

Low Bone Density and Bisphosphonate Use and the Risk of Kidney Stones

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Abstract

Background and objectives Previous studies have demonstrated lower bone density in patients with kidney stones, but no longitudinal studies have evaluated kidney stone risk in individuals with low bone density. Small studies with short follow-up reported reduced 24-hour urine calcium excretion with bisphosphonate use. We examined history of low bone density and bisphosphonate use and the risk of incident kidney stone as well as the association with 24-hour calcium excretion.

Design, setting, participants, & measurements We conducted a prospective analysis of 96,092 women in the Nurses' Health Study II. We used Cox proportional hazards models to adjust for age, body mass index, thiazide use, fluid intake, supplemental calcium use, and dietary factors. We also conducted a cross-sectional analysis of 2294 participants using multivariable linear regression to compare 24-hour urinary calcium excretion between participants with and without a history of low bone density, and among 458 participants with low bone density, with and without bisphosphonate use.

Results We identified 2564 incident stones during 1,179,860 person-years of follow-up. The multivariable adjusted relative risk for an incident kidney stone for participants with history of low bone density compared with participants without was 1.39 (95% confidence interval [95% CI], 1.20 to 1.62). Among participants with low bone density, the multivariable adjusted relative risk for an incident kidney stone for bisphosphonate users was 0.68 (95% CI, 0.48 to 0.98). In the cross-sectional analysis of 24-hour urine calcium excretion, the multivariable adjusted mean difference in 24-hour calcium was 10 mg/d (95% CI, 1 to 19) higher for participants with history of low bone density. However, among participants with history of low bone density, there was no association between bisphosphonate use and 24-hour calcium with multivariable adjusted mean difference in 24-hour calcium of -2 mg/d (95% CI, -25 to 20).

Conclusions Low bone density is an independent risk factor for incident kidney stone and is associated with higher 24-hour urine calcium excretion. Among participants with low bone density, bisphosphonate use was associated with lower risk of incident kidney stone but was not independently associated with 24-hour urine calcium excretion.

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Introduction

Kidney stones are common, with a lifetime risk of 9% in women and 19% in men (1), and account for billions of dollars in annual healthcare expenditures (2–4). Individuals with kidney stones may have a systemic disorder of calcium metabolism (5–8). Multiple studies have demonstrated lower bone mineral density and higher fracture risk in individuals who form kidney stones (6,8–14). Higher risk of low bone density is related in part to higher bone turnover and negative calcium balance from higher urinary calcium excretion (15,16). Furthermore, individuals without a history of kidney stones but with low bone density also have higher urinary calcium excretion (17). However, there are no published prospective studies of incident stone risk in individuals with low bone density.

Bisphosphonates inhibit bone resorption and are commonly used to treat reduced bone mineral density

and prevent fracture (13). Bisphosphonate use has also been shown to lower urinary calcium excretion in animal models (18,19) and by 50–100 mg/d in small human studies (20–23), an effect thought to be due to the reduction in bone resorption (19). These human studies were limited by small sample sizes and short follow-up, and did not examine risk of kidney stone formation.

To examine whether a history of low bone density or bisphosphonate use is associated with risk of an incident kidney stone, we performed a prospective analysis in 96,092 participants in the Nurses' Health Study II, an ongoing cohort study. In addition, we performed a cross-sectional analysis of low bone density, bisphosphonate use, and 24-hour urinary calcium excretion in 2294 participants. We hypothesized that low bone density would be associated with higher risk of a kidney stone whereas

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bisphosphonate use would be associated with lower risk of a kidney stone. We hypothesized that low bone density would be associated with higher 24-hour urinary calcium excretion whereas bisphosphonate use would be associated with lower 24-hour urinary calcium excretion.

Materials and Methods

Study Population

The Nurses' Health Study II cohort was initiated in 1989 with 116,430 female registered nurses aged 25–42 years. This cohort is followed every 2 years with questionnaires providing updated information on lifestyle and disease. The average cohort follow-up is >90% of eligible person-time. The baseline year for this analysis was 1995 because this was the first time period for which we had an adequate number of cases and statistical power to detect a difference in relative risk of incident kidney stone for participants with low bone density compared with those without low bone density. A secondary analysis limited to participants with a history of low bone density started in 2007 because this was when data on bisphosphonate use was first collected. Individuals with a history of kidney stones at baseline were excluded from the prospective analyses.

Assessment of Low Bone Density and Bisphosphonate Use

Participants were asked if they had ever been diagnosed with low bone density and, if so, the date of first diagnosis on the 2005 questionnaire and this was asked again on the 2009 and 2013 questionnaires. Each participant with low bone density was assigned to the low bone density group starting at that participant's reported date of first diagnosis and remained in the low bone density group until study end. Self-reported diagnosis of low bone density, either osteoporosis or low bone density/osteopenia, was demonstrated to be valid in Nurses' Health Study II (NHS II). A random sample of participants who reported diagnosis of low bone density/osteopenia or osteoporosis on a biennial questionnaire was sent an additional questionnaire requesting permission to obtain medical records for bone density tests. Self-reported diagnoses were confirmed in 114 out of 120 (95%) using World Health Organization criteria for osteopenia/osteoporosis (a T score of ≤ -1 at either the lumbar spine, femoral neck, or hip) (24).

Starting in 2007, and every 2 years thereafter, participants were asked if they were currently taking a bisphosphonate (e.g., Fosamax, Actonel). Participants who reported current bisphosphonate use were included in the bisphosphonate group for that period and exposure status was updated for subsequent periods on the basis of the response to the questionnaire.

Assessment of Diet

Dietary intake was assessed using information from semiquantitative food frequency questionnaires in 1995, 1999, 2003, 2007, and 2011. Participants reported average use of >130 different food items and >20 beverages over the previous year. The validity and reproducibility of the food frequency questionnaire has been previously reported

(25–28). Nutrient variables were energy adjusted to reflect the nutrient composition of the diet independent of total food consumed. Intake of supplemental calcium and vitamin D, isolated or in multivitamin form, was determined by frequency and amount of use as well as supplement brand and type.

Assessment of Nondietary Covariates

Information on age, weight, and height was obtained on the 1989 questionnaire, and age and weight were updated on each biennial questionnaire. The validity of self-reported weight was reported for two similar cohorts (29). Information on diagnosis of hypertension and diabetes mellitus was updated on each biennial questionnaire. Validation of the self-report of these conditions has been documented (30–32). Information on thiazide use was updated every 2 years.

Ascertainment of Kidney Stones

Participants reported a diagnosis of an incident kidney stone on the biennial questionnaires. To confirm a self-reported incident kidney stone, participants who reported a new kidney stone diagnosis were mailed a supplemental questionnaire requesting information such as date of diagnosis, pain, and hematuria. A validation study performed in 858 women in NHS II confirmed 98% of self-reports compared with medical records (33). Of these, 79% of study participants with a stone composition report in the medical record had a stone composed of at least 50% calcium oxalate (33).

Twenty-Four-Hour Urine Collection

In 2010–2011, 2567 NHS II participants performed one 24-hour urine collection using the Litholink (Chicago, IL) system. The participants excluded from the urine collection had a history of cancer other than nonmelanoma skin cancer or history of hypertension before the invitation to participate being sent. Participants with a previously reported history of hypertension on a biennial questionnaire were not invited to participate in the 24-hour urine collection project because the collection was done as part of a study examining urinary risk factors for incident hypertension. The participants with hypertension likely developed hypertension after meeting criteria for inclusion in the initial study, but before completion of the urine collection. Participants with a 24-hour creatinine value in the top or bottom 1% of the urinary creatinine distribution were excluded from the analysis to remove outliers that may have been the result of over- or under-collection, leaving 2294 urine collections for the analysis.

Statistical Analyses

Prospective Analyses of Incident Kidney Stones. We used multivariable Cox proportional hazards regression models to estimate age- and multivariable-adjusted relative risks with 95% confidence intervals (95% CIs) for the risk of an incident kidney stone among women with and without a history of low bone density and separately among women with low bone density who did and did not use bisphosphonates. Variables included in the

multivariable models were age (continuous), body mass index (BMI; continuous), calcium supplement use (none, 0–100 mg/d, 101–500 mg/d, >500 mg/d), use of thiazide diuretics, family history of kidney stones, history of hypertension, history of diabetes mellitus, menopausal status (premenopausal, postmenopausal, and indeterminate), and quintiles of intake of fluid, dietary calcium, animal protein, sodium, potassium, magnesium, phosphorus, sucrose, vitamin C, vitamin D, and alcohol intake (six categories). Participants were included in the low bone density group from reported date of first diagnosis until study end. Bisphosphonate use was updated every 2 years. Nondietary variables were updated in the model every 2 years and dietary variables every 4 years. Participants with data missing in any period were excluded for the time period in which data were missing. These participants were included in subsequent periods, provided there were no missing data.

In addition, several secondary analyses were performed: excluding participants with primary hyperparathyroidism; stratifying by menopausal status; and excluding all participants on supplemental calcium and vitamin D.

Cross-Sectional Analysis of 24-Hour Urine. We used multivariable linear regression to examine the association between low bone density and 24-hour urinary calcium excretion adjusted for age (continuous), BMI (continuous), thiazide use, dietary calcium (continuous), supplemental calcium (continuous), total vitamin D (continuous), low bone density, menopausal status (premenopausal, postmenopausal, and indeterminate), 24-hour urine volume (continuous), and 24-hour urine excretion of creatinine, sodium, citrate, magnesium, oxalate, sulfate, phosphorus, potassium, and ammonium (all continuous).

Among participants who had a history of low bone density, we used multivariable linear regression to examine the association between bisphosphonate use and 24-hour urinary calcium excretion adjusting for the above covariates.

We also examined the associations after stratifying by urinary calcium excretion >200, >250, and >300 mg/d. Among participants with low bone density, we used multivariable linear regression to examine the association between bisphosphonate use and 24-hour urinary volume, oxalate excretion, citrate excretion, and calcium oxalate supersaturation adjusted for the above covariates where appropriate.

For this analysis, low bone density was ascertained from the biennial questionnaires where participants provided information on a history of low bone density before the urine collection. Bisphosphonate use was obtained from the 2011 NHS II questionnaire for 2009–2011, the time period during which the 24-hour urine samples were collected.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The research protocol for this study was approved by the institutional review board of the Brigham and Women's Hospital.

Results

Incident Kidney Stones

The prospective analysis of incident kidney stone formation included 96,092 participants with 1,179,860 person-years of follow-up. Characteristics of participants are presented in Table 1 according to history of low bone density at approximate study midpoint (2003). Baseline characteristics of participants are presented in Supplemental Table 1 according to history of low bone density. Participants with low bone density were older, had lower BMI, were more likely to be postmenopausal, more likely to be taking a bisphosphonate, and had higher supplemental calcium intake. During follow-up, 2564 participants developed a symptomatic incident kidney stone.

A self-reported history of low bone density was independently associated with a higher risk of an incident kidney stone. The multivariable adjusted relative risk for participants with low bone density compared with

Table 1. Characteristics by reported low bone density from study midpoint (2003)

Characteristic	No Low Bone Density (n=57,338)	Low Bone Density (n=3402)
Age, yr	48 (5)	51 (4)
Race, white	55,491 (97)	3331 (98)
Body mass index, kg/m ²	27.1 (6.3)	24.5 (5.1)
Postmenopausal	18,604 (32)	2192 (64)
Bisphosphonate use	95 (<1)	282 (8)
History of hypertension	9788 (18)	531 (16)
History of diabetes	1697 (3)	65 (2)
Family history of kidney stones	8026 (14)	535 (16)
Thiazide use	4038 (7)	237 (7)
Fluid intake, L/d	1.9 (0.8)	1.9 (0.8)
Dietary calcium intake, mg/d	949 (420)	958 (438)
Dietary potassium intake, mg/d	3228 (1034)	3250 (1017)
Median calcium supplement (25%–75%), mg/d	450 (0, 1162)	1000 (500, 1167)
Total vitamin D intake, IU	487 (320)	679 (379)

Data are presented as N (%) with dietary intake and urinary factors presented as mean (SD) unless otherwise indicated.

Table 2. Age- and multivariable-adjusted relative risks for incident kidney stones by low bone density (1995–2013)

	No Low Bone Density	Low Bone Density	P Value
Cases	2302	262	
Person-yr	1,081,620	98,240	
Age-adjusted RR	1.0 (ref)	1.24 (1.08, 1.42)	0.002
MV-adjusted RR	1.0 (ref)	1.39 (1.20, 1.62)	<0.001

Data are presented as number of cases or person-years and RR (95% confidence interval). Multivariable model: Adjusted for age, body mass index, dietary factors (calcium, magnesium, potassium, sucrose, fructose, sodium, animal protein, vitamin D, vitamin C, phosphorus, alcohol, caffeine, total fluid), supplemental calcium intake, thiazide, family history of kidney stones, history of hypertension, history of diabetes mellitus, menopausal status, bisphosphonate use, and postmenopausal hormone use. RR, relative risk; ref, reference; MV, multivariable.

participants without low bone density was 1.39 (95% CI, 1.20 to 1.62) (Table 2). Body mass index was the major negative confounder.

In a secondary analysis excluding the 1.2% of participants who reported primary hyperparathyroidism, the results were similar. In a secondary analysis stratifying by menopausal status, results were similar for pre- and postmenopausal status. In a sensitivity analysis excluding participants on supplemental calcium and vitamin D, the multivariable-adjusted relative risk of kidney stone for participants with low bone density was 1.79 (95% CI, 1.35 to 2.39) compared with participants who did not have low bone density.

In an analysis limited to 17,075 participants with a history of low bone density, bisphosphonate use was associated with a lower risk of an incident kidney stone. The multivariable adjusted relative risk was 0.68 (95% CI, 0.48 to 0.98) for participants using bisphosphonates compared with those who were not (Table 3).

Twenty-Four-Hour Urine

The characteristics of the 2294 participants who performed a 24-hour urine collection are shown in Table 4. The 458 (20%) participants with a history of low bone density were older, had a lower BMI, were more likely to be postmenopausal, and had higher intakes of supplemental calcium and total vitamin D compared with those who did not have low bone density.

The 24-hour urinary calcium excretion was higher in participants with a history of low bone density. The

multivariable adjusted mean difference was 10 mg/d (95% CI, 1 to 19 mg/d) for participants with low bone density compared with those without (Table 5). In a secondary analysis excluding the 15 participants who reported primary hyperparathyroidism, the results were similar. In a secondary analysis of the 679 participants who were not taking calcium supplements, the mean difference in 24-hour calcium excretion was 3 mg/d (95% CI, -17 to 23).

In the analysis limited to the 458 participants with a history of low bone density, urinary calcium excretion did not differ by bisphosphonate use around the time of the urine collection. The multivariable adjusted mean difference in 24-hour calcium excretion was -2 mg/d (95% CI, -25 to 20) (Table 6) for participants (n=68) using a bisphosphonate compared with those who were not. When the analysis included participants who had ever been on a bisphosphonate before the collection, the results were not materially changed. Urinary calcium excretion did not differ by bisphosphonate use in stratified analyses using 24-hour urinary calcium excretion of 300, 250, or 200 mg/d as stratification cutoff points. There was no significant difference in the other urinary predictors of calcium stone formation that were examined (Supplemental Table 2).

Discussion

Our study found a history of low bone density was independently associated with higher risk of kidney stones

Table 3. Age- and multivariable-adjusted relative risks of incident kidney stones by bisphosphonate use among participants (n=17,075) with low bone density (2007–2013)

	No Bisphosphonate Use	Bisphosphonate Use	P Value
Cases	154	42	
Person-yr	52,240	20,494	
Age-adjusted RR	1.0 (ref)	0.69 (0.49, 0.97)	0.03
MV-adjusted RR	1.0 (ref)	0.68 (0.48, 0.98)	0.03

Data are presented as number of cases or person-years and RR (95% confidence interval). Multivariable model: Adjusted for age, body mass index, dietary factors (calcium, magnesium, potassium, sucrose, fructose, sodium, animal protein, vitamin D, vitamin C, phosphorus, alcohol, caffeine, total fluid), supplemental calcium, thiazide, family history of kidney stones, history of hypertension, history of diabetes mellitus, menopausal status, and postmenopausal hormone use. RR, relative risk; ref, reference; MV, multivariable.

Characteristics	No Low Bone Density (n=1836)	Low Bone Density (n=458)
Age, yr	53.6 (3.2)	55.3 (2.8)
Race, white	1792 (98)	449 (98)
BMI, kg/m ²	25.8 (4.9)	23.6 (3.9)
Postmenopausal	1121 (61)	379 (82)
History of hypertension	49 (3)	11 (2)
History of diabetes	26 (1)	9 (2)
History of kidney stones	46 (46 (2.5))	16 (3.5)
Family history of kidney stones	296 (16)	88 (19)
Thiazide use	37 (2)	12 (3)
Dietary intake		
Fluid intake, L/d	1.7 (0.7)	1.6 (0.7)
Vitamin D intake, IU	1006 (786)	1340 (794)
Calcium intake, mg/d	959 (409)	954 (414)
Median calcium supplement (25%–75%), mg/d	500 (0–1000)	800 (500–1024)
Urinary factors		
Volume, L/d	2.1 (0.9)	2.1 (0.8)
Calcium, mg/d	200 (92)	214 (98)
Sodium, mEq/d	139 (54)	125 (52)
Oxalate, mg/d	31 (11)	31 (12)
Magnesium, mg/d	107 (37)	111 (43)
Citrate, mg/d	804 (283)	789 (262)
Potassium, mEq/d	65 (20)	65 (21)
Sulfate, mEq/d	38 (11)	35 (11)
Phosphorus, mg/d	846 (244)	766 (234)
Ammonium, mmol/d	30 (10)	27 (9)
Creatinine, mg/d	1254 (206)	1151 (190)

Categoric variables are presented as N(%) unless otherwise indicated. Continuous variables are presented as mean (SD) unless otherwise indicated. BMI, body mass index.

and higher 24-hour urinary calcium excretion. Bisphosphonate use was independently associated with lower risk of incident kidney stones among participants with a history of low bone density but was not associated with 24-hour urinary calcium excretion.

There are no previously published longitudinal studies that have examined the association between history of low bone density and risk of subsequent incident kidney stone formation. Prior studies have examined a history of kidney stones and higher urinary calcium excretion and the subsequent risk of low bone density and fracture (5,6,9–12,14). Higher urinary calcium excretion may lead to negative calcium balance, which has been shown to be predictive of lower bone density (5,15,16). A previous study has also found higher urinary calcium excretion in

individuals with low bone density but without a history of kidney stones (17). Our study demonstrated a significantly higher mean 24-hour urinary calcium excretion in participants (2.7% with history of kidney stones) who had low bone density compared with those without. The higher risk of kidney stones for individuals with low bone density is likely related to higher urinary calcium because higher urinary calcium is a strong predictor of being a stone former (34). Of note, participants with low bone density in our study had higher supplemental calcium use and supplemental calcium use is associated with higher risk of kidney stones (35), although we did adjust for supplemental calcium use in our models.

This was the largest longitudinal study to examine bisphosphonate use and risk of kidney stones. Among

Model	Difference in Urinary Calcium (mg/d) for Low Bone Density	95% CI	P Value
Age-adjusted	16	6 to 26	0.002
MV-adjusted	10	1 to 19	0.02

Multivariable model: Adjusted for age, body mass index, bisphosphonate use, thiazide use, supplemental calcium intake, dietary calcium intake, total vitamin D intake, menopausal status, and urinary factors (volume, sodium, magnesium, citrate, potassium, sulfate, phosphorus, creatinine). 95% CI, 95% confidence interval; MV, multivariable.

Table 6. Adjusted difference in 24-hour urinary calcium excretion for participants with history of low bone density who were on a bisphosphonate (n=68) compared with participants who were not on a bisphosphonate (n=390)

Model	Difference in Urinary Calcium (mg/d) for Bisphosphonate Use	95% CI	P Value
Age-adjusted	3	–23 to 28	0.82
MV-adjusted	–2	–25 to 20	0.83

Multivariable model: Adjusted for age, body mass index, thiazide use, supplemental calcium intake, dietary calcium intake, total vitamin D intake, menopausal status, and urinary factors (volume, sodium, magnesium, citrate, potassium, sulfate, phosphorus, creatinine). 95% CI, 95% confidence interval; MV, multivariable.

those who had a history of low bone density, participants who used a bisphosphonate had a lower risk of an incident kidney stone compared with participants not taking a bisphosphonate. A potential mechanism to explain the lower risk is that bisphosphonates might change the composition of the urine by affecting the urinary excretion of either a promotor or inhibitor of calcium stone formation. Urinary calcium excretion is an important urinary factor in stone formation that has been previously studied with bisphosphonates medications (20–23,36). A study of postmenopausal women (n=77) with elevated urinary calcium and reduced bone mineral density reported the 24-hour urinary calcium was 100 mg/d lower and bone mineral density test scores improved after 12 months of bisphosphonate therapy for the 25 participants in the alendronate monotherapy arm of the study (36). Lower urinary calcium excretion in these studies was thought to be due to reduction in bone resorption with bisphosphonate therapy (19,36). We found a lower risk of kidney stone formation in participants with low bone density taking bisphosphonates compared with those not on bisphosphonates but found no difference in any of the urinary predictors of stone formation. It is possible that bisphosphonates affect the urinary excretion of a promotor or inhibitor of calcium stone formation that we did not measure.

There are several potential reasons why our results differ from the prior studies of bisphosphonate use and urinary calcium excretion. Our study of 2294 participants was cross-sectional with one urine collection and the bisphosphonates could have been used for years, whereas previous studies were small, short-term, longitudinal studies often with single pre- and post-treatment urine collections. For example, in a study with 18 participants, including nine stone formers, with a mean baseline urinary calcium excretion of 252 mg/d, there was a nonsignificant trend toward a reduction of 48 mg/d in urinary calcium after administration of alendronate (23). The mean urinary calcium excretion in our study and percentage of participants with a history of stones were each much lower. It is possible that the effect of bisphosphonates is different in participants who form stones and have a higher bone resorption contribution to urinary calcium excretion. To examine this in our study, we performed stratified analyses of the participants with urinary calcium excretion 300 mg/d or higher but found no difference by bisphosphonate use.

Furthermore, in the Giusti *et al.* study, the 77 postmenopausal participants had only one post-treatment 24-hour urine collection, raising the possibility of regression to the mean (36).

In our study we updated the exposure at 2-year periods, so it is possible that the effect, if any, of bisphosphonates on urinary calcium excretion is not sustained or that the duration or magnitude of effect varies among different generations of bisphosphonates (37). Previous studies using alendronate (22) and pamidronate (20) showed lower urinary calcium at follow up. Our study did not have the ability to examine individual bisphosphonates or timing of initiation.

There are limitations to this study. The design was observational so we cannot rule out residual confounding. We did not have stone composition reports on the majority of stone formers, but in our validation study close to 80% were predominantly calcium oxalate stones (33). We only had one urine collection per participant so were unable to prospectively examine change in urinary calcium excretion. We did not have information on eGFR so we were unable to adjust for this in our analyses. Diagnosis of kidney stone was on the basis of self-report which is typically timed with stone passage. Undetected stone formation may have occurred many years before passage and possibly before diagnosis of low bone density. Lastly, generalizability may be limited because cohort participants are all women, predominantly white, and only a small number had hypertension.

In conclusion, low bone density was associated with higher risk of incident kidney stones and higher 24-hour urinary calcium excretion. Bisphosphonates may reduce the risk of incident kidney stones among participants with low bone density but the mechanism is uncertain. Additional research is needed to better understand the relation between bisphosphonate medications, urine calcium excretion, and kidney stone formation.

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Disclosures

None.

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