variables in normal post-menopausal women. J Am Geriatr Soc. 1993;41:513-6. [PMID: 8486884]

38. **Lajeunesse D, Delalandre A, Guggino SE.** Thiazide diuretics affect osteocalcin production in human osteoblasts at the transcription level without affecting vitamin D3 receptors. J Bone Miner Res. 2000;15:894-901. [PMID: 10804019]

39. **Aubin R, Ménard P, Lajeunesse D.** Selective effect of thiazides on the human osteoblast-like cell line MG-63. Kidney Int. 1996;50:1476-82. [PMID: 8914012]

40. **Onder G, Gambassi G, Landi F, Pedone C, Cesari M, Carbonin PU, et al.** Trends in antihypertensive drugs in the elderly: the decline of thiazides. J Hum Hypertens. 2001;15:291-7. [PMID: 11378830]

41. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288:2981-97. [PMID: 12479763]

42. **Savage PJ, Pressel SL, Curb JD, Schron EB, Applegate WB, Black HR, et al.** Influence of long-term, low-dose, diuretic-based, antihypertensive therapy on glucose, lipid, uric acid, and potassium levels in older men and women with isolated systolic hypertension: The Systolic Hypertension in the Elderly Program. SHEP Cooperative Research Group. Arch Intern Med. 1998;158:741-51. [PMID: 9554680]

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