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*Original Article*

# A Prospective Study of Thiazide Use and Fractures in Women

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**Abstract.** Thiazide diuretics reduce urinary calcium and may inhibit bone resorption, and hence may help to attenuate age-related bone loss and to lower the risk of osteoporotic fracture. We followed 83 728 women, who were 36–61 years of age at baseline in 1982, for 10 years with biennial mailed questionnaires on which they reported incident fractures, use of thiazide diuretics, and other medical behavioral information. From descriptions of fracture sites and circumstances, 251 hip (proximal femur) and 1594 forearm (distal radius) fractures were identified as low or moderate trauma events. After controlling for age, body mass index, menopausal status, postmenopausal hormone use, cigarette smoking and dietary factors, we observed a statistically significant 22% reduction in the risk of forearm fractures among current thiazide users compared with women who reported no thiazide use. Risk appeared to decline with longer duration of use, reaching a 37% reduction in risk among women who had been using thiazides for 8 or more years. For hip fractures, thiazide use was protective among the postmenopausal women (relative risk = 0.69, 95% confidence interval 0.48–0.99). We conclude that the potential benefit of thiazide diuretics for osteoporosis should be considered when prescribing antihypertensive treatment.

**Keywords:** Bone fracture; Femur; Hip; Osteoporosis; Questionnaire; Radius; Thiazide diuretics; Women

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## Introduction

Thiazide diuretics, which are commonly used to treat hypertension, may be of benefit in the prevention of osteoporosis because they reduce urinary calcium [1–3] and may inhibit bone resorption [4]. In cross-sectional studies, thiazide use has been associated with higher bone densities at the hip, spine, os calcis, and the distal and mid-radius [5–8]. In case–control and longitudinal investigations, lower rates of hip fractures have been reported among thiazide users compared with non-users in most [8–12] but not all [13,14] studies. Slower rates of bone loss at the radius and os calcis have been observed in hypertensive male thiazide users compared with non-hypertensive controls [15], and a recent clinical trial of chlorthalidone in hypertensive women found a significant reduction in the annual rate of bone loss at the proximal radius and significant increases in bone density at the distal radius and os calcis in the treated women compared with those in the placebo group [16]. It is possible, however, that such benefits may be transitory and that rates of bone loss may return to that of non-users after a few years of treatment [3].

Some of the previous research on osteoporosis and thiazide use has been limited by cross-sectional or retrospective designs, assessment of bone density but not fracture, minimal control for other major risk factors, and no measure of duration of use. In this 10-year prospective study of middle-aged and older women, we assessed the risk of hip and distal forearm fracture for past thiazide users and by years of current thiazide use while controlling for age, body mass index, smoking, menopausal status, postmenopausal estrogen use, dietary intakes, and other factors related to osteoporosis.

## Methods

### *Data Collection*

The Nurses' Health Study includes the 121 701 female registered nurses, 30–55 years of age in 1976 when the study began, who returned the initial mailed questionnaire on medical conditions and health behaviors. About 98% of the women are white. Follow-up questionnaires have been mailed every 2 years to identify incident diseases and to update or obtain new information on lifestyle characteristics. In 1980, the women were asked whether they were currently taking a thiazide diuretic and, if so, the number of years of use. Information on dosage was not obtained. Current use (yes or no) was ascertained again on the 1982 and 1988 questionnaires.

A history of hip and forearm fractures was collected in 1982 when participants were asked to report the date of occurrence and to describe the circumstances and exact fracture site. Incident fractures were similarly reported on subsequent biennial follow-up questionnaires. Only fractures of the proximal femur were included as hip fracture cases and only those of the distal radius were included as forearm (or Colles') fractures. Also, only those likely to involve low or moderate amounts of trauma (i.e. tripping, falling from the height of a chair, dancing) were included as endpoints in this study (about 75% of all reported fractures). We expected accurate reporting of fractures in a cohort of registered nurses, and this was validated in a sample of 30 cases for which all self-reports were confirmed by medical records [17].

A semiquantitative food frequency questionnaire was included with the 1980 mailing. Participants reported how often they consumed each of 61 food items by checking one of nine frequency-of-use categories, and daily nutrient intakes were calculated from this information. In a comparison with multiple weeks of food records, the food frequency questionnaire demonstrated that it could discriminate between levels of intake for most nutrients [18]. Diet was reassessed in 1986 with an expanded food frequency questionnaire which included probes for salt used in cooking and for salt added at the table. Information on calcium supplement use was collected in 1982 and on subsequent biennial questionnaires.

Weight was reported every 2 years and a current body mass index ($kg/m^2$) was calculated using the height reported in 1976. Information on cigarette smoking, menopausal status, use of postmenopausal estrogens, and diagnoses of osteoporosis and heart disease (myocardial infarction, angina pectoris, coronary bypass) was collected on each of the biennial questionnaires.

### *Data Analysis*

Follow-up for this analysis began in 1982 with 83 728 participants who reported their thiazide use on both the 1980 and 1982 questionnaires. Women were excluded at baseline if they reported any previous diagnosis of cancer (except non-melanoma skin cancer). Participants contributed person-time for each 2-year reporting period until death, a report of incident cancer or a hip or forearm fracture, or until end of follow-up on 1 June 1992. For age, body mass index, menopausal status, use of postmenopausal estrogens, cigarette smoking, and calcium supplement use, person-time was allocated to the variable status at the beginning of each 2-year follow-up period. For heart disease and osteoporosis, a woman was considered free of disease until a diagnosis was reported on a biennial questionnaire. In the main analyses, we used the nutritional factors as measured in 1980 without further updating. In specific analyses with sodium intake, we used the 1986 measure which included an assessment of discretionary salt use.

The status and duration of thiazide use at the 1982 baseline were calculated from the information on the 1980 and 1982 questionnaires. Current use of thiazides (yes or no) and years of use among current users were taken from the 1980 questionnaire, and 2 years were added to the duration if current use was "yes" on both the 1980 and 1982 questionnaires; 1 year duration was assigned if current use was "yes" in 1982 but "no" in 1980. A woman was defined as a past user if she responded "yes" in 1980 but "no" in 1982, and she was placed in the non-user category if she responded "no" to thiazide use in both 1980 and 1982. Women were characterized by these baseline thiazide variables until 1988 when current thiazide use was again obtained from the questionnaire. Six years were added to duration of use if current use was "yes" on the 1982 and 1988 questionnaires; 3 years duration was assigned if current use was "yes" in 1988 but "no" in 1982. A woman was defined as a past user if she responded "yes" in 1980 or 1982 but "no" in 1988, and she remained in the non-user category if she responded "no" to thiazide use on all three questionnaires.

To investigate the relationship between thiazide use and hip and forearm fractures, age-adjusted fracture rates were calculated by dividing the number of fractures by the person-time of follow-up in each category of thiazide use, and relative risks were computed as the incidence rate for past and current users compared with non-users. Proportional hazards models were used to adjust simultaneously for potential confounding variables. Stratified analyses were conducted to assess the association between thiazide use and risk of fractures among women with hypertension, postmenopausal women, postmenopausal users and non-users of estrogen replacement therapy, and within categories of calcium and sodium intakes.

## Results

During 771 605 person-years of follow-up, 1594 forearm (distal radius) fractures and 251 hip (proximal femur) fractures due to low or moderate trauma were reported.

**Table 1.** Age and age-standardized characteristics of the study population by category of thiazide diuretic use at baseline in 1982

| | Non-user | Past user | Current user | | |
|---|---|---|---|---|---|
| | | | <4 years | 4–7 years | ≥8 years |
| No. of women | 69 665 | 2652 | 7251 | 2359 | 1801 |
| *Population mean* | | | | | |
| Age (years) | 48.5 | 49.7 | 51.5 | 52.2 | 52.8 |
| Body mass index (kg/m$^2$) | 24.3 | 26.2 | 26.8 | 27.1 | 26.4 |
| Daily dietary intakes | | | | | |
| Calcium (mg) | 714 | 694 | 695 | 677 | 669 |
| Vitamin D (IU)[a] | 278 | 287 | 268 | 262 | 276 |
| Protein (g) | 75 | 75 | 76 | 75 | 76 |
| Caffeine (mg) | 394 | 384 | 368 | 360 | 369 |
| Alcohol (g) | 6.5 | 7.4 | 7.1 | 7.6 | 7.9 |
| *Percentage of population* | | | | | |
| Calcium supplement use | 11 | 14 | 11 | 12 | 12 |
| Cigarette smoking | 27 | 28 | 25 | 27 | 29 |
| Postmenopausal estrogen use[b] | 11 | 15 | 14 | 14 | 17 |

[a] Includes intake from multivitamins.
[b] Percentage of postmenopausal women only.

**Table 2.** Relative risks (RR) with 95% confidence intervals (CI) for hip and forearm fracture by status and duration of thiazide diuretic use among 83 728 women 36–61 years of age at baseline in 1982 and followed for 10 years

| Thiazide use | Person-years | Hip fractures | | | | Forearm fractures | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Cases | RR[a] | RR[b] | 95% CI | Cases | RR[a] | RR[b] | 95% CI |
| Non-user | 629 048 | 187 | 1.00 | 1.00 | – | 1306 | 1.00 | 1.00 | – |
| Past user | 37 901 | 22 | 1.48 | 1.66 | (1.06–2.61) | 81 | 0.87 | 0.87 | (0.70–1.10) |
| Current user | | | | | | | | | |
| All | 104 656 | 42 | 0.97 | 1.16 | (0.82–1.64) | 207 | 0.76 | 0.78 | (0.67–0.91) |
| <4 years | 59 996 | 28 | 1.22 | 1.44 | (0.96–2.15) | 125 | 0.84 | 0.86 | (0.71–1.03) |
| 4–7 years | 22 334 | 4 | 0.42 | 0.51 | (0.19–1.38) | 43 | 0.72 | 0.74 | (0.54–1.00) |
| ≥8 years | 22 326 | 10 | 0.93 | 1.13 | (0.59–2.15) | 39 | 0.61 | 0.63 | (0.46–0.87) |

[a] Adjusted for age (5 year intervals) and follow-up period (2-year intervals).
[b] Simultaneously adjusted for age; follow-up period; body mass index (quintiles); menopausal status and postmenopausal estrogen use (premenopausal, postmenopausal – never user, postmenopausal – past user, postmenopausal – current user); cigarette smoking (never, past, current); dietary intakes (quintiles) of calcium, vitamin D (including multivitamins), protein, alcohol, caffeine, and sodium; calcium from supplements (none, <400, 400–900, 901–1300, 1301+ mg/day); previous diagnosis of heart disease (yes or no); and previous diagnosis of osteoporosis (yes or no).

As shown in Table 1, current thiazide users were somewhat older than non-users. Cigarette smoking and nutrient intakes were not associated with the status or duration of thiazide use after adjusting for age, while body mass index was higher among the current users compared with non-users. About 11% of the cohort reported use of calcium supplements in 1982, and this practice was not associated with thiazide use at that time. Calcium supplements became more popular during the period of study, such that 47% of the cohort were using supplements in 1988.

In 10 years of follow-up, we found a statistically significant 22% reduction in the risk of forearm fracture among current thiazide users compared with non-users after adjusting for age, body mass index, menopausal status, use of postmenopausal estrogen, cigarette smoking, dietary intakes of calcium, vitamin D, protein, alcohol, caffeine, and sodium, use of calcium supplements, and previous diagnoses of heart disease and osteoporosis (Table 2). Protection appeared to increase with longer duration of use, such that risk was reduced by 37% among women who had been using thiazides for 8 or more years. A non-significant 13% reduction in risk was observed among women who used thiazides in the past.

In contrast to these results for forearm fracture, thiazide use did not appear beneficial in the prevention of hip fractures, even among women with longer durations of use (Table 2). Three women with hip fracture were steroid users, but results were unchanged when these women were excluded from analysis.

To investigate whether hypertension itself might

**Table 3.** Relative risks (RR) with 95% confidence intervals (CI) for hip and forearm fractures by thiazide diuretic use within categories of postmenopausal estrogen use, calcium intake and sodium intake

| | | Hip fractures | | | Forearm fractures | | |
|---|---|---|---|---|---|---|---|
| | | Non-user | Past user | Current user | Non-user | Past user | Current user |
| *Postmenopausal estrogen*[a] | | | | | | | |
| Current user | RR[b] | 1.00 | 0.35 | 1.12 | 1.00 | 0.83 | 0.99 |
| | 95% CI | – | (0.05–2.58) | (0.53–2.38) | – | (0.45–1.53) | (0.68–1.44) |
| | No. of cases | 34 | 1 | 9 | 159 | 11 | 36 |
| Never user | RR[b] | 1.00 | 1.61 | 0.72 | 1.00 | 0.64 | 0.84 |
| | 95% CI | – | (0.77–3.38) | (0.38–1.37) | – | (0.42–0.97) | (0.67–1.05) |
| | No. of cases | 84 | 8 | 11 | 552 | 23 | 93 |
| *Calcium intake*[c] | | | | | | | |
| <500 mg/day | RR[d] | 1.00 | 1.68 | 1.87 | 1.00 | 0.99 | 0.65 |
| | 95% CI | – | (0.58–4.88) | (0.94–3.73) | – | (0.63–1.54) | (0.47–0.91) |
| | No. of cases | 32 | 4 | 12 | 284 | 22 | 41 |
| >800 mg/day | RR[d] | 1.00 | 1.28 | 0.61 | 1.00 | 0.99 | 0.63 |
| | 95% CI | – | (0.54–3.01) | (0.27–1.35) | – | (0.67–1.47) | (0.47–0.84) |
| | No. of cases | 62 | 6 | 7 | 419 | 28 | 51 |
| *Sodium intake*[e] | | | | | | | |
| >2500 mg/day | RR[d] | 1.00 | 2.87 | 1.18 | 1.00 | 0.82 | 0.78 |
| | 95% CI | – | (1.40–5.88) | (0.58–2.40) | – | (0.53–1.28) | (0.57–1.06) |
| | No. of cases | 39 | 10 | 10 | 271 | 22 | 50 |
| ≥2500 mg/day | RR[d] | 1.00 | 1.19 | 1.19 | 1.00 | 0.75 | 0.67 |
| | 95% CI | – | (0.51–2.79) | (0.66–2.15) | – | (0.50–1.12) | (0.50–0.90) |
| | No. of cases | 65 | 6 | 14 | 415 | 25 | 54 |

[a] Analysis conducted for 1982–1992 among postmenopausal women.
[b] Simultaneously adjusted for age (5-year intervals); follow-up period (2-year intervals); body mass index (quintiles); cigarette smoking (never, past, current); calcium from supplements (none, <400, 400–900, 901–1300, 1301+ mg/day); previous diagnosis of heart disease (yes or no); and previous diagnosis of osteoporosis (yes or no).
[c] Calcium intake from food was assessed in 1980; analysis conducted for 1982–1992.
[d] Simultaneously adjusted for age; follow-up period; body mass index; menopausal status and postmenopausal estrogen use (premenopausal, postmenopausal – never user, postmenopausal – past user, postmenopausal – current user); cigarette smoking; calcium from supplements (none, <400, 400–900, 901–1300, 1301+ mg/day); previous diagnosis of heart disease; and previous diagnosis of osteoporosis.
[e] Sodium intake was assessed in 1986; analysis conducted for 1986–1992.

explain the observed associations between thiazide use and fracture risk, we limited the study population to only those women who reported a physician diagnosis of high blood pressure. In these analyses, we observed reductions in the risk of forearm fracture among hypertensive thiazide users compared with hypertensive non-users that were similar to those for the entire cohort. Thiazide use continued to show no association with hip fracture in this subgroup.

Since the cohort included younger women who were unlikely to fracture due to osteoporosis, we examined the association between thiazide use and fractures among the women in their postmenopausal years. These analyses included approximately 55% of the person-years of follow-up and over 80% of the fractures of the full cohort. For forearm fractures, postmenopausal women experienced the same benefits from thiazide use as those observed for the full cohort of premenopausal and postmenopausal women. For hip fractures, however, current thiazide users showed a significant reduction in risk of hip fracture (RR = 0.69, 95% CI 0.48–0.99) compared with the non-users among the postmenopausal women in the cohort.

Since estrogen replacement therapy is highly protective against bone loss and fractures, we examined the effects of thiazide use separately among postmenopausal estrogen users and non-users. Among current estrogen users, neither hip nor forearm fracture risk was reduced with thiazide use (Table 3). However, among women who never used postmenopausal estrogens, current thiazide users showed non-significant reductions in risk for both types of fractures. With 8 or more years of thiazide use, the risk of forearm fracture among these women was significantly reduced (RR = 0.51, 95% CI 0.30–0.89).

We investigated the possibility that diet may alter the effects of thiazides on bone. For forearm fractures, we found no evidence to suggest that either calcium or sodium intakes modify the apparent protective effects of thiazide use (Table 3). In contrast, we found that calcium may affect the relationship between thiazides and hip fractures. Current thiazide use was inversely, but non-significantly, related to fracture risk among women with calcium intakes greater than 800 mg/day (RR = 0.61, 95% CI 0.27–1.35) but not among those with calcium intakes of less than 500 mg/day (RR = 1.87, 95% CI 0.94–3.73). However, based on a measure of total calcium intake (diet plus supplements) in 1984,

thiazide use provided no protection against hip fracture among women consuming more than 1200 mg/day of calcium (RR = 1.76, 95% CI = 0.79–3.92).

## Discussion

In this 10-year prospective study of thiazide diuretic use and bone fractures in women, we observed a protective effect of thiazides against distal forearm fractures. After adjusting for age and a number of other factors related to osteoporotic fractures, a statistically significant 22% reduction in risk was observed for all current thiazide users, and an even greater reduction of 37% was observed among those with 8 or more years of thiazide use. Among past thiazide users, the risk of forearm fracture was 13% lower than that among non-users, suggesting that protection extends for some time after thiazide use is discontinued. These results are in agreement with reports of higher radial bone mineral densities [5–8] and slower rates of radial bone loss [15,19] among thiazide users compared with non-users. They are also in agreement with a recent clinical trial that reported a significantly greater gain in distal radial bone density among elderly women taking chlorthalidone compared with those in the placebo group [16]. In the one previously reported longitudinal study that assessed forearm fractures, a 34% reduction was observed among women with more than 10 years of thiazide use [8], though the smaller size of this study (9700 women with 250 incident forearm fractures) provided less power to detect significant differences in fracture risk.

In our full cohort of women, we found no reduction in risk of hip fracture among the thiazide users, even for those with 8 or more years of use. This is in contrast to most studies, which have reported inverse associations between thiazide use and hip fracture [8–12], and a recent meta-analysis that yielded an 18% reduction in risk of hip fracture for current thiazide users [20]. However, one difference between these investigations and our current research is that previous results were based primarily on postmenopausal or elderly women, while many of the women with hip fractures in our cohort were younger (mean age at fracture 60 years) than the age at which hip fractures commonly occur. Indeed, when we limited our analyses to postmenopausal women, we observed a significant 31% reduction in risk of hip fractures for current thiazide users. LaCroix et al. [10] reported a similar reduction in risk of hip fractures for thiazide users in a longitudinal study of men and women over 65 years of age.

Thiazide diuretics are prescribed primarily as a treatment for hypertension, and 25% or more of an elderly community may be current thiazide users [7,10]. It is possible that a hypertensive condition or some factor associated with hypertension could be responsible for the observed relationships between thiazide use and bone fractures. However, our data did not support this hypothesis. In a subanalysis with the hypertensive women in our cohort, thiazide use continued to have a protective association in relation to forearm fractures and no apparent effect on hip fractures. Our findings support a previous report from the Rancho Bernardo study [7] in which higher bone densities were observed in both hypertensive and non-hypertensive thiazide users.

Biological evidence that thiazide diuretics reduce urinary excretion of calcium [1–3] adds plausiblity to our observations of a lower incidence of fractures in thiazide users. If this is indeed part of the mechanism by which thiazides help to preserve bone mass, we might expect the association between thiazide use and fracture incidence to be modified by level of calcium intake. However, calcium intake did not modify the significant protective association between thiazide use and forearm fracture that was observed for this cohort. We did see a reduced risk of hip fractures among women with dietary calcium intakes greater than 800 mg/day but not among women with intakes less than 500 mg/day, but the results were not statistically significant and are therefore only suggestive. We did not find any protective effect of thiazide use among women with total calcium intakes (from food plus supplements) greater than 1200 mg/day, though it is possible that results may be biased if the women who selected to use calcium supplements were those most at risk for fractures. In the Study of Osteoporotic Fractures [8], calcium intake did not affect the protective association between thiazide use and wrist and hip fractures.

Higher sodium intakes cause an increase in urinary sodium excretion which is accompanied by a greater urinary loss of calcium and an increase in biochemical markers of bone turnover [21], suggesting that higher sodium intakes may contribute to bone loss. Indeed, a recent longitudinal study with postmenopausal women reported an inverse association between urinary sodium excretion and changes in bone density for the intertrochanter and total hip [22]. Based on these findings, we expected that the benefits of thiazide use would be most pronounced among women with low sodium intakes and would be attenuated among women with higher sodium diets. Our data did not substantiate this hypothesis as the thiazide and fracture associations were similar among women with sodium intakes above or below 2500 mg/day. However, sodium intake is difficult to measure reliably and misclassification may have obscured a sodium effect.

Decreased levels of hydroxyproline among thiazide users [2–4] indicate that inhibition of bone resorption may be another mechanism by which thiazides retard bone loss. Estrogen treatment also inhibits bone resorption, and higher bone mineral density has been reported among women using both thiazides and estrogen than among women using only one of the medications [7,23]. In our cohort, we did not observe such additive effects. Thiazide use appeared to be associated with reduced risk for both hip and forearm fractures among postmenopausal women who never used estrogen replacement therapy, but thiazides

provided no protection against fractures for women currently using postmenopausal estrogens.

Questions remain as to the safety of thiazide use among normotensive adults. Though the hypothesis that postural hypotension may increase the risk of falling is not well supported [24,25] and previous reports of elevated cholesterol were not confirmed with moderate dosages of 25–50 mg of chlorthalidone [26], other adverse effects could develop if blood pressure is decreased among normotensive adults using thiazide medications. Another question is the dose required for reducing bone loss. Previous studies have not observed greater benefits in bone mineral density with higher dosages [5,7], though amounts less than 25 mg/day were not considered. On the other hand, protection against hip fractures was more pronounced for users of pure thiazide than for those who used combination drugs [9], perhaps suggesting that the quantity of thiazide in the combination drugs was not sufficient to produce a full beneficial effect.

The results of this study may be generalized to white women middle-aged and older. One limitation of this study was the lack of validation of fractures by radiographs or medical records, though the nurses that comprise this cohort are particularly capable of reporting the type and location of their bone fracture [17].

Given the evidence from this and other studies, the potential benefits of thiazides for osteoporosis should be considered when prescribing antihypertensive treatment.

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