Standard calcium supplementation may increase kidney stone risk: a study in women with postmenopausal osteoporosis.

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Abstract

The US prevalence of kidney stones has increased from 2.6% in 1972 to 8.4% in 2010. The majority of stones contain calcium (Ca) with hypercalciuria (hCa) highly associated with stone formation. Postmenopausal osteoporosis is a common problem affecting 30% of postmenopausal women in the US. Supplementation with Ca and vitamin D (D) is recommended for most older women.

Purpose: To determine the percentage of patients who become hypercalciuric while receiving Ca and D supplementation for postmenopausal osteoporosis and to identify biochemical predictors for higher risk of developing hCa with Ca and D supplementation.

Method: 84 ambulatory women aged ≥55 years enrolled in a RT comparing alendronate (ALN) and sustained-release sodium fluoride (SRF) for the treatment of postmenopausal osteoporosis. Both groups received daily standard Ca and D supplements (1000mg Ca citrate, 800 IU D). 24-hr urinary Ca (uCa) and serum 25-D, PTH, urinary deoxypyridinoline and serum bone-specific alkaline phosphatase were measured at baseline and 12 months. Secondary data analysis determined the percentage of patients who became hypercalciuric (uCa >250 mg/24hr) during treatment and identified predictors of hCa. Changes over time in biochemical variables were assessed with mixed model repeated measures analysis. Logistic regression analysis was used to assess predictors of elevated uCa and construct receiver operating characteristic (ROC) curves.

Results: 42 patients were randomized to ALN and 42 to SRF. Sixty-seven patients completed greater than one year. More early drop-outs were in the ALN group with 31 vs. 36 completing 12 months in the ALN and SRF groups respectively. 90% (27/30) of the ALN group and 92% (33/36) of the SRF group had normal uCa excretion at baseline. Patients with normal uCa at baseline experienced significant increases in uCa during the first year (ALN p=0.01, SRF p<0.0001). However, baseline hypercalciurics experienced no significant increase in uCa from baseline after Ca and D supplementation. In all, 13% (4/30) of ALN patients became hypercalciuric (p= 0.41) vs. 28% (10/36) in the SRF group (p=0.002).

The best-fit multi-variable model determined baseline uCa (p=0.017) and D (p=0.025) were strong predictors of hCa at 12 months and produced a favorable ROC curve (ROC=0.90). Baseline uCa was a consistently strong predictor of hCa and a simple logistic regression analysis generated a ROC curve (ROC=0.84) which determined that 180 mg/d uCa at baseline was a strong predictive cut-point for detection of patients at higher risk of hCa with treatment.

Conclusion: A considerable number of patients (14/67) became hypercalciuric on recommended doses of Ca and D. Current Ca and D supplementation practice may have significant long-term public health consequences by contributing to the growing incidence of nephrolithiasis. Practice guidelines should consider assessing baseline 24-hr uCa in all patients and 12 mo. 24-hr uCa in patients with baseline uCa ≥180 mg/24hr.

Introduction

The incidence and prevalence of nephrolithiasis is increasing. In the United States (US), prevalence has been increasing steadily since from 2.62% between 1964 and1972 to 8.4 % by 2010 (1 in 11).[1,2] The US lifetime risk of stone formation exceeds 12% in men and 6% in women.[4] The prevalence of kidney stones increases with age, and as many as 12% of patients seen for urinary stone disease are over the age of 65.[5] Annual incidence of kidney stones in geriatric patients is estimated at to be 2%.

The majority of kidney stones in the US are composed of calcium salts, with calcium oxalate predominating in 70–80% of stones.[6] Hypercalciuria is strongly associated with the formation of stones.

Calcium and vitamin D supplementation are commonly recommended to older women to prevent and treat postmenopausal osteoporosis, which affects 30% of postmenopausal women in the US.[7] Recommendations for daily calcium (1200 mg/day) and vitamin D (600 IU/day) intake for bone health may have the unintended consequence of increasing the risk of nephrolithiasis.[8]

Objectives

To determine the percentage of women with postmenopausal osteoporosis who become hypercalciuric while receiving standard recommended doses of calcium citrate and vitamin D supplementation. We explored the correlation between baseline urinary calcium status and the changes in urinary calcium, vitamin D, parathyroid hormone (PTH), and markers of bone metabolism during treatment for osteoporosis. Results were analyzed to identify any baseline biochemical values that may indicate higher risk for hypercalciuria with supplementation, and thus potentially higher risk for stone formation.

Subjects and Methods

Patients were participants in a 36 month randomized control trial for the treatment of postmenopausal osteoporosis who completed a minimum of 12 months of treatment with either sustained-release sodium fluoride (SRF) or alendronate (ALN). All subjects received daily supplementation with calcium (1000 mg calcium citrate) and vitamin D (800 IU).

Fasting blood samples and 24-hour urine specimens were analyzed prior to treatment (month 0) and at 6 and 12 months for levels of urinary calcium, vitamin 25(OH)D (Vit D) and parathyroid hormone (PTH). Urinary deoxypyridinoline adjusted for creatinine (uDPD) and serum bone-specific alkaline phosphatase (BAP) were measured as markers of bone resorption and formation respectively.

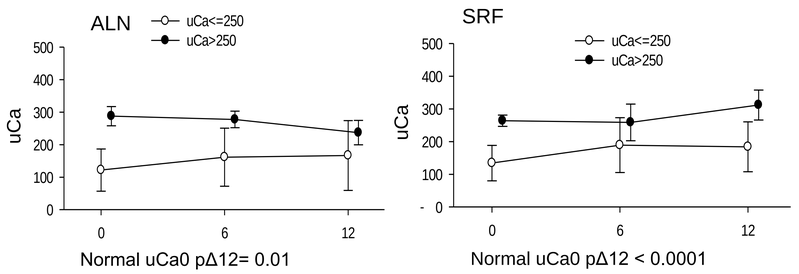
Participants were stratified by baseline 24-hour urinary calcium status, normal vs. hypercalciuric (> 250 mg/24hr). Changes over time for biochemical variables were assessed with mixed model repeated measures analysis. For categorical variables, comparisons of baseline and 12 month responses were performed using McNemar's test.

Logistic regression analysis was conducted to assess predictors of elevated urinary calcium (>250 mg/24hr) and to construct receiver operating characteristic (ROC) curves. Independent variables evaluated in the logistic regression models included treatment group, age, weight, and baseline measurements of urinary calcium, deoxypyridinoline/calcium and serum parathyroid hormone (PTH), Vit D, and bone specific alkaline phosphatase (BAP).

Results

Forty-two patients were randomized to each treatment group. N=31 and n=36 patients completed 12 months of treatment in the ALN and SRF groups respectively.

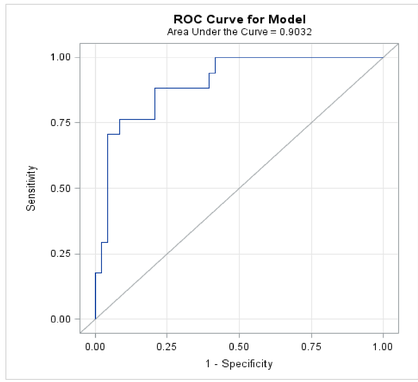
At baseline, 90% (27/30) of the ALN group and 92% (33/36) of the SRF group had normal urinary calcium excretion. In both treatment groups, patients who were normocalciuric at baseline experienced significant increases in urinary calcium excretion during the first year of the study (ALN +45 mg/d; SRF +50 mg/24hr). The baseline hypercalciurics for both treatment groups did not experience any significant change in urinary calcium levels for the first year of the trial.

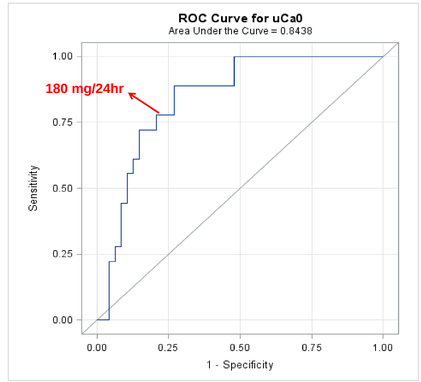


Thirteen percent (4/30) of patients in the ALN group became hypercalciuric (p= 0.41). In the SRF group, 28% (10/36) of participants became hypercalciuric after 12 months of treatment (p=0.002).

The best-fit version of a multi-variable logistic regression model to predict the occurrence of hypercalciuria at twelve months of treatment included treatment group, age, baseline urinary calcium, baseline serum Vit D, and an interaction term between urinary calcium and Vit D. Baseline uCa (p=0.017) and VitD (p=0.025) were strong predictors of hypercalciuria at 12 mo. The model was used to construct a favorable receiver operating characteristic curve (ROC=0.90).

Because baseline urinary calcium was a consistently strong predictor, a simple logistic regression analysis was used to generate a ROC curve with a value of 0.84. For each 10 mg increase in baseline calcium, the risk of hypercalciuria at 12 months increased by 20%. We identified 180 mg/24hr urinary calcium excretion at baseline as a strong predictive cut-point for detection of patients at higher risk of hypercalciuria with treatment.





Limitations

Small number of subjects.

There were considerably more individuals who dropped out of the ALN group in the first year, which may have contributed to the difference between groups in number of participants who converted to hypercalciuria.

Detailed dietary history was not available.

All participants were taking bone active agents in addition to supplemental calcium and Vit D, which may limit the application of findings.

Conclusions

A large number of patients (14/67) became hypercalciuric while taking recommended doses of calcium citrate and Vit D. Current calcium and Vit D supplementation practice may have significant long-term public health consequences by contributing to the growing incidence of nephrolithiasis.

Based on the ROC curve and balancing sensitivity and specificity, baseline urinary calcium of 180 mg/24-hours best predicts patients that are at increased risk of hypercalciuria. Physicians should consider assessing baseline 24-hour urinary calcium in women with postmenopausal osteoporosis. In women with baseline urinary calcium greater than 180 mg/24hr a follow-up 12 month urine calcium study should be obtained to assess for the development of hypercalciuria (> 250 mg/24-hours).

Obtaining 24 hour urine collections may be logistically difficult in the outpatient clinical setting. Other readily available options, including a baseline spot morning urinary calcium to creatinine ratio, should be explored.

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