Prospects for Dietary Therapy of Recurrent Nephrolithiasis

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The goal of this article is to propose a randomized controlled trial (RCT) that tests a hypothesis that dietary manipulation prevents recurrent kidney stones. Dietary interventions based on epidemiologic and pathophysiologic data are reviewed. The only diet trial successful in preventing stones showed that calcium intake of 1,200 mg/d, accompanied by restriction of animal protein, salt, and oxalate ingestion, was superior to 400 mg of calcium and restricted oxalate intake. This study may be worth repeating in women and in a society in which salt restriction might be less effective (eg, United States). The net result of diet trials establishes significant positive effects on urine chemistries, but these have not yet shown efficacy with regard to stone recurrence. Oxalate restriction alone could be effective, but many questions regarding which populations to study are not defined, and dietary oxalate's contribution to stone formation is disputed. Would such a study be limited to patients identified as having high dietary oxalate intake or high intestinal oxalate absorption? Would colonization with *Oxalobacter formigenes* influence the result? The increased prevalence of stones is linked to weight gain and obesity, making weight loss a possible therapy to prevent stones. Randomized trials show that diets consisting of low-fat content or low-caloric content cause modest weight loss and might be effective in reducing stone formation. Because the efficacy of thiazides in the prevention of stones in patients with hypercalciuria is clear, I propose dietary comparison of higher calcium intake to thiazides for the prevention of calcium-based kidney stones.

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The goal of this article is to propose a randomized controlled trial (RCT) that tests a hypothesis of dietary manipulation to achieve the prevention of recurrent kidney stones. The number of interventions that have been tested, whether achieving positive or negative results, is small. These will be reviewed briefly, recognizing that repeating a previously completed trial with a different study population or with a different study design might be worthwhile. Some dietary hypotheses that are commonly recommended in practice despite a lack of trial evidence will be discussed. I will conclude with a proposal for a study of a dietary manipulation in comparison to pharmacologic therapy.

In designing a study with an eye toward an interpretable and useful result, one must consider several competing values. Greater sample size reduces the risk of a type II error but may also lead to the inclusion of more heterogeneous study populations. Although larger studies may make extrapolation of study results applicable to more diverse patients, patient subgroups of interest should be defined prospectively at the time of enrollment. On the other hand, more exclusion criteria and more rigorous inclusion criteria will complicate efforts to find eligible patients.

I will consider the restriction of dietary oxalate and weight loss as possible interventions. I will briefly review the only RCT that succeeded in preventing stones using an experimental diet, an increase in dietary calcium combined with a reduction in dietary salt, protein, and oxalate as compared with a low-calcium, low-oxalate diet[1] in men with hypercalciuria. I, therefore, consider the possibility of manipulating dietary calcium. Protein restriction alone has been thought to be potentially important, but the trials performed have not yielded positive effects.[2,3] Therefore, I do not review the epidemiologic evidence

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and the pathophysiologic mechanisms by which animal protein ingestion can cause stones. Increasing fluid intake is the standard of care proven by RCTs to be effective and is not considered further.[4] The net result of diet trials is that the effects on urine chemistry are significant, but the efficacy of diet for prevention of recurrent stones is not established. Because the efficacy of thiazides in the prevention of stones in patients with hypercalciuria is clear, I propose a comparison of diet to thiazides. The discussion that followed the talk on which this article is based indicated that the proposed design was not necessarily embraced by all the meeting's attendees. The intention is not to be comprehensive and exclusive but to raise relevant issues.

Oxalate

Oxalate is an important determinant of urine supersaturation of calcium oxalate, the relatively insoluble salt that forms most calcium stones. The reduction of urine oxalate excretion is always considered a desirable goal, yet no trial of the reduction of urine oxalate excretion, with stone recurrence as an outcome, has been attempted. The problem is that lowering urine oxalate through dietary restriction of intake is not simply achieved. One interesting issue is that recent estimates of dietary oxalate intake based on more modern estimates of food oxalate content do not confirm that stone formers have higher dietary oxalate intake than nonstone formers.[5] This surprising finding was true in women in the Nurses Health Study (both younger and older cohorts) and in men in the Health Professionals Follow-up Study. Furthermore, dietary oxalate appears to make only a small contribution to urinary oxalate excretion in the same populations.[6]

If one were to design a study of the benefit of lowering oxalate excretion via dietary intervention, there would be a number of variables to consider in planning a successful trial. One question would be which patients with hyperoxaluria to include. Would it be best to only include patients with very high oxalate excretion? Such patients might have the greatest lowering of oxalate excretion with dietary manipulation and perhaps the greatest impact on calcium oxalate supersaturation resulting from the restriction of dietary oxalate. Neither of these suggestions has been conclusively studied and proven. Even patients with "normal" or mildly elevated urinary oxalate excretion might benefit if oxalate is as important a determinant of stone outcomes as is often assumed. If, as some recent data suggest, oxalate secretion across the bowel mucosa from blood to lumen occurs, limitation of dietary oxalate could stimulate secretion and reduce excretion in many patients.[7] In any case, the practical issue is that the higher the amount of urinary oxalate required for inclusion, the more difficult the enrollment of adequate numbers of patients would be. Another choice that might make the urine oxalate excretion less critical as an inclusion criterion would be whether to define patients whose oxalate excretion derives from high dietary oxalate intake as opposed to patients with high endogenous synthesis of oxalate. The latter group would be less likely to benefit from the restriction of dietary oxalate. Methods to discriminate between these 2 populations have not been methodically applied to stone-forming patients. Using the absorption of oxalate radiolabeled with ^{14}C as a means to identify hyperabsorbers of oxalate, one could choose to include only those patients with a positive test. Although the methodology is not broadly available, it is relatively costly compared with other tests and might be an impediment to patient enrollment.[8] The recent development of an absorption test using nonradioactive $^{13}C_2$-oxalate may make such tests more widely available and popular.[9] Another option would be to have patients fill out food-frequency questionnaires, perhaps in collaboration with a nutritionist, in order to identify those patients with the most dietary oxalate ingestion.[5]

An additional variable to consider in designing an oxalate-restricted diet study is dietary calcium. Increases in dietary calcium are associated with reductions in urine oxalate excretion, presumably because of calcium-oxalate binding in the intestine, with a subsequent reduction in oxalate absorption.[10] Increased calcium intake is associated with fewer stones in epidemiologic studies.[11,12] Although oxalate restriction was advised for patients in both arms of the Borghi study, only the group in the higher calcium intake group showed reduced urine