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Grapefruit Juice and Kidney Stones

To the Editor: Of 17 beverages evaluated in Curhan and colleagues' cohort of more than 80 000 women in the United States, grapefruit juice was the only drink associated with increased risk for kidney stones (1). This new health concern can be added to concern raised by the evidence of increased oral drug bioavailability by grapefruit juice (2).

The mechanisms of these physiologic effects need to be elucidated. In the case of drug interactions, one or more components of grapefruit juice is thought to inhibit metabolic enzymes in the gastrointestinal tract or to inhibit a P-glycoprotein pump that transports drugs and other chemicals through membranes. The mechanism for kidney stone formation by grapefruit juice is more speculative; Curhan and colleagues note that it is unlikely to be related to alteration of urinary pH or absorption of oxalate (1).

Numerous phenolic compounds can bind divalent cations. As an in vitro test of oxidation of low-density lipoproteins, inhibition of Cu^{2+}-catalyzed oxidation of low-density lipoprotein is a model widely used to evaluate antioxidant potential of flavonoid and flavonoid-like constituents of fruits and their juices, vegetables, and teas (3). Flavanones are the type of flavonoid abundant in grapefruit; the predominant flavanone is naringin. It occurs only rarely in noncitrus plants and may confer properties unique to grapefruit juice. It is interesting to speculate whether naringin, which is excreted in the urine (4), binds to calcium and delivers it to the renal system, thus increasing the chance of stone formation because of high renal concentrations of calcium.

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2. **Ameer B, Weintraub RA.** Drug interactions with grapefruit juice. Clin Pharmacokinet. 1997;33:103-21.
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4. **Ameer B, Weintraub RA, Johnson JV, Yost RA, Rouseff RL.** Flavanone absorption after naringin, hesperidin and citrus administration. Clin Pharmacol Ther. 1996;60:34-40.

In response: We agree with Dr. Ameer that it would be scientifically and clinically interesting to determine the mechanism by which drinking grapefruit juice may increase the risk for kidney stone formation. It is unlikely to be due to the oxalate content of grapefruit juice itself, which is relatively low. Perhaps grapefruit juice increases oxalate absorption from other dietary sources, but no data on this are available.

It is interesting to speculate about certain components of grapefruit juice, but it is unlikely that the proposed mechanism for naringin is responsible. Naringin is found in both oranges and grapefruits. We found no association between orange juice and risk for stone formation in women or men (1). In addition, binding of calcium by naringin in the blood would not necessarily lead to an increase in the glomerular filtration of calcium. Unbound calcium is freely filtered at the glomerulus, so there is no need to have it delivered to the renal system. Furthermore, if naringin binds tightly to calcium, this may reduce the actual amount of calcium filtered and act as a natural inhibitor of crystal formation in the urine by interfering with the interaction between calcium and oxalate. Additional studies are needed to examine the effect of grapefruit juice on known urinary factors.

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Reference

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Intensive Therapy Preserves Insulin Secretion

To the Editor: I see near-identical objectives and conclusions in the Diabetes Control and Complications Trial Research Group's article (1) and writings of J.M. Brush, but the former did not cite the latter. Were Brush's studies not conducted in a different era, he could have coauthored the current paper.

His studies were done at a time when there were two conflicting schools of thought about management of diabetes: one chemical, championed by the Joslin School, and one clinical, followed by Tolstoi and his group. Brush occupied center stage more than 50 years ago with his intensive therapy for residual insulin secretion in patients with newly diagnosed type 1 diabetes. Without C-peptides and by relying on the much-maligned urine glucose testing, he arrived at the same conclusion as did the DCCT group. Both demonstrated that intensive therapy for type 1 diabetes helps to sustain endogenous insulin secretion.

Brush's patients paralleled the intensive therapy group of the DCCT. Potential variables (exercise and diet) were kept constant, and regular insulin was administered with four daily injections. Within a week, hypoglycemia was seen; this was heralded as a return of endogenous insulin production and was the signal to reduce administrative insulin. At time of discharge, children were receiving a single daily injection of 2 to 8 U of regular insulin. Unfortunately, in both studies, the steady state achieved at discharge did not last; the "honeymoon" was over in a year or two.

The message "hyperglycemia is glucotoxic" was embraced by many and was applied to the larger group of patients with type 2 diabetes, a group with windows of retained β-cell function that were open for a longer period. The physiologic studies from early in this century demonstrating that overwork inhibited recovery of stressed islet tissue were picked up by and clinically applied by Brush in the 1940s. In the 1990s, the DCCT confirmed Brush's work that demonstrated the importance of initiating early aggres-

sive intervention and also demonstrated the effect of such control on chronic complications.

Hyperglycemia has to remain a target even when a handle is placed on the autoimmune causes of diabetes. The golden opportunity for bringing about maximum functional recovery presents itself only once. Yes, yesterday may have had the answer to today's questions.

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Reference

1. Effect of intensive therapy on residual β-cell function in patients with type 1 diabetes in the Diabetes Control and Complications Trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. Ann Intern Med. 1998;128:517-23.

To the Editor: The most recent article by the DCCT Research Group (1) was intriguing and thought-provoking. I wish to hypothesize another potential benefit of sustaining islet-cell function apart from maintenance of C-peptide secretion. The hypothesis may also partially explain the better metabolic control and lower risk for hypoglycemia seen in the C-peptide responders.

Amylin (islet amyloid polypeptide) is normally co-secreted with insulin by pancreatic β cells (2). It is reasonable to assume that preservation of β-cell function in patients with type 1 diabetes should not only permit a residual insulin (C-peptide) response but also maintain detectable plasma amylin levels, albeit low levels. Preserved amylin secretion would be expected to contribute to improved glycemic control by reducing postprandial hyperglycemic excursions through retarding gastric emptying and inhibiting amino acid–stimulated glucagon secretion (3).

Suppressed glucagon secretion may result in reduced postprandial hepatic glucose production but would not inhibit the counterregulatory glucagon response to hypoglycemia (4), thus reducing the risk for severe hypoglycemic events. The reduced incidence of hypoglycemia may also be due to residual amylin's effect of increasing plasma concentrations of growth hormone and cortisol and by the release of gluconeogenic substrates, such as lactate, from skeletal muscles (5). In the fasting state, lactate may also help to replenish depleted glycogen stores.

I believe that these mechanisms warrant attention and would merit a reanalysis of any stored plasma samples from DCCT participants for the presence of physiologic levels of amylin.

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In response: We appreciate Dr. Gumpel's historical perspective on the preservation of insulin secretion in type 1 diabetes and Dr. Charles-Marcel's suggestion of another potential mechanism to explain our findings. With regard to the historical perspective, J.M. Brush reported the uncontrolled results of a therapeutic regimen that grew out of an "effort to simplify the management of diabetic children" (1). Comparison of his observations with the controlled experiment of the DCCT reveals the enormous strides made in clinical research, in general, and diabetes clinical research and care, in particular, in the past 50 years. Brush reported experience with a 1-month inpatient regimen in which children with new-onset diabetes were treated with relatively large doses of insulin, administered as regular insulin divided into four doses (including one at 4 a.m.). Total insulin dose was adjusted to render the urine glucose free—routine blood glucose testing was not easily available—and was continued until hypoglycemic "shock" occurred. Insulin doses were subsequently decreased, and patients left the hospital receiving relatively small doses of insulin, having achieved a new "steady state." Brush ascribed the decreased insulin requirements to recovery of pancreatic function, although he recognized that he could not prove his "teleologic imagery."

Brush's work was hampered by the absence of acceptable controls—the first controlled clinical trial in the modern era didn't occur until 1948 (2)—and by the lack of readily available quantitative measures of glycemia, or any direct assay of insulin (which was not developed until 1960 [3]). In contrast to Brush's empirical methods, the DCCT performed a carefully controlled experiment and had the advantage of using blood glucose, glycosylated hemoglobin, and C-peptide assays. Although the stage during which the interventions were applied (all DCCT participants had had diabetes for at least 1 year) and the intensive treatment regimens differed, β-cell function was preserved in Brush's experience and in the DCCT. That the DCCT was able to prove Dr. Brush's theory, with rigorously applied methods, is a testament to his prescience and to the power of modern experimental methods.

Dr. Charles-Marcel's suggestion that restoration of amylin secretion concurrent with insulin secretion may have contributed to the observed metabolic results is intriguing. The potentially opposing effects of amylin on glucose metabolism—inhibiting insulin secretion (4) compared with slowing gastric emptying and inhibiting glucagon secretion—would need to be weighed carefully to determine, on balance, whether restoration of amylin secretion would benefit or worsen glycemia in the setting of type 1 diabetes with residual insulin secretion.

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Pharmacokinetic Interaction between Saquinavir and Cyclosporine

To the Editor: An HIV-positive kidney transplant recipient who was receiving cyclosporine and prednisone started zidovudine and lamivudine therapy shortly after kidney function had stabilized. When protease inhibitors became available, saquinavir was added; levels of both drugs were monitored.

Without saquinavir, the cyclosporine trough levels in this patient were stable at a dosage of 150 mg twice daily (150 to 200 μg/L). Within 3 days after saquinavir therapy began at a dosage of 1200 mg three times daily, the patient reported fatigue, headache, and gastrointestinal discomfort and the trough level of cyclosporine tripled to 580 μg/L. After cyclosporine and saquinavir dosages were decreased to 75 mg twice daily and 600 mg three times daily, respectively, the symptoms subsided. Time curve analysis showed that an area under the concentration–time curve (AUC_{0-12}) seen with 75 mg of cyclosporine during treatment with saquinavir was 90% of the AUC_{0-12} seen with 150 mg of cyclosporine alone (**Figure**, *top*). Meanwhile, saquinavir showed an AUC_{0-12} 4.3 times higher than the average value of five control patients who were receiving an identical saquinavir dosage of 600 mg twice daily without cyclosporine (**Figure**, *bottom*) and 11.1 times higher than the AUC_{0-12} reported in the literature (0.47 h per mg/L) (1).

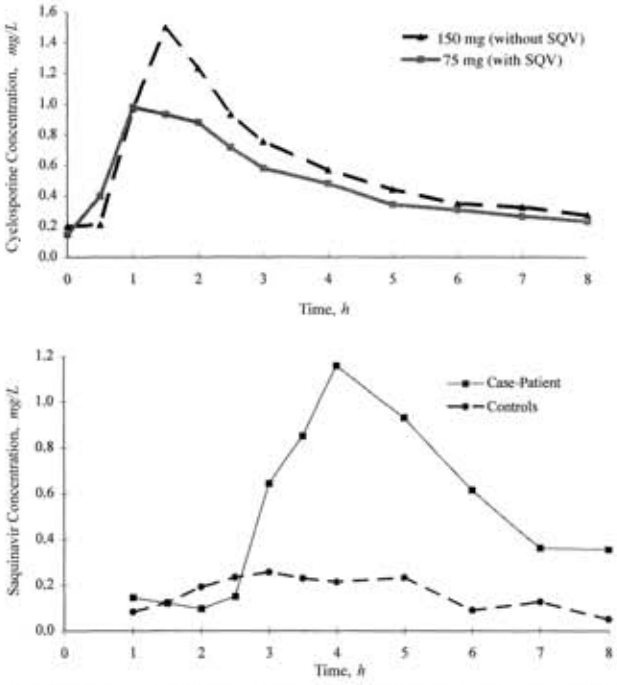

Figure. Time-curve analyses of cyclosporine and saquinavir concentrations. Top. Area under the concentration–time curve (AUC_{0-12}) alone and combined with saquinavir (*SQV*) (5.48 h per mg/L and 4.93 h per mg/L, respectively). **Bottom.** AUC_{0-12} of saquinavir in the case-patient combined with cyclosporine (5.20 h per mg/L) and the average AUC_{0-12} of saquinavir in five controls not receiving cyclosporine (1.21 h per mg/L).

This observation confirms the anticipated pharmacokinetic interaction between protease inhibitors and cyclosporine. This inhibitory interaction is most likely explained by the similar metabolism of both drugs via CYP3A. An additional explanation might be that both drugs also display high affinity for the drug-transporting P-glycoprotein (2, 3) and might therefore increase the absorption or decrease the clearance of the other drug, as was recently postulated by others (4, 5).

This interaction has not previously been reported in the literature or in the records of the drug manufacturer. This report reemphasizes the importance of pharmacokinetic interaction between protease inhibitors and concomitantly administered drugs.

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Cutting Waste and Keeping Faith

To the Editor: I was deeply disturbed by Bloche's editorial "Cutting Waste and Keeping Faith" (1).

The author states that "physicians risk running afoul of these statutes primarily through careless documentation and trying to be too clever." He goes on to say "rather than railing against these confusing laws or, even worse, campaigning to broaden their exceptions, physicians should heed the sobering message the laws send—that Americans have lost faith in their physicians' ability to restrain themselves when tempted by money."

What nonsense! Why shouldn't physicians attempt to alter these unreasonable and capricious laws? Where does the author get the idea that the public has lost faith in physicians? How does the author deduce that we are guilty of "upcoding" or "careless documentation"?

We in the trenches of private practice are attempting to receive fair compensations for our services on the basis of vague criteria for coding. Has the author ever tried to treat a patient and then attempt to figure out what level of care and what documentation are warranted?

Now the Health Care Financing Administration (HCFA) is attempting to use "fraud and abuse" statutes to intimidate us to downcode when it is not warranted. Unfortunately, the American Medical Association has cooperated with HCFA in promulgating these attempts to intimidate physicians. I have the distinct impression that the author's antiphysician bias is also shared by the editors of *Annals* and the American College of Physicians–American Society of Internal Medicine.

We physicians should reject these attacks on our honesty and do all in our power to alter the present "fraud and abuse" threats. We should also fight to eliminate HCFA's attempts to require extensive, unnecessary, and time-wasting documentation. Finally, we practicing physicians should work to educate or replace editorial boards of journals that seek to impugn our dedication or honesty.

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Reference

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In response: Yes, the fraud and abuse laws are frustratingly complex and ambiguous. They impose large administrative burdens. Perhaps more painful for many practitioners, they embody a skeptical attitude toward professional motives and judgment. The subjectivity of many diagnostic and therapeutic coding decisions makes compliance and enforcement daunting. The threat of stiff civil and even criminal penalties can feel intimidating. Criminal prosecution has at times been overzealous (1).

Yet a wholesale attack on the concept of fraud and abuse regulation would serve the medical profession poorly. Individual practitioners can protect themselves, albeit at some cost, through conservative coding and careful documentation. The profession as a whole can best restore and preserve the public's confidence by recommitting itself, in visible ways, to the Hippocratic ideal of undivided loyalty to patients (2). An indiscriminate, high-profile campaign against fraud and abuse regulation would risk sending the opposite signal.

Were the U.S. public utterly confident in the medical profession's immunity to financial temptation, neither Congress nor the current administration would see political advantage in the enactment and aggressive enforcement of fraud, abuse, and self-referral legislation. To attribute "antiphysician bias" to professional leaders who have perceived and struggled with the relation between bedside financial incentives and patient confidence is to mistake friend for foe, at a time when friends are much needed. And to call for the heads of editors with the foresight to identify and invite discussion of issues vital to the welfare of physicians and their patients is to attack the profession's capacity for adaptation to its rapidly changing environment.

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