STONE DISEASE

Effect of dietary calcium on stone forming propensity

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Purpose: Epidemiological studies have reported that high calcium diet protects against kidney stone formation in normal subjects. This metabolic study was designed to elucidate the physiological and physicochemical effects conferring this apparent protection.

Materials and Methods: A total of 21 normal volunteers underwent 2 phases of study in a crossover, randomized design, wherein they consumed constant metabolic diets that matched the estimated highest and lowest quintiles of calcium intake from published epidemiological studies.

Results: Urinary calcium was significantly greater on the high calcium diet (148 +/- 55 versus 118 +/- 43 mg. daily, $p < 0.01$, $p < 0.01$) but urinary oxalate did not differ between diets. There was no difference in relative saturation ratio of calcium oxalate between the 2 diets. The high calcium diet significantly increased saturation of brushite and decreased that of uric acid. Due to the other differences between the diets (more fluid, potassium, magnesium and phosphate in the high calcium diet), the high calcium diet also increased 24-hour urinary volume, potassium, phosphorus, pH and citrate. After adjustment of these confounding variables, the high calcium diet significantly increased relative saturation ratio of calcium oxalate by 24%.

Conclusions: High calcium diet from published epidemiological studies does not alter the propensity for calcium oxalate crystallization in normal subjects despite increased urinary calcium and unaltered urinary oxalate because of the greater amounts of ingested fluid, potassium and phosphate. However, high calcium intake alone, without concomitant changes in the diet, poses a modest risk for calcium stone formation.

Editorial Comment

The role of dietary calcium in stone formation is controversial. Although high urinary calcium has been implicated in calcium stone disease, no prospective randomized trial has definitively established a link between urinary calcium and stone disease. Indeed, a recent long-term prospective, randomized trial demonstrated a higher incidence of stone formation in a group of hypercalciuric stone formers maintained on a low calcium diet compared with a similar group taking a normal calcium, low protein, low sodium diet. Likewise, 2 large populational studies showed a higher rate of incident stone formation in subjects in the highest quintile of calcium intake compared with the lowest. In both cases, the protective effect of a high calcium diet was attributed to reduced urinary oxalate as a result of intestinal binding of oxalate by calcium, which reduces intestinal oxalate absorption and decreases urinary oxalate excretion.

Heller and colleagues attempted to reproduce the high and low calcium diets from the observational studies by Curhan and colleagues in order to assess the physiological and physicochemical responses to changes in dietary calcium. In this 2-phase, randomized crossover study, 21 normal subjects were maintained on a constant metabolic diet matched to the dietary compositions of the highest and lowest quintiles of calcium intake in the epidemiological studies. Not surprisingly, urinary calcium was higher on the high calcium diet; however urinary oxalate and the relative saturation ratio for calcium oxalate were not significantly different between groups as a result of other stone-protective factors in the high calcium diet such as higher fluid, potassium and magnesium, which resulted in increased urinary volume, citrate and pH. Controlling for these confounding factors, the high calcium diet in fact increased the relative saturation ratio of calcium oxalate.

Based on this study, the “protective effect” of a high calcium diet may well not reside not in lowering of urinary oxalate but rather in the other favorable factors associated with a high calcium diet such as high fluid intake and an alkali load. Indeed urinary calcium increases significantly with a high calcium diet. As oxalate intake was fairly limited in this study, no increase in urinary oxalate was seen with the low calcium diet as had been speculated in the previous studies. However, with a more liberal oxalate intake, urinary oxalate could potentially increase in response to a low calcium diet. Nonetheless, indiscriminate recommendations to increase calcium intake in stone formers based on the findings of these recent studies may in fact pose additional risk of stone formation if concomitant measures, such as increased fluid and alkali intake are not taken.

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Durability of the medical management of cystinuria

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Purpose: Cystinuria is an autosomal recessive disorder of dibasic amino acid transport in the kidney that leads to an abundance of cystine in the urine. This molecule is poorly soluble in urine and it is prone to crystallization and stone formation at concentrations above 300 mg./l. Medical treatment in these patients has incorporated increasing urine volumes, alkalinization and thiol medications that decrease the availability of free cystine in urine. Despite a reasonable prognosis for reduced stone formation we and others have noted difficulties in patients complying with medical management recommendations. Therefore, we evaluated the durability of treatment success in our patients with cystinuria.

Materials and Methods: A retrospective chart review was performed in all patients with cystinuria referred to the comprehensive kidney stone center at our institution for an 8-year period. Medical therapy, stone recurrence rates, compliance with medications and scheduled followup, and the results of metabolic evaluations via 24-hour urine collections were reviewed. The average concentrations of urinary cystine in initial and followup 24-hour samples were compared in patients compliant and noncompliant with medical treatment. In addition, each patient was mailed a 1-page questionnaire to assess the self-perception of medical compliance.

Results: We identified 26 patients with a mean age of 32 years at referral (range 13 to 67) who were followed an average of 38.2 months (range 6 to 83). Females represented 58% of those with cystinuria. Overall compliance with medical recommendations was poor with a short duration of success. Of the 26 patients followed at our stone center only 4 (15%) achieved and maintained therapeutic success, as defined by urine cystine less than 300 mg./l. An additional 11 patients (42%) achieved therapeutic success but subsequently had failure at an average of 16 months (range 6 to 27). Of these patients 7 (64%) regained therapeutic success at an average of 9.4 months (range 4 to 20). Five patients (19%) never achieved therapeutic success, while an additional 6 (23%) failed to present to followup appointments or provide subsequent 24-hour urine studies despite referral to a tertiary care center. Patient self-assessment of medical compliance was uniformly high regardless of physician perceptions or treatment results.

Conclusions: The durability of medically treating patients with cystinuria is limited with only a small percent able to achieve and maintain the goal of decreasing cystine below the saturation concentration. Greater

physician vigilance in these complicated stone formers is required to achieve successful prophylactic management. Furthermore, these patients require better insight into the own disease to improve compliance.

Editorial Comment

Despite the relative simplicity of the pathophysiology of cystinuria compared with calcium oxalate nephrolithiasis, stone prevention in cystinurics remains a frustratingly difficult problem. Once hydration and alkalinization fail to prevent stone recurrence in cystinuria, the addition of chelating agents becomes necessary. Unfortunately, the choice of available agents is strikingly few, the medication is expensive and the side effects are often prohibitive. Consequently compliance with medication regimens is uniformly poor.

This sobering article by Pietrow and colleagues reviews the outcomes and perceptions of 26 cystinuric patients at a tertiary stone center. Although just over half the patients initially achieved therapeutic success as determined by urinary cystine levels, only 15% of patients maintained levels below cystine solubility. Moreover, nearly one quarter of patients was lost to follow-up. Interestingly, patients achieving and not achieving therapeutic success had similar perceptions of their compliance with medication and dietary regimens.

This article underscores the importance of close monitoring of cystinuric patients to maximize compliance and ultimately therapeutic success. Furthermore, it emphasizes the need for pharmaceutical companies to simplify drug regimens through higher dose pills to reduce the unwieldy number of pills required daily (12 on average in this series) and to make an effort to develop new medications with fewer side effects and lower cost. Unfortunately, the relatively low incidence of this disorder has discouraged pharmaceutical companies from pursuing active research and development in this area. For now, close patient follow-up is the best way to monitor and encourage these patients to follow a prescribed medical regimen that has proven efficacy in reducing stone recurrence.

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