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Hydrochlorothiazide and Bone Mineral Density in Patients with Kidney Stones

Post Hoc Analysis of the NOSTONE Trial

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Key Points

- Loss of bone mineral density at 3 years was similar in patients with calcium kidney stones randomized to hydrochlorothiazide or placebo.
- There was no association between hydrochlorothiazide dose and change in bone mineral density at 3 years.
- Results were consistent across sensitivity and per-protocol analyses.

Abstract

Background Low bone mass and fractures are common among kidney stone formers, yet it remains unclear whether thiazides can help preserve bone mass. We aimed to evaluate the effectiveness of a range of hydrochlorothiazide (HCTZ) doses compared with a placebo on bone mineral density (BMD) over a 3-year period.

Methods This *post hoc* analysis was conducted on data from the NOSTONE trial, a multicenter, randomized, controlled study. A total of 416 adults with recurrent calcium stones participated in the study, receiving either placebo or HCTZ at doses of 12.5, 25, or 50 mg daily. BMD was measured using computed tomography at the T12–L3 vertebrae at both baseline and the end of the study.

Results Over a median follow-up period of 2.92 years, the mean BMD decreased by 6.4±15.7 Hounsfield units (HU) in the placebo group, 5.1±15.1 HU in the 12.5 mg HCTZ group (β coefficient versus placebo, 0.37 HU; 95% confidence interval [CI], −1.74 to 2.47; $P = 0.73$), 4.1±16.3 HU in the 25 mg HCTZ group (β, 0.93 HU; 95% CI, −1.34 to 3.19; $P = 0.42$), and 4.8±15.9 HU in the 50 mg HCTZ group (β, 0.70 HU; 95% CI, −1.45 to 2.85; $P = 0.52$). No association was observed between HCTZ dose and BMD at the end of the study ($P = 0.43$). The results were confirmed in sensitivity analyses for eGFR, urine calcium, net gastrointestinal alkali absorption, and body mass index; in subgroup; and in per-protocol analyses.

Conclusions In patients with recurrent calcium kidney stones, loss of BMD was similar in patients receiving HCTZ at a dose of 12.5, 25, or 50 mg or placebo once daily.

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Introduction

Bone disease is an important yet insufficiently addressed condition in patients with nephrolithiasis. Decreased bone mineral density (BMD) and defects in bone remodeling are highly prevalent in patients with kidney stones.[1–3] A population-based study revealed a nearly four-fold higher risk of vertebral fractures in individuals with a history of kidney stones.[4] The risk of vertebral fracture was elevated among both men and women and associated with increasing age. At 30 years of follow-up, the cumulative incidence of fractures was 45% in woman and 28% in men. A higher fracture risk associated with nephrolithiasis has also been observed in other population-based studies.[5–7] Loss of BMD depends on the activity of the underlying kidney stone disease, being higher in individuals with recurrent stone disease compared with individuals with a single past stone event.[8]

Mechanisms linking nephrolithiasis with bone disease remain incompletely understood. The highest prevalence of low BMD is found in patients with calcium-containing kidney stones and idiopathic hypercalciuria.[9–13] Hence, it has been assumed that the negative calcium balance associated with idiopathic hypercalciuria constitutes an important factor contributing to loss of BMD in this population.[14–17] In support of this, both fasting and post oral calcium load urine calcium after 1 week of a sodium and calcium-restricted diet, as well as calcium oxalate dihydrate stone content, were shown to be negatively associated with BMD at the lumbar spine.[18] By contrast, histomorphometry studies suggest that reduced bone formation is the primary defect encountered in individuals with kidney stones.[19–25] If only the hypercalciuria-associated negative calcium balance played a pathogenetic role, excessive bone resorption would be expected as the primary defect. Thus, additional factors, such as diet, comorbidities, medications, and genetic variants, likely contribute to bone disease in individuals with kidney stones.

Thiazide and thiazide-like diuretics (thiazides) reduce urine calcium and stimulate osteoblast differentiation and bone mineral formation *in vitro*.[26–28] Therefore, thiazides may both prevent loss of bone mass and attenuate fracture risk in patients with kidney stones. However, the results of the NOSTONE trial recently challenged the effectiveness of thiazides in reducing urinary calcium excretion and hence the incidence of kidney stone recurrence.[29] No randomized controlled trial has ever been conducted to examine the effect of thiazides on BMD or fracture risk in patients with kidney stones. To address this important knowledge gap, we performed a *post hoc* analysis of the NOSTONE trial[29] by investigating the change of mean BMD from baseline to study end at the thoracolumbar spine in patients with recurrent calcium-containing kidney stones randomized to 12.5, 25, or 50 mg hydrochlorothiazide (HCTZ) once daily or placebo once daily.

Methods

Study Population

Details of the NOSTONE trial design have been published previously.[29,30] The trial protocol was approved by the lead ethics committee in Bern, Switzerland, on October 25, 2016, and subsequently by all other ethics committees in Switzerland (Approval 2016_01475). Approval for the study investigational product was obtained from Swissmedic on February 24, 2017 (Approval 2017DR3035). The trial was conducted in accordance with all applicable regulations. Patient recruitment in the NOSTONE trial commenced on March 30, 2017, at 12 centers throughout Switzerland. Enrollment was completed by October 31, 2019. All the patients provided written informed consent before participation.

Key eligibility criteria included age 18 years or older, ≥2 kidney stone episodes in the 10 years before study participation, and a previous kidney stone that contained at least 50% calcium oxalate, calcium phosphate, or a mixture of both. The trial excluded patients with secondary causes of kidney stones, as well as those who were receiving drugs that could interfere with the formation of kidney stones. A total of 416 participants were randomized in four groups with a 1:1:1:1 ratio, to receive 12.5, 25, or 50 mg HCTZ or placebo once daily.[29,30]

Measurements and Definitions

At randomization and at the study end, participants underwent a low-dose noncontrast computed tomography (CT) limited to the kidneys. Baseline and end of study CT were performed on the same CT scanner using identical acquisition settings according to a standard operating procedure.[29] All study participants had a clinical follow-up visit 3 months after randomization and yearly thereafter, as well as telephone visits every 3 months. The median follow-up time was 2.92 years. All CT images were anonymized on-site with the Digital Imaging and Communications in Medicine anonymizer PRO software (NeoLogica, Italy) and transferred to an external solid state drive hard disk. The US Food and Drug Administration and ethics committee approved Digital Imaging and Communications in Medicine workstation Osirix MD 11 (Pixmeo, Switzerland) was used for image analysis. A low-dose CT protocol to measure BMD was applied, by reducing the tube current (100 mAs) while maintaining the tube voltage at a standard high-dose level of 120 kV. BMD measurements using such a CT protocol correlate very well with the gold standard dual-energy X-ray absorptiometry (DXA) because both procedures use X-ray tube voltages of 120 kV.[31–36] Two radiologists, blinded to the study intervention, measured the vertebral BMD from T12 to L3 segments. CT attenuation for each vertebra was documented in Hounsfield units (HU), and care was taken to exclude measurements near the cortical bone and additional nonuniform areas (Supplemental Figure 3). Inter-reader agreement was assessed in the whole cohort with available CT scans (N=388); the corresponding Pearson's correlation coefficient was 0.95 (confidence interval [CI], 0.94 to 0.95). Intra-reader agreement of radiologist one was assessed in a randomly selected subsample of 50 patients 1 month after the first measurements; the weighted kappa coefficient was 0.98 (CI, 0.975 to 0.983). Blood and 24-hour urine parameters were measured at baseline and at scheduled follow-up visits (3, 12, 24, and 36 months). All blood and urine analyses were performed centrally at the Core Laboratory of the Bern University Hospital, Bern, Switzerland, using standard laboratory methods. Net gastrointestinal alkali absorption (NGIA) from 24-hour urines was calculated using the Oh formula.[37]

Statistical Analyses

Continuous variables are reported as medians with 25th–75th percentiles or means with SDs, and categorical variables are reported as counts with percentages, as appropriate. Measured BMD was analyzed both as mean value of all vertebral segments (primary outcome) and singularly at T12–L3. For each treatment group, we calculated the mean observed values at baseline and during follow-up for the primary analysis (BMD) and exploratory analysis (plasma parameters: calcium, phosphate, magnesium, alkaline phosphatase, parathyroid hormone, 25(OH)-, and $1,25(OH)_2$ vitamin D_3). As this was a predefined secondary analysis of an already conducted randomized clinical trial, no sample size calculations are provided. An analysis was conducted with a two-level mixed-effects linear regression, random-intercept model to assess the association between different HCTZ doses versus placebo and both intraindividual and interindividual changes of the outcome variables (BMD and plasma biomarkers, respectively) at multiple time points. The treatment was included as fixed effect, participant and time point as random effect. This model was adjusted for age, sex, time of follow-up, number of past stone events, and baseline outcome variables as covariables in the model. The treatment effect was first analyzed in the intention-to-treat population, which included all patients who underwent randomization. For the analysis of BMD, we further performed a per-protocol analysis, consisting of all participants in the full analysis set without a protocol deviation that could confound the interpretation of analyses (not receiving the allocated treatment, not fulfilling anymore the eligibility criteria, and no visit/call performed). On the basis of the per-protocol analysis set, we analyzed data regarding patients as dependently censored at the day a patient withdrew, was lost to follow-up or at the first time a patient became noncompliant for a medically or nonmedically indicated, voluntary reason. Confidence distribution analysis was performed for the primary outcome and calculated using a normal approximation of the estimated mean difference.[38] Outcome variables were log-transformed to ensure normal distributions as needed. Regression residuals were analyzed for normality using visual inspection. For each variable, the number of available observations, the β coefficient (β), and the 95% CI were computed. Statistical tests were two-sided. P values of statistical tests were interpreted as exploratory and as a measure of statistical precision rather than for null-hypothesis significance testing. Consequently, no adjustments for multiple testing were performed. Analyses were performed using the software Stata, version 16 (StataCorp, College Station, TX).

Results

Primary Outcomes

CT scans at baseline and at the end of the study were available in 388 of 416 NOSTONE participants. The median (interquartile range) follow-up time was 2.92 years (2.08–3.11), the mean age at randomization was 48 (SD, 12.2) years, and most patients were men

Table 1. Baseline characteristics of study population

Characteristics	All Participants (N=388)	12.5 mg HCTZ (N=98)	25 mg HCTZ (N=103)	50 mg HCTZ (N=90)	Placebo (N=97)
Age, yr	48.0 (12.2)	48.5 (12.4)	47.5 (11.8)	48.8 (11.5)	47.2 (13.2)
Men	312 (80.4)	83 (84.7)	83 (80.6)	72 (80.0)	74 (76.3)
BMI, kg/m^2	27.1 (24.4–30.3)	27.0 (24.4–29.7)	27.5 (24.2–30.5)	26.9 (24.2–30.2)	27.5 (24.7–31.5)
No. of past stone events					
2 or 3	203 (52.3)	54 (55.1)	51 (49.5)	45 (50.0)	53 (54.6)
≥4	185 (47.7)	44 (44.9)	52 (50.5)	45 (50.0)	44 (45.4)
eGFR CKD-EPI 2009, ml/min per 1.73 m^2	94.4 (80.8–104.8)	92.1 (77.5–103.5)	93.2 (81.7–106.8)	96.5 (84.3–103.5)	94.8 (80.8–105.9)
Intact PTH, ng/L	38.8 (31.0–49.1)	37.6 (29.9–49.8)	39.4 (31.6–49.8)	39.0 (30.8–49.0)	38.8 (31.4–46.6)
Alkaline phosphatase, IU/L	66.0 (56.0–77.0)	63.0 (54.0–77.0)	66.0 (56.0–77.0)	70.0 (57.0–83.0)	63.0 (55.0–72.5)
25-OH vitamin D_3, nmol/L	50.0 (36.0–66.0)	49.0 (33.0–68.0)	48.5 (36.5–61.5)	49.0 (34.0–64.0)	53.5 (38.0–73.0)
$1,25(OH)_2$ vitamin D_3, pmol/L	124.0 (99.0–149.0)	118.0 (99.0–147.0)	129.0 (105.0–154.0)	117.0 (98.0–140.0)	125.0 (96.0–149.0)
Urinary calcium excretion, mmol/24 h	6.0 (4.1–8.3)	5.9 (4.1–7.9)	6.0 (4.1–8.6)	5.9 (4.2–8.3)	6.4 (3.9–8.3)
NGIA, mEq/24 h	44.4 (29.0–60.5)	45.2 (29.9–61.4)	47.5 (27.6–60.5)	42.9 (30.0–59.2)	44.2 (28.3–63.3)
Smoking status					
Current	127 (33.2)	33 (34.7)	41 (40.2)	23 (25.8)	30 (31.3)
Former	85 (22.3)	17 (17.9)	24 (23.5)	25 (28.1)	19 (19.8)
Never	170 (44.5)	45 (47.4)	37 (36.3)	41 (46.1)	47 (49.0)
Alcohol consumption					
None	86 (22.5)	21 (22.1)	26 (25.5)	22 (24.7)	17 (17.7)
<1 unit per day	266 (69.6)	65 (68.4)	71 (69.6)	60 (67.4)	70 (72.9)
1–3 units per day	28 (7.3)	9 (9.5)	4 (3.9)	7 (7.9)	8 (8.3)
4–5 units per day	2 (0.5)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)

Characteristics are indicated for all participants and separately for each study group. Categorical variables are described by number of participants N (%); continuous variables are described by their mean (SD) or median (25th–75th percentile). One unit alcohol corresponds to 1 dl wine, 3 dl beer, or 40 ml liquor. BMI, body mass index; HCTZ, hydrochlorothiazide; IU, international units; NGIA, net gastrointestinal alkali absorption; PTH, parathyroid hormone.

Table 2. Bone mineral density at baseline and end of the study

Measurement	12.5 mg HCTZ (*N*=98)	25 mg HCTZ (*N*=103)	50 mg HCTZ (*N*=90)	Placebo (*N*=97)
Baseline				
BMD at T12 segment, HU	176.7 (50.2)	178.5 (48.2)	176.5 (45.4)	182.1 (43.3)
BMD at L1 segment, HU	170.1 (46.5)	172.0 (49.5)	173.4 (44.7)	178.2 (43.0)
BMD at L2 segment, HU	173.9 (59.2)	172.6 (49.8)	172.5 (46.5)	175.9 (44.7)
BMD at L3 segment, HU	164.2 (48.0)	168.3 (48.9)	167.4 (44.7)	172.7 (44.2)
Mean BMD, HU	170.9 (46.8)	172.1 (48.0)	172.4 (44.5)	177.3 (42.9)
End of study				
BMD at T12 segment, HU	170.4 (45.0)	175.4 (51.8)	173.1 (44.0)	178.8 (42.9)
BMD at L1 segment, HU	165.5 (43.9)	167.1 (52.2)	169.1 (43.1)	171.7 (43.2)
BMD at L2 segment, HU	169.1 (53.6)	169.1 (53.6)	167.6 (52.9)	167.9 (44.9)
BMD at L3 segment, HU	159.7 (48.4)	163.5 (50.5)	162.1 (41.7)	164.9 (43.6)
Mean BMD, HU	165.8 (44.7)	168.0 (50.8)	167.7 (42.5)	170.9 (42.6)
Change of BMD at end of study				
BMD at T12 segment, HU	−3.6 (19.4)	−2.8 (19.3)	−5.0 (20.3)	−5.3 (19.6)
BMD at L1 segment, HU	−4.6 (15.6)	−4.9 (19.5)	−4.3 (18.5)	−6.5 (17.1)
BMD at L2 segment, HU	−5.7 (16.8)	−4.9 (16.9)	−4.6 (17.6)	−6.7 (18.3)
BMD at L3 segment, HU	−4.5 (18.9)	−4.8 (17.3)	−5.3 (16.9)	−8.4 (18.2)
Mean BMD, HU	−5.1 (15.1)	−4.1 (16.3)	−4.8 (15.9)	−6.4 (15.7)

Absolute bone mineral density values at baseline and end of the study, and the change of bone mineral density at the end of the study in all participants, stratified by randomization group. Variables are described by their mean (SD). BMD, bone mineral density; HCTZ, hydrochlorothiazide; HU, Hounsfield units.

(*N*=312, 80.4%). Baseline characteristics were similar between study groups (Table 1). Detailed results of 24-hour urinary kidney stone risk profiles of NOSTONE participants have been published previously.[29] Mean and per-segment BMD measured at baseline and at the end of the study across incremental HCTZ doses and placebo groups are presented in Table 2. Baseline association analyses showed a direct correlation between measured BMD and factors known *a priori* to influence bone mass. The mean BMD was inversely and strongly associated with age (Rho Spearman, −0.58; $P < 0.001$) and directly associated with eGFR (Rho Spearman, 0.27; $P < 0.001$) (Supplemental Figures 1 and 2, respectively). On the contrary, no baseline correlation between mean BMD and 24-hour urinary calcium excretion (Rho Spearman, −0.007; $P = 0.89$) or body mass index (BMI) was noted (Rho Spearman, −0.07; $P = 0.19$). Furthermore, there was no association between urinary citrate excretion and baseline BMD or change of BMD at the end of the study (Rho Spearman, −0.08; $P = 0.13$ and −0.05, $P = 0.35$, respectively).

At the end of the study, the absolute mean BMD was similar in all study groups (Table 2). No association between changes in BMD at any segment and 24-hour urinary calcium excretion was evident at the end of the study (Supplemental Table 1). The intention-to-treat analysis, adjusted for age, sex, time of follow-up, number of past stone events, and baseline BMD, showed no evidence for a difference in mean BMD at the end of the study across each HCTZ group versus placebo (Table 3). The mean BMD decreased by 6.4±15.7 HU in the placebo group, by 5.1±15.1 in the 12.5 mg HCTZ group (β coefficient versus placebo, 0.37 HU; 95% CI, −1.74 to 2.47; $P = 0.73$), by 4.1±16.3 in the 25 mg HCTZ group (β, 0.93 HU; 95% CI, −1.34 to 3.19; $P = 0.42$), and by 4.8±15.9 in the 50 mg HCTZ group (β, 0.70 HU; 95% CI, −1.45 to 2.85; $P = 0.52$; Figure 1). The results were confirmed when each vertebral segment was analyzed separately and when overall HCTZ treatment was compared with placebo (Table 3). We found no evidence for a relation between increasing HCTZ dose and BMD at the end of the study (P for trend, Table 3).

On the basis of a recent large meta-analysis encompassing 91,779 participants of 23 randomized, placebo-controlled osteoporosis trials, a 1.4% increase of mean vertebral BMD compared with baseline can be considered a clinical meaningful change associated with a reduced fracture risk.[39] With a mean baseline BMD of 170 HU, this translates to a 2.4 HU change in our cohort that can be considered as a minimally clinically relevant effect. Confidence distribution analysis indicates a 97% confidence that the maximum effect of HCTZ on BMD is <2.4 HU (Figure 2). An effect equal to or greater than this threshold showed only 3% confidence, suggesting a low likelihood of HCTZ achieving a clinically meaningful effect on BMD.

To further test our results, a per-protocol analysis was conducted among participants adhering to the study protocol. Similarly, subgroup analyses for younger than 50 years and 50 years or older and sex distribution and sensitivity analyses for possible variables that may have confounded the association between HCTZ treatment and BMD, such as 24-hour urine calcium, NGIA, eGFR, and BMI, were conducted. The results of these models remain consistent with the main results, as presented in Table 3, and no evidence for an association between different HCTZ doses versus placebo or overall HCTZ treatment and BMD at any vertebral segment was found (Supplemental Tables 2–5) in any of these models.

Exploratory Outcomes

Exploratory analyses were conducted to investigate the association between treatment and changes in mineral metabolism markers measured at multiple time

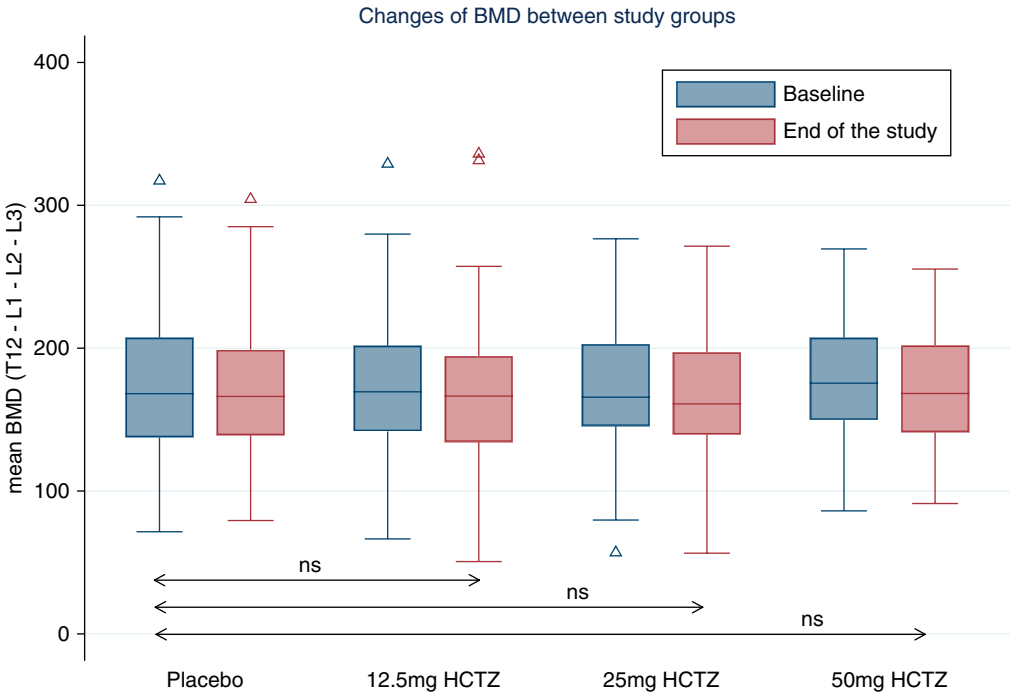

Figure 1. Box plots depicting changes in mean BMD at the end of the study compared with baseline, at incremental HCTZ doses or placebo. Boxplots show medians with 25th–75th percentiles. Whiskers represent the range of values within 1.5 times the IQR from the first and third quartiles. BMD, bone mineral density; HCTZ, hydrochlorothiazide; IQR, interquartile range; ns, nonstatistically significant.

points during the study. These analyses revealed a reduction of 1,25$(OH)_2$ vitamin D_3, alkaline phosphatase, and plasma phosphate in patients receiving HCTZ compared with placebo (Figure 3 and Table 4). Overall, plasma calcium was not higher in patients receiving HCTZ compared with patients receiving placebo. However, in the subgroup of patients receiving the highest dose of 50 mg HCTZ, plasma calcium was higher compared with patients receiving placebo (Table 4). Similarly, plasma magnesium was lower compared with placebo only in the subgroup of patients receiving 50 mg HCTZ (Table 4). There was no association with parathyroid hormone and 25-OH vitamin D_3 in any of our models (Figure 3 and Table 4).

Discussion

This *post hoc* analysis of the NOSTONE trial provides for the first-time unbiased evidence on the effect of a thiazide on BMD in kidney stone formers, a group of patients at high risk of vertebral fractures. The results of the NOSTONE trial outlined similar incidence for kidney stone recurrence between HCTZ and placebo. Data presented here further demonstrate that loss of BMD at the thoracolumbar spine over a period of 3 years was similar among patients randomized to HCTZ 12.5, 25, or 50 mg once daily or placebo once daily. We also found no evidence for a relation between HCTZ dose and change in BMD. The results of the primary analysis were consistent across several sensitivity analyses. In addition, the per-protocol and intention-to-treat analysis yielded similar results, indicating that poor treatment adherence cannot explain the findings.

These results contradict two previous studies conducted in individuals with hypercalciuria and kidney stones, which found a protective effect of thiazides on BMD.[40,41] However, these studies were very small (24 and 28 patients, respectively), open-label, and evaluated fixed combination therapies of thiazides with potassium citrate. NOSTONE, on the other hand, was a large double-blind, placebo-controlled trial using a range of HCTZ doses as monotherapy in comparison with placebo. In unselected adult individuals, *post hoc* analyses of randomized controlled trials for arterial hypertension and observational studies have yielded inconclusive results on the use of thiazides and fracture risk.[42–47] With respect to BMD, an established surrogate of fracture risk, the existing body of evidence in unselected adult individuals, is also inconclusive. Studies have reported either an increase or no significant change in BMD in response to thiazide treatment.[48–51]

Biochemically, patients receiving HCTZ displayed hallmarks of thiazide action, including a significant reduction of urine calcium.[29] However, the HCTZ-induced reduction of urine calcium (9%–17% compared with baseline and 15%–16% compared with placebo) was modest. The efficacy of thiazides in reducing urine calcium correlates with sodium intake, and guidelines recommend a low sodium intake (<100 mmol/d or <2.3 g/d).[52–54] In NOSTONE, sodium intake was similar across groups (182–199 mmol/d, corresponding to 4.2–4.6 g/d) yet higher than recommended, despite repeat dietary instructions. This observation is comparable with past thiazide trials for kidney stone recurrence prevention reporting similar sodium intake during trial follow-up and

Table 3. Main results

Outcome Variables	*N*	12.5 mg HCTZ versus Placebo			25 mg HCTZ versus Placebo			50 mg HCTZ versus Placebo			*P* for Trend	Overall HCTZ versus Placebo		
		β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value		β	95% CI	*P* Value
BMD at T12 segment, HU	716	0.59	(−2.07 to 3.24)	0.67	1.05	(−1.79 to 3.88)	0.47	0.10	(−2.65 to 2.86)	0.94	0.75	0.61	(−1.66 to 2.87)	0.60
BMD at L1 segment, HU	776	0.51	(−1.73 to 2.74)	0.66	0.49	(−2.08 to 3.07)	0.71	0.94	(−1.48 to 3.35)	0.45	0.65	0.63	(−1.35 to 2.62)	0.53
BMD at L2 segment, HU[a]	774	0.004	(−0.01 to 0.02)	0.59	−0.001	(−0.02 to 0.02)	0.94	0.01	(−0.007 to 0.02)	0.32	0.64	0.004	(−0.009 to 0.02)	0.59
BMD at L3 segment, HU	774	1.53	(−1.04 to 4.11)	0.24	1.52	(−0.93 to 3.97)	0.23	1.37	(−1.02 to 3.76)	0.26	0.93	1.48	(−0.57 to 3.53)	0.16
Mean BMD, HU	776	0.37	(−1.74 to 2.47)	0.73	0.93	(−1.34 to 3.19)	0.42	0.70	(−1.45 to 2.85)	0.52	0.71	0.67	(−1.13 to 2.48)	0.47

Multivariable association between the explanatory variable hydrochlorothiazide treatment, overall and at different doses, and bone mineral density, measured at T12–L3 vertebral segments, as outcome variable, adjusted for age, sex, time of follow-up, number of previous stone events, and baseline bone mineral density. Analyses conducted in the entire study population. *P* values are indicated for each hydrochlorothiazide dose versus Placebo, overall hydrochlorothiazide versus Placebo and for the trend across hydrochlorothiazide doses. β, β coefficients; BMD, bone mineral density; CI, confidence interval; HCTZ, hydrochlorothiazide; HU, Hounsfield Units; *N*, number of observations.

[a]Natural logarithm transformed.

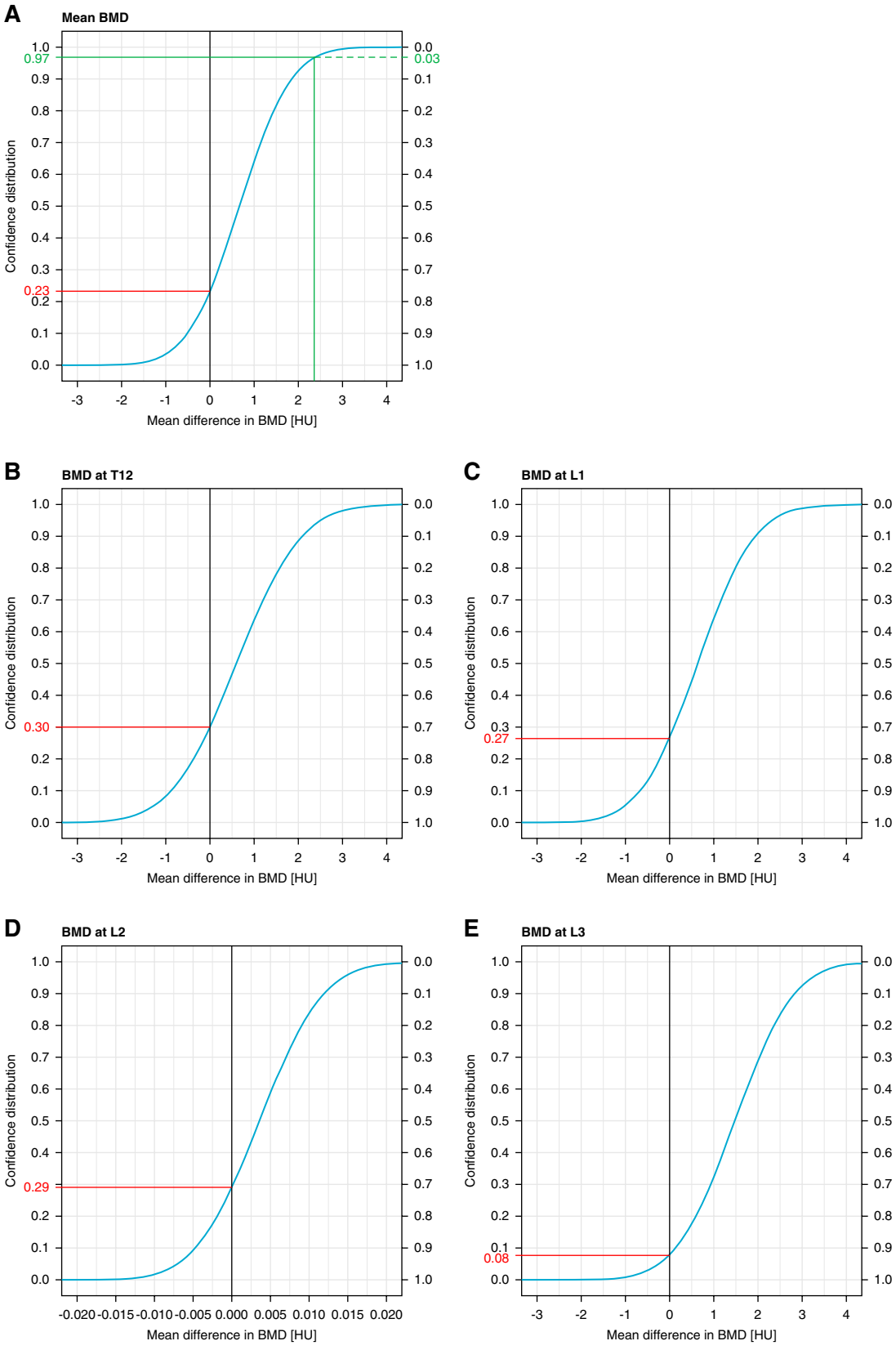

Figure 2. Confidence distributions for the primary outcome BMD. Confidence distribution for (A) mean BMD HCTZ versus placebo and (B–E) segment-specific BMD HCTZ versus placebo. Curves at a specific point indicate the confidence to have a specified maximal effect of HCTZ (therefore cumulative). Positive mean difference indicates benefit of HCTZ and a negative mean difference harm. The graph can be used as follows: if one is interested to know how confident one can be that HCTZ has at least a given effect, *e.g.*, it reduces BMD loss by

Figure 2. *(Continued)* 2.4 HU as compared with placebo, identify the respective intersection to the confidence distribution, and the *y* axis indicates how confident one can be that the effect is of this size or smaller. For mean BMD, we can be 97% confident that the effect is a maximum of 2.4 HU or, inverted, we have 3% confidence that HCTZ has at least a minimally clinically relevant effect (green line). Red lines indicate confidence at the null effect. Note the different *x* axis scale in (D, log transformed variable). HU, Hounsfield units.

demonstrates the difficulty to achieve a sustained reduction of sodium intake for several years in kidney stone formers in the outpatient setting.[55,56] We cannot exclude the possibility that a more stringent sodium restriction or daily HCTZ doses >50 mg would have shown a beneficial effect of HCTZ on BMD compared with placebo. Similarly, the more potent thiazides chlorthalidone and indapamide may have caused a more conspicuous decline in urine calcium than HCTZ and hence resulted in different findings with respect to BMD changes. Our analysis indicates that HCTZ affects circulating mineral metabolism markers such as alkaline phosphatase and $1,25(OH)_2$ vitamin D3, with a trend toward greater plasma calcium in patients assigned to HCTZ. Because the more potent chlorthalidone was previously associated with a positive calcium retention,[57] this observation might indicate a HCTZ-induced modest increase in total calcium balance,[58] which however is not sufficient to significantly modify BMD after 3 years of follow-up.

HCTZ is by far the most frequently prescribed thiazide, universally available at low cost and an effective antihypertensive medication preventing adverse cardiovascular outcomes.[59] Hypertension is common in kidney stone formers[60]; 43% of NOSTONE participants were hypertensive.[29] Yet, adverse events associated with long-term use of HCTZ as well as the lack of efficacy of HCTZ in preventing kidney stone recurrence[29] and preserving BMD in the short term (this study) need to be considered when initiating HCTZ treatment in kidney stone formers, especially in young adults.

DXA is the gold-standard to assess BMD.[61] CT is an established and well-validated alternative radiologic imaging modality for BMD assessment because it has both the advantage of overcoming some of the potential pitfalls and limitations of DXA, such as osteophytes, fractures, endplate sclerosis, aortic, and paravertebral calcifications,[61] and it allows for volumetric three-dimensional acquisition, which is not possible with DXA.[33–35,62,63] Osteopenia and

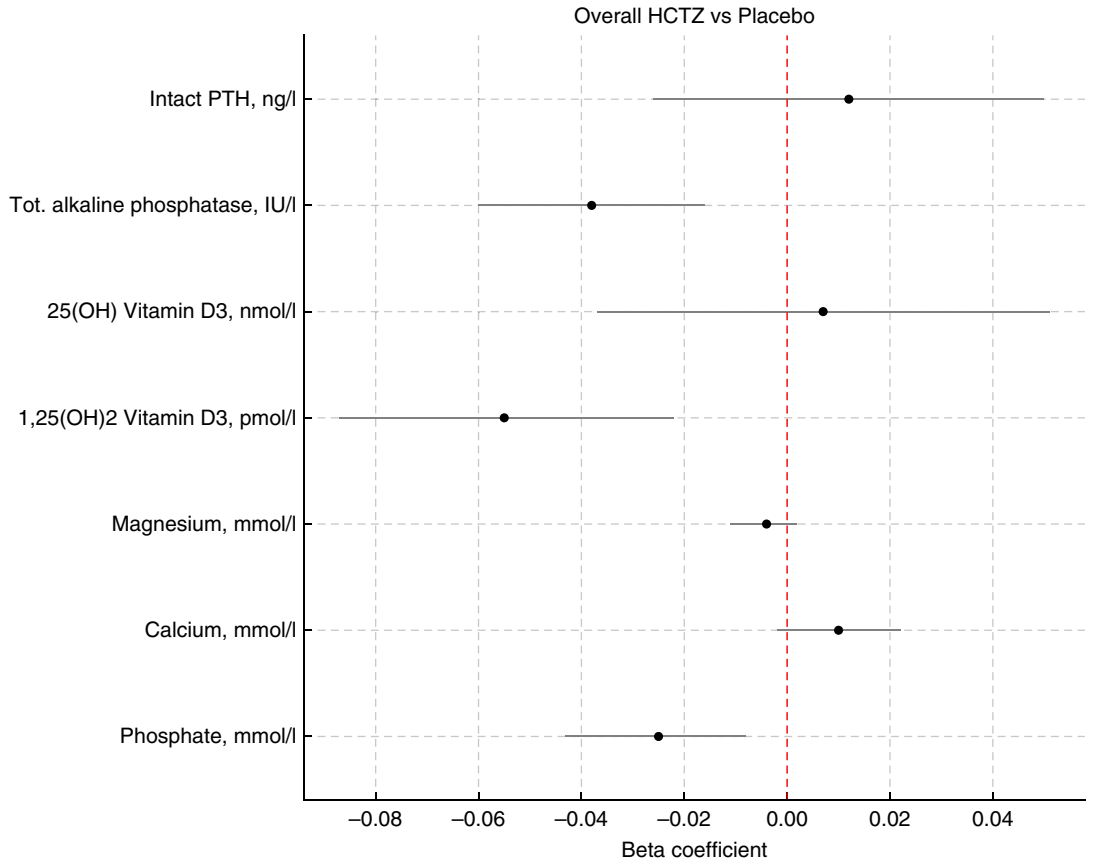

Figure 3. Forest plot of the association between bone biomarkers and overall HCTZ treatment versus placebo. Values adjusted for age, sex, time of follow-up, number of previous stone events, and baseline BMD. β coefficients (β) and their relative 95% CI are reported. CI, confidence interval; IU, international units; PTH, parathyroid hormone.

Table 4. Exploratory analysis of circulating mineral metabolism parameters

Outcome Variables	*N*	12.5 mg HCTZ versus Placebo			25 mg HCTZ versus Placebo			50 mg HCTZ versus Placebo			*P* for Trend	Overall HCTZ versus Placebo		
		β	95% CI	*P* Value	β	95% CI	*P* Value	β	95% CI	*P* Value		β	95% CI	*P* Value
Intact PTH, ng/L	1406	0.004	(−0.04 to 0.05)	0.85	0.03	(−0.01 to 0.08)	0.15	−0.009	(−0.06 to 0.04)	0.69	0.57	0.01	(−0.03 to 0.05)	0.60
Alkaline phosphatase, IU/L	1418	−0.03	(−0.05 to −0.003)	0.03	−0.04	(−0.07 to −0.02)	0.002	−0.05	(−0.08 to −0.02)	0.001	0.12	−0.04	(−0.06 to −0.02)	<0.001
25-OH vitamin D_3, nmol/L	1390	−0.007	(−0.06 to 0.05)	0.80	0.001	(−0.05 to 0.05)	0.98	0.05	(−0.009 to 0.10)	0.10	0.05	0.01	(−0.03 to 0.06)	0.58
$1,25(OH)_2$ vitamin D_3, pmol/L	1393	−0.06	(−0.10 to −0.01)	0.02	−0.05	(−0.09 to −0.009)	0.02	−0.06	(−0.01 to −0.01)	0.01	0.10	−0.05	(−0.09 to −0.02)	0.002
Magnesium, mmol/l	1395	0.000	(−0.008 to 0.008)	0.94	−0.003	(−0.01 to 0.005)	0.47	−0.01	(−0.02 to −0.003)	0.007	0.11	−0.004	(−0.01 to 0.002)	0.18
Calcium, mmol/l	1419	0.004	(−0.01 to 0.02)	0.61	0.01	(−0.004 to 0.02)	0.17	0.02	(0.001 to 0.03)	0.04	0.06	0.01	(−0.001 to 0.02)	0.08
Phosphate, mmol/l	1418	−0.03	(−0.05 to −0.007)	0.01	−0.03	(−0.05 to −0.006)	0.01	−0.02	(−0.04 to 0.004)	0.11	0.50	−0.02	(−0.04 to −0.007)	0.006

Multivariable association between the explanatory variable hydrochlorothiazide treatment, overall and at different doses, and log-transformed mineral metabolism parameters measured at multiple time points, as outcome variable, adjusted for age, sex, time of follow-up, number of previous stone events, and baseline variables. Analyses conducted in the intention to treat population. *P* values are indicated for each hydrochlorothiazide dose versus Placebo, overall hydrochlorothiazide versus Placebo and for the trend across hydrochlorothiazide doses. β, β coefficients; CI, confidence interval; HCTZ, hydrochlorothiazide; IU, international units; *N*, number of observations; PTH, parathyroid hormone.

osteoporosis can be diagnosed with high accuracy with a noncontrast enhanced CT when compared with DXA.[35] In addition, CT is the imaging method of choice for a plethora of other clinical indications. This is of particular relevance in patients with nephrolithiasis, for which abdominal CT imaging is the gold-standard to assess stones in the kidney and urine tract. The use of available CT images for BMD measurements avoids cost, patient time, equipment, software, and radiation exposure associated with additional DXA measurements. CT acquisition in NOSTONE was highly standardized, allowing direct comparisons of BMD measurements between baseline and end of study CTs. As expected from a patient population with a median age of 49 years and a high percentage of men, BMD significantly decreased over the 3 years of study.[64,65] In line with the well-established associations of BMD with age and kidney function, we observed a highly significant positive association of BMD with eGFR and a highly significant negative association of BMD with age in our study cohort, further supporting the validity of our BMD measurements. As outlined in the Methods section, there was excellent intra-reader and inter-reader agreement of CT-based BMD measurements in our study. The wide SDs of mean BMD observed in our study therefore do not reflect lack of precision in BMD measurements but can be attributed to the substantial heterogeneity in the study population.

Strengths of our study include the prospective, double-blind, placebo-controlled multicenter design; the large sample size; and the detailed phenotypic data available. Our study also has several limitations. First, BMD was measured at the thoracolumbar spine, where trabecular bone prevails. We did not assess the effect of treatment on trabecular bone density at other skeletal sites (*e.g.*, femoral neck) or on cortical bone (*e.g.*, clavicle or femoral diaphysis). Second, study duration was 3 years; we cannot exclude a beneficial effect of HCTZ on BMD with a longer treatment duration. Third, although stone formers are at significantly higher risk of fractures compared with the general population, we acknowledge that the underrepresentation of women and older adults in our cohort may limit the generalizability of our findings to populations with a higher baseline risk for osteopenia and osteoporosis. Fourth, although there is excellent correlation between the two methods, BMD was measured using low-dose CT and not by the gold-standard DXA. Finally, although sodium intake was similar in all groups, it exceeded the current recommendations and thus may have blunted the hypocalciuric response and thereby mitigated the effect of HCTZ on BMD.

In conclusion, we found no evidence that HCTZ at a dose of 12.5, 25, or 50 mg once daily preserves BMD at the thoracolumbar spine in patients with recurrent calcium-containing kidney stones.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/CJN/C197.

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Data Sharing Statement

Partial restrictions to the data and/or materials apply. The full dataset of deidentified individual participant data and the data dictionary that underlie the results reported in this article are available from the corresponding author (Daniel G. Fuster) for research purposes and for advancing the management of patients with kidney stone disease, in line with existing national regulations. Data sharing will be possible from publication onwards. Proposals with specific aims and an analysis plan should be directed to the corresponding author (daniel.fuster@unibe.ch). Timelines can vary depending on the type of request, but data will be provided within a maximum of 3 months. Additional documents related to the NOSTONE trial are published elsewhere and available online (study protocol, statistical analysis plan).

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/C196.

Supplemental Table 1. Association between BMD and urinary calcium excretion at the end of the study.

Supplemental Table 2. Per-protocol analysis.

Supplemental Table 3. Sensitivity analysis for BMI, urinary calcium excretion, NGIA, and renal function.

Supplemental Table 4. Subgroup analysis for sex distribution.

Supplemental Table 5. Subgroup analysis for age of participants.

Supplemental Figure 1. Scatterplot of the association between mean BMD and age of participants at baseline visit.

Supplemental Figure 2. Scatterplot of the association between mean BMD and eGFR of participants at baseline visit.

Supplemental Figure 3. BMD measurement on the sagittal representation in the midline through the spine.

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