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Oral Calcium Supplementation Does Not Increase Risk of Calcium Nephrolithiasis in Postmenopausal Women

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Abstract

**Background:** The American Association of Clinical Endocrinologists (AACE) current recommendation is 1000-1200 mg calcium daily for postmenopausal and osteoporotic women. Some patients are reluctant to supplement calcium due to the fear of developing a kidney stone (nephrolithiasis). In the United States, every adult will have a 10% to 15% chance to get kidney stones in their lifetime. And the recurrence rate is up to 50% after 10 years. There is no clear theory on how kidney stones are formed. There are lots of factors that play into the role of kidney stone generation, such as urinary calcium, oxalate, citrate, phosphate, and pH levels. About 75% of kidney stones are calcium oxalate stones. And most patients with calcium oxalate stones are hypercalciuric and hyperoxaluric. Calcium supplements can increase calcium excretion in the urine, and in theory can increase the risk of calcium kidney stones. The purpose of this review is to find out if calcium supplementation does indeed increase risk of kidney stones in postmenopausal women.

**Methods:** An exhaustive search was conducted using Medline-OVID, Medline-PubMed, CINAHL, and Web of Science using the keywords: calcium supplementation, kidney calculi and postmenopausal women. Relevant articles were assessed for quality using GRADE.

**Results:** The initial search yielded 19 articles for review. After additional reading of the abstracts, two studies met inclusion criteria and were included in this systematic review. These articles include one randomized controlled trial and one observational study.

**Conclusion:** According to the results from the two studies and data collected, calcium supplementation in postmenopausal women does not increase the risk of calcium oxalate kidney stones. Also postmenopausal patients who had an incidence of kidney stones in the past should not be discouraged from taking calcium supplements to prevent them from having osteoporosis. Dietary and supplemental calcium intake in these studies seems to actually decrease the risk of kidney stone formation.

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Master of Science in Physician Assistant Studies

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**Keywords**
calcium supplementation, kidney calculi, postmenopausal women

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The student author attests that this work is completely his/her original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
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Wei Kuang

A Clinical Graduate Project Submitted to the Faculty of the
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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

Background: The American Association of Clinical Endocrinologists (AACE) current recommendation is 1000-1200 mg calcium daily for postmenopausal and osteoporotic women. Some patients are reluctant to supplement calcium due to the fear of developing a kidney stone (nephrolithiasis). In the United States, every adult will have a 10% to 15% chance to get kidney stones in their lifetime. And the recurrence rate is up to 50% after 10 years. There is no clear theory on how kidney stones are formed. There are lots of factors that play into the role of kidney stone generation, such as urinary calcium, oxalate, citrate, phosphate, and pH levels. About 75% of kidney stones are calcium oxalate stones. And most patients with calcium oxalate stones are hypercalciuric and hyperoxaluric. Calcium supplements can increase calcium excretion in the urine, and in theory can increase the risk of calcium kidney stones. The purpose of this review is to find out if calcium supplementation does indeed increase risk of kidney stones in postmenopausal women.

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Results: The initial search yielded 19 articles for review. After additional reading of the abstracts, two studies met inclusion criteria and were included in this systematic review. These articles include one randomized controlled trial and one observational study.

Conclusion: According to the results from the two studies and data collected, calcium supplementation in postmenopausal women does not increase the risk of calcium oxalate kidney stones. Also postmenopausal patients who had an incidence of kidney stones in the past should not be discouraged from taking calcium supplements to prevent them from having osteoporosis. Dietary and supplemental calcium intake in these studies seems to actually decrease the risk of kidney stone formation.

Keywords: calcium supplementation, kidney calculi, postmenopausal women
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List of Abbreviations

IU........................................................................................................................................ International Units
USPSTF............................................................................................................................. US Preventive Services Task Force
AACE................................................................................................................................. American Association of Clinical Endocrinologists
GRADE........................................... Grading of Recommendations, Assessment, Development and Evaluations
Oral Calcium Supplementation Does Not Increase Risk of Calcium Nephrolithiasis in Postmenopausal Women

BACKGROUND

“Osteoporosis is a generalized skeletal disorder characterized by compromised bone strength, which causes its sufferers to be predisposed to an increased risk of fractures.”¹

Postmenopausal women are prone to osteoporosis due to the loss of estrogen’s effect on bones. At the time of the Surgeon General’s report in 2004, an estimated 8 million women were affected.¹² According to current recommendations, daily 1200mg calcium and 800 IU vitamin D are advised in postmenopausal women with osteoporosis.³ At the same time, the American Association of Clinical Endocrinologists (AACE) current recommendation is 1000-1200 mg calcium daily for postmenopausal and osteoporotic women. However, they recommend dietary calcium over supplemental calcium medication.⁴ Some patients are reluctant to supplement calcium due to the fear of developing a kidney stone (nephrolithiasis), and with all the divergent recommendations and guidelines, the first thing a clinician must keep in mind is to do no harm.

Kidney stones are quite common.⁵ In the United States, every adult will have a 10% to 15% chance to get kidney stones in their lifetime.⁶⁻⁸ And the recurrence rate is up to 50% after 10 years.⁵⁹ There is no clear theory on how kidney stones are formed. But it was proposed that it’s due to urine supersaturation.¹⁰ There are many factors that play into the role of kidney stone generation, such as urinary calcium, oxalate, citrate, phosphate, and pH levels. About 75% of kidney stones are calcium oxalate stones.⁵ And most patients with calcium oxalate stones are hypercalcuiuric and hyperoxaluric. It is known that urinary calcium and oxalate both play a critical role in calcium oxalate stone formation.¹¹ Nevertheless, it still remains controversial whether calcium or oxalate is more important in the supersaturation of urinary calcium oxalate.¹¹⁻¹⁴
Calcium supplements can increase calcium excretion in the urine, and in theory can increase the risk of calcium kidney stones. The purpose of this review is to find out if calcium supplementation does indeed increase risk of kidney stones in postmenopausal women. Is it safe to recommend calcium supplementation to postmenopausal women without putting them at a greater risk of kidney stones?

METHODS

An exhaustive search was conducted using Medline-OVID, Medline-PubMed, CINAHL and Web of Science using the keywords: calcium supplementation, kidney calculi and postmenopausal women. Relevant articles were assessed for quality using Grading of Recommendations, Assessment, Development and Evaluation (GRADE).15

RESULTS

The initial search yielded 19 articles for review. After additional reading of the abstracts, two studies met inclusion criteria and were included in this systematic review. These articles include one randomized controlled trial16 and one observational study17. See Table I.

Domrongkitchaiporn et al Trial

This randomized trial16 with 53 Thai women who were more than 10 years postmenopausal were selected in order to evaluate if supplemental calcium would increase risk of calcium oxalate stones. Risk of calcium oxalate stone formation was assessed by using the Tiselius’s index called AP(CaOx).18 AP(CaOx) was calculated before and after 3 months of daily supplementation with 750 mg calcium alone or with 0.5ug calcitriol.16

Study population mean age was 65.3+/− 1.1 years, and enrollment criteria included 10 years postmenopausal with osteoporosis. Patients who were currently on medications such as
bisphosphonates, diuretics, vitamin D, or hormones were excluded from the study due to their effects on calcium balance. Patients were randomly assigned to receive either 250 mg calcium alone at the end of 3 meals everyday (group C) or with 0.25 ug calcitriol after breakfast and dinner (group CD). The treatment groups’ total energy intake, subdivided into carbohydrate, fat, protein, sugar, crude fiber content, was calculated at the beginning of the study, and the participants were told to maintain their normal diet during the 3 months period.16

At the end of the study, 24-hour urine was collected to measure its volume and components including calcium, magnesium, citrate, sodium, potassium, oxalate, phosphate and creatinine. Then the AP(CaOx) was calculated using the following formula of AP(CaOx) index= \( A \times Ca^{0.84} \times Ox^{1.0} \times Mg^{-0.12} \times Cit^{-0.22} \times V^{-0.13} \).18 Authors used AP(CaOx) index as an measurement of risk of calcium oxalate kidney stones formation due to the relationship and correlation that has been established and clinically proven.19-22 And an AP(CaOx) greater than 2.0 is related to an increased risk of calcium oxalate kidney stone.18

The study showed that calcium supplementation with or without calcitriol did not increase AP(CaOx) significantly, (group C: AP(CaOx) 1.17+/-.39 before treatment, 1.36+/-.28 after treatment; group CD: 1.09+/-.17 before treatment, 1.09 +/-0.19 after treatment). They also calculated the AP(CaOx) value from 56 non-stone-forming normal women, where 95% of normal values fell within a range of 1.05-1.52. Before treatment, there were three in group C and six in group CD that had an AP(CaOx) of greater than 1.52. After treatment there were six in group C and six in group CD who had AP(CaOx) more than 1.52. This finding is not significant. But there was a significant increase in urinary calcium excretion in group CD (baseline 2.87+/-0.41, after treatment 4.08+/-0.57). See Table II. Their study concluded that
calcium supplementation does not increase the risk of calcium oxalate kidney stones in the “majority of postmenopausal women with osteoporosis”.16

**Sorensen et al Study**

This retrospective observational study17 with 7982 women evaluated whether or not dietary and supplemental calcium would decrease fractional calcium absorption. They also researched whether higher fractional calcium absorption was related to a higher incidence of kidney stones. The study population was primarily Caucasian women 65 years old or older. At the fourth visit, 5452 women were further evaluated for intestinal fractional calcium absorption. The study divided patients in 5 quintiles by their calcium supplementation dose. Within each quintile, patients were subdivided into two groups: with or without history of nephrolithiasis. Then each groups’ fractional calcium absorption was calculated and compared. This study shows that in each calcium supplement intake quintile, higher fractional calcium absorption is seen in populations with history of nephrolithiasis. Also, Sorensen et al17 found that “women were 30% more likely to report a history of nephrolithiasis for every 10% increase in fractional calcium absorption (OR 1.30, 95% CI 1.12-1.52, P<0.001)”. Moreover, in patients without a history of nephrolithiasis, the higher dietary and supplementary calcium intake, the lower the fractional calcium absorption rate was.17 See Table III.

The study concluded that calcium supplement decreases fractional calcium absorption. Higher fractional calcium absorption is seen in patients with history of kidney stones. The authors concluded that calcium supplementation does not increase the risk of kidney stones, but on the contrary, may decrease the risk.17

**DISCUSSION**
With the two studies,\textsuperscript{16,17} it is very difficult to make a direct comparison with each other due to a lot of reasons, such as the apparent different nature and characteristics of the study type, the different methods and endpoints used in both studies, the different population with different prognostic factors and etc. However, both studies point out that with calcium supplements, there is likely to be no increase in risk of kidney stones formation in postmenopausal women. Moreover the Sorensen et al\textsuperscript{17} study even concluded that calcium supplementation could protect against kidney stones. This could be due to that with calcium supplementation, there would be more combination of oxalate with calcium in the intestine, which in turn decreases the oxalate in the urine, and therefore decreases calcium oxalate kidney stone incidence.\textsuperscript{12,17,23}

Moreover, kidney stone formation is a very complicated process with a lot of factors involved. Besides supplements, diet is another aspect worth considering. A diet called the DASH diet has been proven to decrease the supersaturation of calcium oxalate, and in turn decrease incidence of calcium oxalate kidney stones.\textsuperscript{24,25} The DASH diet is basically a diet high in fruit and vegetables, low in protein and salt, and moderate in low-fat dairy products.\textsuperscript{24,25} So as a clinician, clarifying the confusion and wrong impression that most patients had about calcium supplementation in postmenopausal women is very important.

**Limitation of the Domrongkitchaiporn et al Trial**

The first study\textsuperscript{16} was randomized but without a real control group. Its AP(CaOx) value was compared with a baseline value calculated from 56 non-stone forming women with a 95% CI. The control group age was younger than the study group, average 36.7+/−1.8 yrs, verses the study group age average 65.3+/− 1.1 yrs. The total population sample size was very small and limited to the nationality of Thai women. Their dietary habits are not quite the same as the Western population. And the control group diet component was not discussed in the study. The
use of AP(CaOx) as a surrogate endpoint of the study was a limitation instead of using patient reported kidney stone events as endpoint.

The 3 months follow-up could also be a limitation. There is no study showing the length of study needed to understand kidney stone formation with all of its risk factors. Therefore there can be clinically significant events occurring after 3 months of follow-up, although in another study conducted by the Haghighi et al\textsuperscript{12}, a 1 year follow up of 53 postmenopausal women with 1000 mg calcium supplementation per day did not show any influence on kidney stone formation either.

Dosage of supplementation is another issue. A calcium supplementation of 750 mg of calcium supplementation is lower than the current recommendation of 1200 mg in postmenapausal women. Could adding 450mg more of calcium per day can make a significant change in the result?

The study’s timing of the calcium and calcitriol supplementation fixed at the end of the meal was the best possible scenario. This made up for the limitation of a similar previous study, Curhan et al\textsuperscript{26}, in which timing of the calcium supplementation was not standardized. Curhan et al\textsuperscript{26} authors found that nonfood calcium supplementation has a higher risk of kidney stone formation compared to dietary calcium. However, in their discussion part, they suggested that this finding could be due to the timing of supplemental calcium ingestion not being strictly controlled. It is commonly thought that calcium supplementation is not recommended in patients with a history of nephrolithiasis. Curhan et al\textsuperscript{26} study showed that higher dietary intake of calcium as a matter of fact decreases the risk of kidney stone formation in women.

**Limitations of the Sorensen et al study**
This study\textsuperscript{17} was unique in the way that it tried to find the relationship between intestinal calcium absorption and kidney stones. Although this study was retrospective with no control group, it provided a much bigger sample size. Most importantly, it used kidney stone as a clinical endpoint instead of using surrogate endpoint such as AP(CaOx) index or hypercalciuria, which correlated with but did not necessarily lead to kidney stones. However noticeably, Domrongkitchaiporn et al\textsuperscript{16} trial directly focused on risk of calcium oxalate kidney stones. Sorensen et al\textsuperscript{17} study did not differentiate the subtypes of kidney stones. Without going into too much details of different types of kidney stones and their compositions, there are uric acid kidney stones caused by metabolic disorder of high uric acid and struvite stones caused by urinary tract infections. The subtypes of stones should have been screened and discussed to ensure an accurate correlation between calcium supplementation and kidney stones.

Sorensen et al\textsuperscript{17} study also included patients on vitamin D supplements, estrogen, and thiazide diuretics, who were excluded in Domrongkitchaiporn et al\textsuperscript{16} study. Both vitamin D and thiazide use can alter calcium homeostasis. So in data analysis, authors used “multivariate logistic regression analysis” to adjust the variables.\textsuperscript{16} The data would be more reliable if the factors that could influence the calcium homeostasis are excluded from the study population. Overall, the quality of evidence for the association between calcium supplementation and risk of kidney stone formation is low (see Table I).

After reviewing these studies, having more RCTs done with longer follow up and larger sample sizes is recommended in order to increase the body of evidence for fully establishing the relationship between calcium supplementation and risk of calcium oxalate kidney stones. Also, the studies would be better if it had control group with similar prognostic factors. Moreover,
using a direct outcome measure such as rate of kidney stone formation as an endpoint is recommended verses using surrogate endpoints.

CONCLUSION

According to current AACE recommendations, daily 1000-1200mg calcium is advised in postmenopausal women with osteoporosis. But some patients and even clinicians are concerned about the risk of calcium kidney stone formations with oral calcium supplementations. From the results of the two studies and data collected, calcium supplementation in postmenopausal women does not likely increase the risk of calcium oxalate kidney stones. Also postmenopausal patients who had an incidence of kidney stones in the past should not be discouraged from taking calcium supplements to prevent them from having osteoporosis.

Furthermore, the DASH diet can be recommended to postmenopausal women. From the two studies discussed, dietary and supplemental calcium intake in these studies seems to actually decrease the risk of kidney stone formation. Clinicians and healthcare providers should feel comfortable recommending calcium supplementation in postmenopausal women with or without history of kidney stones to prevent them from the effects of osteoporosis.
References


Table I. Characteristics of Reviewed Studies

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Inconsistency</th>
<th>Publication bias likely</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>Domrongkitchaporn et al(^{16})</td>
<td>RCT</td>
<td>Serious(^a,b)</td>
<td>Not serious</td>
<td>Serious(^c)</td>
<td>Not serious</td>
<td>No bias likely</td>
<td>Low</td>
</tr>
<tr>
<td>Sorensen et al(^{17})</td>
<td>Observational</td>
<td>Serious(^d)</td>
<td>Not serious</td>
<td>Not serious</td>
<td>Not serious</td>
<td>No bias likely</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

\(^a\) No mention of level of blinding of study  
\(^b\) Strong use of surrogate outcomes no control group  
\(^c\) Small sample size  
\(^d\) Lack of strong control group
### Table II. Summary of Findings a

<table>
<thead>
<tr>
<th>outcome</th>
<th>Baseline</th>
<th>Post intervention</th>
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<tr>
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<td>calcium supplement</td>
<td>calcium+calcitriol</td>
</tr>
<tr>
<td></td>
<td>calcium supplement</td>
<td>calcium supplement</td>
</tr>
<tr>
<td></td>
<td>calcium+calcitriol</td>
<td>calcium+calcitriol</td>
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<td>3.58+/−0.54</td>
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<td>urine oxalate</td>
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<td>0.29+/−0.03</td>
<td>0.22+/−0.02</td>
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<td>1.09+/−0.17</td>
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<tr>
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<td>1.09+/−0.19</td>
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### Table III. Summary of Findings b

<table>
<thead>
<tr>
<th>Sorensen et al study¹⁷</th>
<th>current calcium supplementation dose</th>
<th>mean calcium absorption</th>
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<td>fractional calcium absorption</td>
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<td>35.2+/−8.4</td>
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