Comparison of Dietary Calcium with Supplemental Calcium and Other Nutrients as Factors Affecting the Risk for Kidney Stones in Women

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Background: Calcium intake is believed to play an important role in the formation of kidney stones, but data on the risk factors for stone formation in women are limited.

Objective: To examine the association between intake of dietary and supplemental calcium and the risk for kidney stones in women.

Design: Prospective cohort study with 12-year follow-up.

Setting: Several U.S. states.

Participants: 91,731 women participating in the Nurses' Health Study I who were 34 to 59 years of age in 1980 and had no history of kidney stones.

Measurements: Self-administered food-frequency questionnaires were used to assess diet in 1980, 1984, 1986, and 1990. The main outcome measure was incident symptomatic kidney stones.

Results: During 903,849 person-years of follow-up, 864 cases of kidney stones were documented. After adjustment for potential risk factors, intake of dietary calcium was inversely associated with risk for kidney stones and intake of supplemental calcium was positively associated with risk. The relative risk for stone formation in women in the highest quintile of dietary calcium intake compared with women in the lowest quintile was 0.65 (95% CI, 0.50 to 0.83). The relative risk in women who took supplemental calcium compared with women who did not was 1.20 (CI, 1.02 to 1.41). In 67% of women who took supplemental calcium, the calcium either was not consumed with a meal or was consumed with meals whose oxalate content was probably low. Other dietary factors showed the following relative risks among women in the highest quintile of intake compared with those in the lowest quintile: sucrose, 1.52 (CI, 1.18 to 1.96); sodium, 1.30 (CI, 1.05 to 1.62); fluid, 0.61 (CI, 0.48 to 0.78); and potassium, 0.65 (CI, 0.51 to 0.84).

Conclusions: High intake of dietary calcium appears to decrease risk for symptomatic kidney stones, whereas intake of supplemental calcium may increase risk. Because dietary calcium reduces the absorption of oxalate, the apparently different effects caused by the type of calcium may be associated with the timing of calcium ingestion relative to the amount of oxalate consumed. However, other factors present in dairy products (the major source of dietary calcium) could be responsible for the decreased risk seen with dietary calcium.

Dietary factors are believed to play an important role in the formation of kidney stones [1, 2], but data on the influence of diet on stone formation in women are limited. The incidence of kidney stones in women is one third the incidence in men[3]; the reason for this marked difference is unknown. Although differences in diet may contribute, the only available data on which comparisons between men and women can be based are from case-control studies that included few women. No studies have provided prospective data on the relation between diet and kidney stones in women.

In the past, a diet high in calcium was suspected of increasing the risk for calcium-containing kidney stones, particularly stones consisting of calcium oxalate (the most common type). This finding has often led to restriction of calcium intake in patients who have had kidney stones in an attempt to decrease the likelihood of recurrence. In a large prospective study in men, however, we recently found that high intake of dietary calcium was associated with a decreased risk for stone formation [2]. One possible explanation of this observation is that high calcium intake reduces oxalate absorption and subsequent urinary excretion of oxalate by binding oxalate in the gastrointestinal tract. Urinary oxalate may be more important than urinary calcium with respect to formation of calcium oxalate crystals [4]. Moreover, restriction of dietary calcium intake may result in negative calcium balance and decreased bone mineral density, particularly in patients with idiopathic hypercalciuria [5].

Supplemental calcium, such as calcium carbonate, is commonly used by adults in the United States. Large doses have been recommended for the prevention of various common disorders in women, such as osteoporosis and preeclampsia [6, 7]. Although some researchers are concerned that high doses of supplemental calcium may increase the risk for kidney stone formation [7], no data are available on this issue in women. Use of supplemental calcium increases urinary calcium excretion; if not taken with meals, these supplements do not decrease urinary oxalate excretion. Thus, the overall effect of supplemental calcium may actually be an increased risk for stone formation. Clearly, information on the risk for stone formation associated with intake of supplemental calcium is essential to help patients decide whether to begin or continue to use calcium supplements.

Other dietary factors may also be associated with the risk for kidney stone formation [1, 2]. A diet high in sodium [8], sucrose [9], or animal protein [10] may increase the risk for stone formation, whereas a diet high in potassium [11], magnesium [12], or fluid may decrease this risk.
To study the association between intake of dietary and supplemental calcium and other nutrients and the incidence of kidney stones in women, we conducted a 12-year prospective analysis among 91,731 women who were participating in the Nurses’ Health Study and had no history of kidney stones at study entry.

Methods

Study Sample

In 1976, 121,700 female registered nurses who were 30 to 55 years of age and resided in 1 of 11 U.S. states completed and returned the initial questionnaire. These women constitute the Nurses’ Health Study cohort [13]. The cohort is followed by using biennial mailed questionnaires that ask about lifestyle practices and other exposures of interest, as well as the incidence of newly diagnosed disease. The sample for our analysis was limited to the 91,731 women who answered the 1992 questionnaire, which included a question on lifetime history of kidney stones, and who had completed at least one of the four dietary questionnaires since 1980 (the first year in which information on diet was collected).

Assessment of Diet

In 1980, 1984, 1986, and 1990, the participants were asked to complete semiquantitative food-frequency questionnaires, on which they reported the average intake of specified foods and beverages during the past year. The 1980 dietary questionnaire contained 61 items, and the subsequent questionnaires contained 131 items. Nutrient intake was computed from the reported frequency of consumption of each specified unit of food or beverage and from published data on the nutrient content of the specified portions [14]. Beginning in 1984, information was also collected on the amount of supplemental calcium (such as calcium carbonate) ingested, either as separate supplements or as part of multivitamin preparations. The reproducibility and validity of the questionnaires completed by women in this cohort have been documented elsewhere [14]. A similar questionnaire has been shown to be valid and reproducible in men [15].

Nutrient values were adjusted for total energy intake by regressing total caloric intake on absolute nutrient intake [16, 17]. Because total energy intake for a given person tends to be fixed within a narrow range, variations in nutrient intake are largely attributable to changes in composition of diet, not the total amount of food consumed. Energy-adjusted values reflect the nutrient composition of the diet independent of the total amount of food consumed. In addition, adjustment for energy reduces any variation introduced by questionnaire responses that underreported or overreported intake, thereby improving the accuracy of nutrient measurements [16, 17].

To obtain additional information on the typical pattern of the use of supplemental calcium, we mailed a questionnaire to a random sample of 100 women who reported taking supplemental calcium on the 1994 biennial questionnaire. Eighty-six of these women responded. The questionnaire asked about the specific type of calcium salt ingested and whether the supplement was taken alone or with particular meals.

Follow-up and Ascertainment of Cases

The 1992 questionnaire asked whether the woman had ever received a diagnosis of a kidney stone and, if so, the date of the first occurrence. If the participant reported that a kidney stone had been diagnosed in 1980 (when dietary information was first collected) or later, we mailed her a supplementary questionnaire to confirm the diagnosis and to ascertain the date of occurrence; the type of symptoms; other relevant medical conditions; and, if known, the type of stone. The rate of response to this supplementary questionnaire was 95%. To confirm the validity of the participants’ reports, we obtained the medical records from a random sample of 90 of the women who reported a kidney stone. The records confirmed the diagnosis for all but 1 woman.

We considered only cases of kidney stones that were diagnosed during the 12 years between the date on which the 1980 questionnaire was returned and 31 May 1992. After we excluded women for whom the date of the kidney stone either could not be confirmed or fell outside of the study period, 91,731 women with no history of kidney stones remained in the study group.

Statistical Analysis

The study design was prospective, and information on diet was collected before the onset of the kidney stone. For each participant, person-months of follow-up were counted from the date on which the 1980 questionnaire was returned 1) to the date on which a kidney stone developed or death occurred or 2) to 31 May 1992, whichever occurred first. Information on exposures of interest that were recorded in responses to the 1980 questionnaire was updated in 1984, 1986, and 1990. We allocated person-months of follow-up according to exposure status at the start of each follow-up period (indicated by the quintile of calcium intake and other variables). Dividing the cohort into quintiles of nutrient intake allowed us to examine a wide range of nutrient intake while maintaining enough participants in the highest and lowest categories. If complete information on diet was missing at the start of a time period, the participant was excluded for that time period.

The relative risk—the incidence among women in a particular category of intake divided by the corresponding rate in the comparison category—was used as the measure of association [18]. Age-adjusted relative risks were calculated after the participants were stratified according to 5-year age categories [18]. The Mantel extension test was used to evaluate linear trends across categories of intake [19]. We used a proportional-hazards model to simultaneously adjust for several risk factors [20]. The variables considered in these models were selected on the basis of factors that published reports had indicated were related to formation of calcium stones. Variables included were age (5-year categories); alcohol consumption (eight categories); body mass index (five categories); intake of vitamin B₆ (five categories); intake of vitamin C (five categories); intake of supplemental calcium (0 mg/d, 1 to 100 mg/d, 101 to 500 mg/d, and ≥ 500 mg/d); and dietary intake of calcium, animal protein, potassium, sodium, sucrose, magnesium, phosphorus, fiber, vitamin D, animal fat, total fat, and fluid (quintile groups). We calculated 95% CIs for all relative risks. All P values are two tailed.

Results
During the 903,849 person-years of follow-up, we documented 864 cases of new symptomatic kidney stones. Seventy-three women had systemic diseases potentially related to stone formation (Table 1). Although 13.4% of the women reported having a urinary tract infection at the time the stone developed, only 3.9% reported that they believed the stone formed as a result of this infection (Table 1). A family history of stone formation was reported by 24.2% of the women with stones. Pain was the most frequent presenting symptom, occurring in 91.1% of cases. Of the 390 women who reported information on the type of stone, 336 (86.2%) reported that the stone contained calcium. The incidence rate for the cohort was slightly less than 1 case per 1000 person-years; the rate did not vary substantially by age (Table 2).

Table 1. Self-Reported Characteristics of the 864 Women with Incident Kidney Stones

Table 2. Incidence of Kidney Stones between 1980 and 1992 among 91,731 Women according to 5-Year Age Groups

Intake of Dietary Calcium

Table 3 shows the characteristics of the cohort according to 1986 quintile values for energy-adjusted intake of dietary calcium. The 1986 values were selected to quantitatively show the boundaries and medians of the quintiles; these values are representative of the ranges of intake during the other time periods. For our analyses, however, the actual dietary values (as calculated from responses to the food-frequency questionnaire) were used for each respective time period. In 1986, the mean daily intake of animal protein; potassium; magnesium; phosphorus; fluid; and vitamins B6, C, and D increased with increasing intake of dietary calcium. The mean sucrose intake decreased with increasing intake of dietary calcium. The mean daily intake of supplemental calcium was similar in all quintiles.

Table 3. Characteristics of the Participants according to Energy-Adjusted Intake of Dietary Calcium in 1986*

After adjustment for age and energy intake, a higher intake of dietary calcium was strongly associated with a reduced risk for kidney stones (P for trend < 0.001) (Table 4). The relative risk among women in the highest quintile of intake of dietary calcium compared with women in the lowest quintile was 0.49 (95% CI, 0.39 to 0.60).

Table 4. Age-Adjusted and Multivariate Relative Risks for Symptomatic Kidney Stones according to Intake of Dietary Calcium*

After adjustment for age; body mass index; and intake of animal protein, alcohol, sodium, sucrose, fluid, and supplemental calcium, the apparent protective effect of dietary calcium was slightly attenuated but remained highly significant (Table 4). The relative risk among women in the highest quintile of intake of dietary calcium compared with women in the lowest quintile was 0.65 (CI, 0.50 to 0.83). Similar results were found in a multivariate analysis that excluded the 73 women who reported a systemic disease that predisposes patients to stone formation (Table 1) and the 34 women who reported a urinary tract infection as the cause of stone formation.

Intake of Supplemental Calcium

We also studied the relation between the intake of supplemental calcium and the risk for kidney stones. In contrast to intake of dietary calcium, we found that after adjustment for age, intake of supplemental calcium was associated with an increased risk for kidney stones (Table 5). After adjustment for potential confounders, the relative risk among women who took supplemental calcium compared with women who did not was 1.20 (CI, 1.02 to 1.41). The relative risk among women who consumed 1 to 100 mg of supplemental calcium per day compared with women who did not take supplemental calcium was 1.26 (CI, 0.79 to 2.00). No additional increase in risk was seen among women who consumed more than 100 mg of calcium per day (Table 5).

Table 5. Age-Adjusted and Multivariate Relative Risks for Symptomatic Kidney Stones according to Intake of Supplemental Calcium*
Other Dietary Factors

Both sucrose intake and sodium intake were associated with an increased risk for kidney stones. In contrast, potassium intake and fluid intake were inversely related to risk (Table 6). In the multivariate model, the relative risks among women in the highest quintiles of intake compared with those in the lowest quintiles were the following: sucrose, 1.52 (CI, 1.18 to 1.96); sodium, 1.30 (CI, 1.05 to 1.62); potassium, 0.65 (CI, 0.51 to 0.84); and fluid, 0.61 (CI, 0.48 to 0.78). Intake of animal protein was not significantly associated with risk when all time periods were combined. However, when follow-up was limited to the last two time periods (1986 to 1992), the relative risk among women in the highest quintile of intake of animal protein compared with those in the lowest quintile was 1.36 (CI, 0.99 to 1.86). In the multivariate model, intake of magnesium and intake of phosphorus were not significantly associated with risk for kidney stones. However, the association seen for dietary calcium was attenuated when these nutrients were included in the models; this reflects the high degree of collinearity of these nutrients (data not shown). The main sources of both dietary calcium and phosphorus were dairy products.

Discussion

Our findings support the hypothesis that greater consumption of dairy products, the major source of dietary calcium, decreases risk for symptomatic kidney stones in women. This result is consistent with the findings we previously reported in a large prospective study of men [2]. These findings are contrary to the previously held belief that intake of dietary calcium increases the risk for stone formation. Moreover, no studies have shown that restriction of calcium intake reduces risk for kidney stones. In fact, patients with hypercalciuria in whom intake of dietary calcium is restricted have a higher probability of stone formation [21, 22]. Our data also suggest that dietary and supplemental calcium have different effects with respect to stone formation.

Dietary oxalate plays an important role in the formation of calcium oxalate stones; research suggests that the apparent protective effect of a diet high in calcium may be mediated through this diet’s effect on oxalate absorption [4, 22-24]. Calcium restriction increases oxalate absorption in the gastrointestinal tract in both normal persons and patients with kidney stones [22, 24-26] and leads to increases in urinary oxalate excretion ranging from 16% [27] to 56% [24]. Notably, urinary oxalate may play an even more important role than urinary calcium in the process of stone formation because saturation of urine with calcium oxalate increases more rapidly with increases in oxalate concentration than with increases in calcium concentration [4].

In our cohort, dairy products were the major source of dietary calcium. Experimental evidence suggests that dietary calcium is associated with a reduced risk for stone formation [2, 22]. However, our data do not exclude the possibility that some other factor present in dairy products is protective. For example, dairy products were also the major source of phosphorus; in addition, intake of dietary calcium and intake of phosphorus were highly correlated (r = 0.83). Researchers have suggested that phosphorus may reduce urinary calcium excretion and calcium oxalate supersaturation in patients with absorptive hypercalciuria [28]; phosphorus supplements are often prescribed to reduce the likelihood of stone recurrence. It is therefore possible, although less likely, that phosphorus is the protective nutrient.

We found that in contrast to dietary calcium, supplemental calcium was associated with a slightly increased risk for kidney stones. An association of similar magnitude was seen in men but was not statistically significant [2]. We suggest that this apparent contradiction may be due to the timing of the ingestion of supplemental calcium. Increased calcium intake, usually in the form of supplements given with meals, has been used effectively to decrease oxalate absorption among patients with malabsorption [29]. Administration of supplemental calcium with oral oxalate loads has resulted in decreased urinary oxalate excretion in patients with ileal disease, patients with kidney stones and hypercalciuria, and healthy controls [26]. In our cohort, 43% of persons who used supplemental calcium consumed the supplements with meals and 24% consumed them only with breakfast (a meal whose oxalate content is likely to be low). If supplemental calcium is not consumed at the time of oxalate ingestion, it may provide little or no protection from oxalate absorption. In addition, calcium absorption may be greater when supplements are not taken with food; this increased absorption may lead to increased urinary calcium excretion and greater risk for stone formation. The following are two possible explanations for the lack of a dose response for supplemental calcium: Women who ingested higher doses may have been more likely to take the supplements with a meal or close to a meal, and some women may have reported the amount of the total supplement preparation rather than the amount of elemental calcium.

Restriction of dietary calcium in an effort to prevent stone formation may produce undesirable biological and clinical effects. Although many researchers believe that the U.S. recommended daily allowance for total calcium intake for women (800 mg/d) is too low [7], women with kidney stones are still frequently advised to reduce their calcium intake well below this level. This calcium restriction may lead to a negative calcium balance, particularly in women who are hypercalciuric, eventually resulting in bone loss and osteoporosis.

Intake of sodium and intake of sucrose were associated with increased risk for stone formation, presumably because of increased urinary calcium excretion [6, 9]. The inverse association observed for potassium intake may be due to 1) reduced urinary calcium excretion [11] or 2) the high alkali content of many potassium-rich foods, which can lead to an increase in urinary citrate, a natural inhibitor of the formation of calcium crystals in the urine [30]. The beneficial effect of increased fluid intake and of the subsequent increase in urinary volume with dilution of lithogenic factors is well known.

When we examined the entire 12-year period, animal protein was not associated with risk. However, when the follow-up period was limited to 1986 to 1992, the relative risk was nearly identical to that seen in men [2]. The range of animal protein intake was also similar to that reported in men. It is possible that the shorter (61-item) 1980 dietary questionnaire did not measure intake of animal protein as well as subsequent versions of the questionnaire did. Intake of animal protein increases urinary excretion of uric acid [31] and calcium [32] and decreases excretion of citrate [32]. These factors predispose patients to formation of calcium oxalate stones.
The proposed mechanisms of action of the different nutrients are only possible explanations for the associations we observed. Foods contain thousands of chemical compounds and are more complex than simply the sum of the individual nutrients. The actual mechanisms of action may be much more complex, involving interactions among the nutrients that affect bioavailability, gastrointestinal absorption, and urinary saturation. Future research may reveal additional factors in foods that play a role in stone formation.

Because information on diet was collected before kidney stones were diagnosed, biased recall of diet was avoided. Selection bias is unlikely but cannot be completely excluded as an explanation for our findings. Women who were most susceptible to the effects of higher calcium intake may have had their first kidney stone before 1980 and thus would have been excluded from our analysis. However, this is an unlikely explanation because many first kidney stones occur after 40 years of age [3, 33]. Moreover, if this type of selection bias were present, the relative risk associated with intake of dietary calcium would then be expected to decrease with age. In fact, the incidence of kidney stones in our cohort was stable across age groups, and the effect of intake of dietary calcium with increasing age did not change.

Our results are most directly generalizable to women who are 34 years of age or older and have no history of kidney stones. It seems likely that the associations we observed would be similar in younger women because the association did not change with increasing age. In addition, our results probably apply to persons in whom calcium stones recur frequently, because the pathophysiology does not change after a stone develops. The relative risks associated with intake of calcium, supplemental calcium, potassium, and fluid in our female cohort are consistent with our previous findings in men [21].

In summary, our findings support the hypothesis that a high intake of dairy products, the major source of dietary calcium, decreases the risk for kidney stones, whereas a high intake of calcium from nonfood supplements increases this risk. Therefore, routine restriction of dairy products for patients with kidney stones that contain calcium should not be recommended. For women currently taking or considering taking supplemental calcium, the increased risk for kidney stone formation that is seen after total calcium intake has been increased through use of supplemental calcium needs to be balanced against the potential benefits. The risk for kidney stone formation attributable to use of supplemental calcium may possibly be reduced if the supplement is consumed with meals.

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