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J. Craig Rowlands, Ph.D./DABT
Food and Drug Administration
CFRAN
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College Park, MD 20740-3835

Dear Dr. Rowlands:

I am responding to your invitation to comment about the request from the Marine Bio USA, Inc. for a qualified health claim that "calcium may reduce the risk of kidney and urinary stones". I am doing so as the chief of the Division of Mineral Metabolism in the Department of Medicine and program director of the General Clinical Research Center at the University of Texas Southwestern Medical Center, where I myself have performed research or have overseen work done in this area. The UT Southwestern was the sponsor of the primary work that led to the introduction of Citracal by the Mission Pharmacal Company (San Antonio, TX). However, I do not personally derive any benefit, and I deny any potential conflict of interest in offering my view. Thus, my comments presented below are based on my personal experience or expertise, intended for clarification and to avert misperception, improper promotion and potential harm to the public.

My objections to the Marine Bio USA's requested claims are:

1. *Lack of Objective Data for the Claims*

The request for qualified claims was based on a literature review by an "expert", whose research work was mostly in veterinary medicine, who lists no peer reviewed article on calcium bioavailability or nephrolithiasis. He devotes only one page to the topic of "Dietary Calcium and Nephrolithiasis" (bottom of page 4 and top of page 5). The main articles cited to support their claims were retrospective epidemiological studies by Curhan et al. (ref. 42, 46, and 47). These works showed that normal subjects in the highest quintile had a lower incidence of stones than those in the lowest quintile of calcium intake. Though no objective data were presented, they explained their finding by the binding of oxalate by calcium in the bowel, lowering urinary oxalate during high calcium intake. However, there were potential confounding variables, since subjects in the highest quintile also had higher intake of fluids, potassium and magnesium,- factors that are potentially protective against stone formation.

Heller et al. from my division of Mineral Metabolism has examined the potential role of confounding variables cited above in a metabolic study (J Urol 169:470, 2000).

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He placed the same subjects on a diet simulating the lowest quintile and highest quintile of calcium intake from estimates reported by Curhan et al. Analysis of actual urine samples collected from subjects consuming above diets showed that the urinary saturation of calcium oxalate (the “driving force” for the formation of calcium oxalate stones) was comparable between the two diets, and not lower on the high calcium diet. However, when adjusted for confounding variables, urinary saturation of calcium oxalate was found to be much higher during the high calcium diet. Moreover, urinary saturation of brushite (driving force for calcium phosphate stones) was significantly higher during the high calcium diet with or without correction for confounding variables.

Thus, it is clear that orally administered calcium itself increases stone forming risk. Subjects on a high calcium diet may not be at increased risk for stones, if they are also taking more fluids, potassium (fruits) and magnesium. However, it is apparent that those who are taking a diet rich in calcium without protective confounding variables would well be at increased risk.

2. Erroneous Interpretation of the Report by Curhan et al. regarding Stone-Forming Risk of Calcium Supplementation

Curhan et al. (ref. 47) reported that calcium supplementation increased the risk for stone formation. A likely explanation is the lack of protective confounding variables when calcium is provided as a supplement. Marine Bio USA chooses to dismiss this finding by suggesting that calcium supplements are generally given separately from meals, and therefore devoid of oxalate binding capacity. However, it neglects to mention that the current recommendation for calcium carbonate is to take it with meals to enhance its bioavailability (Heaney, Amer J Clin Nutr 49:372, 1989). Marine Bio USA cites short term studies by Domrongkitchaiporn et al. (ref. 50-52) to support its claim. Unfortunately, these works did not show that calcium carbonate supplementation reduced the stone forming risk, contrary to the requested claims.

3. Distinction Between Calcium Salts

My group has shown previously that calcium citrate increases urinary citrate (an inhibitor of stones, thereby attenuating the rise in urinary saturation of calcium oxalate that would have occurred from induced hypercalciuria of calcium supplementation (Harvey et al., J Clin Endo Metab 61: 1223, 1985).

I have just conducted a metabolic study carefully assessing the effect of calcium citrate supplementation on stone forming risk in 18 postmenopausal women without stones kept on a constant dietary regimen in the setting of the GCRC. This crossover study will be published in the Journal of Urology. Compared to the placebo phase when no calcium supplement was taken, calcium citrate (800 mg calcium per day) significantly increased urinary calcium (from 180 mg/day to 239 mg/day, $p < 0.0125$). However, urinary oxalate declined (from binding of oxalate by calcium). Urinary citrate

increased (from 695 mg/day to 827 mg/day, $p < 0.0125$), thereby enhancing complexation of calcium by citrate and lowering ionized calcium fraction. Thus, urinary saturation of calcium oxalate did not change (4.08 fold on placebo vs. 4.46 on calcium citrate, NS).

Earlier studies from my Division showed that calcium carbonate does not significantly increase urinary citrate. Without additional complexation of calcium by citrate, I would expect that urinary saturation of calcium oxalate would actually increase significantly with calcium carbonate.

Distinction Between Non-Stone Forming Subjects and Stone Formers

In normal subjects and persons with normal intestinal calcium absorption, the bulk of available evidence suggests that calcium supplements or a high calcium diet is relatively free of stone forming risk. That is because of protective confounding variables associated with a high calcium diet, binding of oxalate by calcium in the bowel, and rise in urinary citrate (in the case of calcium citrate). However, there is no concrete evidence that a high calcium intake reduces the stone forming risk, contrary to the claims of Marine Bio USA.

However, such is not the case in subjects with high intestinal calcium absorption. Calcium absorption is increased in stone-forming patients with absorptive hypercalciuria, a common stone forming condition that has a strong genetic disposition. A minor fraction of postmenopausal women with osteoporosis and a substantial fraction of men with idiopathic osteoporosis suffer from increased calcium absorption. In such patients and affected family members (even without stones), a high calcium intake provokes a very large increase in urinary calcium. Urinary oxalate excretion may also be increased, since increased calcium absorption leaves insufficient amount of calcium to bind oxalate in the bowel leaving more oxalate available for absorption. In such patients, it is very difficult to manage stone formation without controlling hypercalciuria, and hypercalciuria may not be corrected or controlled with a liberal intake of calcium.

4. Misunderstanding Regarding Relative Importance of Urinary Calcium and Oxalate in Stone Formation

The research group at Leeds, England is responsible for the often-cited article disparaging the role of calcium in stone formation (Nordin et al., Clin Endo Metab 1: 169, 1972). This group reported that a rise in urinary calcium was much less effective than a rise in urinary oxalate in increasing the urinary saturation of calcium oxalate, the "the driving force" for stone formation. Our group has recently shown that this is simply not true. The above misleading report is due to overestimating the amount of oxalate and calcium that is bound to each other as a soluble complex. The group from Leeds has acknowledged that it had made this error (Robertson et al., N Engl J Med, 294: 249,

1976). My group has now unequivocal evidence that urinary calcium is just as efficient as urinary oxalate in increasing urinary saturation of calcium oxalate. In a study of 667 patients with predominantly calcium oxalate stones, a rise in urinary calcium concentration within the range encountered in this group, caused a marked increase in urinary saturation of calcium oxalate, to a level indistinguishable from that produced by a rise in urinary oxalate concentration.

The above conclusion emphasizing the importance of urinary calcium is supported by Curhan et al. who had conducted the epidemiological studies that form the main basis for the requested claims. They obtained urinary stone risk factors among a subset of normal subjects and another set of subjects who developed stones (Curhan et al. Kid Intern 59: 2290, 2001). They found urinary calcium carried the highest risk for stones among factors examined, much higher than that for oxalate.

The above studies reinforces the concept that a high calcium intake potentially carries a stone forming risk by increasing urinary calcium, and thereby raising the saturation of calcium oxalate.

In summary, it is my belief that

- There is no firm evidence for the requested claims that a high calcium intake protects against stone formation. The lower incidence of stones in the highest quintile of calcium intake in epidemiological studies can be explained by the fact that a high calcium diet is often taken with protective factors, such as higher fluids, potassium-rich foods (certain citrus fruits), and magnesium. Available objective data have shown either no effect or increased stone forming risk, never a reduced risk, following high calcium diet or calcium supplementation.
- Calcium given as food confers less risk than calcium given as supplement.
- The stone-forming risk depends on the type of calcium supplement, with calcium citrate having lower risk than calcium carbonate due to its enhancement of urinary citrate, an inhibitor of stone formation.
- The stone-forming risk also depends on the state of intestinal calcium absorption. In the latter, a high calcium intake may enhance stone forming risk.
- The notion that urinary oxalate is much more important than urinary calcium in the development of stones is wrong. Urinary calcium is just as effective as urinary oxalate in raising urinary saturation of calcium oxalate.

Sincerely yours,



Khashayar Sakhaee, M.D.