P

atients seek dietary supplements to prevent and/or solve health and aging issues. Two men (a white man aged 67 years and an African American man aged 51 years) developed an unusual course of clinically aggressive prostate cancer within months of starting daily consumption of the same testosterone dietary supplement (TDS).

Both patients developed widely metastatic prostate cancer within 11 months of a normal prostate cancer screening (normal prostate-specific antigen level and digital rectal examination). They purchased the TDS via the Internet after reading an advertisement in a fitness journal. They sought to develop stronger muscles and enhanced sexual performance. Initially, they gained muscle mass and attained a higher than average energy level.

At the time of diagnosis, both patients had very low serum levels of total testosterone, luteinizing hormone, and follicle-stimulating hormone, suggesting a decrease in gonadotropin-releasing hormone pulse frequency secondary to exogenous testosterone.

In vitro experiments in hormone-refractory (DU-145 and PC-3) and hormone-sensitive (LNCaP) human prostate cancer cell lines revealed that the product is a more potent stimulator of cancer cell growth than testosterone and that it stimulates growth regardless of the androgen responsiveness of cancer cells (Figure 1). All 3 cell lines grew in a product dose-dependent fashion (Figure 2). Blocking experiments with serial increases of the potent nonsteroidal competitive antagonist of androgen receptor bicalutamide revealed that the product stimulates prostate cancer cell growth, effectively bypassing the androgen receptor pathway in prostate cancer cells, while also rendering the cancer cells resistant to standard antiandrogen therapy (Figure 3). The concentrations used for in vitro studies are indeed within pharmacologic dosages that can be achieved in patients.

While it is impossible to draw firm conclusions regarding the causative role of this TDS on the development and progression of prostate cancer, we filed an adverse event report with the Food and Drug Administration, which issued a warning letter leading to the removal of this TDS from the market by the manufacturer.

Among the TDSs inundating the marketplace, the sale of androgenic steroids preparations is exponentially increasing. Therefore, there is significant concern that dietary supplements other than the one evaluated in the present study may pose an urgent human health risk. Indeed, this not the first instance in which TDSs have caused potentially serious harm. Aristolochia fangchi has been associated with urinary tract cancers; germander, with

Figure 1. The testosterone dietary supplement (TDS) stimulates prostate cancer cell growth in vitro regardless of the presence or absence of the androgen receptor. Cell growth curves with 95% confidence intervals for the cell lines LNCaP (A), DU-145 (B), and PC-3 (C) treated with increasing doses of the TDS (100 µg/mL), testosterone (24 pg/mL), or no drug (vehicle only). Cell growth is expressed as the relative increase in the number of cells compared with the vehicle-only control. Assays were performed in triplicate and repeated in 3 independent experiments. Differences were assessed using analysis of variance (SPSS version 13.0; SPSS Inc, Chicago, Illinois), with $P<.05$ considered statistically significant.
Figure 2. The testosterone dietary supplement (TDS) enhances prostate cancer cell proliferation in a dose-dependent manner. Cell growth curves with 95% confidence intervals for the cell lines LNCaP, DU-145, and PC-3 treated with serially increasing doses of the TDS (100, 200, 400, 600, 800, and 1000 µg/mL) or no drug (control) are shown. Cell growth is expressed as the relative increase in the number of cells compared with the medium without TDS. Differences were assessed in triplicate and repeated in 3 independent experiments. Differences were assessed using analysis of variance (SPSS version 13.0; SPSS Inc, Chicago, Illinois), with P < .05 considered statistically significant.

Figure 3. The testosterone dietary supplement (TDS) activates an alternative growth pathway that effectively bypasses the androgen receptor causing resistance to the prostate cancer growth inhibitory actions of bicalutamide. Cell growth curves with 95% confidence intervals for the cell line LNCaP treated with either the antiandrogen bicalutamide alone (0.01µM) or the TDS (100 µg/mL) with increasing doses of the antiandrogen bicalutamide (0.01µM to 1µM). The cell growth is expressed as the relative increase in number of cells compared with TDS alone (100 µg/mL). These assays were performed in triplicate and repeated in 3 independent experiments. Differences were assessed using analysis of variance (SPSS version 13.0; SPSS Inc, Chicago, Illinois), with P < .05 considered statistically significant.

acute hepatitis; comfrey, with hepatic veno-occlusive disease; kava kava, with liver toxic effects; yohimbine, with seizures and renal failure; PC-SPES, with endocrinological toxic effects; and ephedra, with cardiovascular death.

The potential for harmful effect of some complementary medicine on patient health (ie, adverse effects, decreased compliance, and drug-supplement interaction) indicates a need for improved physician-patient communication and patient education on alternative therapies. Documentation of dietary supplement use should become part of routine assessment for all patients, particularly patients with cancer. If physicians are aware that patients are using or combining these agents with conventional treatment, they can assist them in making more informed choices and monitor them for possible interactions and adverse effects.

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COMMENTS AND OPINIONS

Bleeding Associated With Warfarin Use: Improving Outcomes

Wysowski et al1 reviewed the prevalence of bleeding complications associated with the use of warfarin sodium for the implementation of a “black box” warning and Medication Guide. These are not appropriate solutions to decrease bleeding adverse events. While the addition of black box warnings to package inserts can be a useful tool for many medications, the information contained in the warning for warfarin is considered general knowledge. It will not affect current practice.

Medication Guides are also an inefficient approach to increasing knowledge at the patient level. Medication Guides, on average, are written at an 11th- to 12th-grade reading level, which is not consistent with the Key- stone recommendations of a sixth- to eighth-grade reading level.2 Furthermore, only 23% of a population with low literacy skills reported attending to Medication Guides.3 These issues are concerning when 43% of adults in the United States have basic or below basic literacy skills.4 The Food and Drug Administration is taking action to improve current Medication Guides, but many patients will not take the initial step to review the information provided.

A better, more practical solution is at the patient-provider level. Health care providers should spend more time properly educating the patient about warfarin along with the recommended monitoring of the international normalized ratio, other drug therapies, comorbidities, and signs and symptoms of bleeding. One way to enhance this education and monitoring is through anticoagulation clinics. This setting can supplement the initial and ongoing interaction between the patient and his or her physician.
tivated vitamin D independent of PTH lowering, the subgroup data regarding calcitriol use in patients with normal PTH levels should be provided. Also, the mean follow-up after starting the calcitriol therapy should be studied to justify its use in reducing mortality. This may highlight the beneficial effects of vitamin D therapy beyond bone health in patients with CKD.4

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In reply
Kumar et al point out that the benefit of calcitriol therapy seen in our study may have been related to PTH level lowering, based on the observation that treated patients in our study had higher initial serum PTH concentrations, which declined subsequently.1 This discrepancy in PTH levels among the 2 groups is probably due to the observational nature of our study and the fact that the indication for calcitriol therapy in our cohort was treatment of secondary hyperparathyroidism. This may lead to confounding by medical indication, making it apparently difficult to assess the impact of calcitriol on those with normal PTH levels, as Kumar et al suggested. Our subgroup analyses, however, showed that the benefit of calcitriol was equally present in patient groups with lower (<103 pg/mL) and higher (≥103 pg/mL) PTH levels (to convert to nanograms per liter, multiply by 0.1053), suggesting a PTH-independent mechanism.1 Furthermore, as mentioned in our article, the PTH levels of the group treated with calcitriol remained higher than those in the untreated group throughout the study period,1 thus it is difficult to postulate that the observed survival benefit was solely related to the lowering of PTH levels, even though higher PTH levels are associated with increased mortality in this patient population.2

There are several other potential mechanisms of action that could explain a benefit of vitamin D receptor activation beyond lowering PTH level. As Delanaye et al pointed out, this receptor activation can occur not only through the action of the activated vitamin D molecule but also via its precursor, native vitamin D (25(OH)D). The role of this precursor in the treatment of patients with CKD remains largely unanswered, though. While physiologically plausible, there is currently only scant proof that such therapy with 25(OH)D can even lower PTH levels effectively in CKD.4 The study by Wolf et al4 indeed showed an association between lower 25(OH)D levels and mortality in hemodialysis patients, but the deleterious effect of this deficit was abrogated by subsequent treatment with activated vitamin D; therapy with 25(OH)D could not be examined in that study.2

Given the extremely complex nature of vitamin D receptor activation,3 we agree with Delanaye et al that further studies are necessary to clarify the role of 25(OH)D replacement relative to therapy with activated vitamin D.

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Editor’s Note
The article by Sharlat et al, published in the January 28 issue of the Archives (2008;168[2]:235-236), is nearly identical to an article by the same authors published in another journal in January 2008. Before publication, the authors provided verification through our manuscript submission Web site that the article had not been published elsewhere and was not under consideration by another publisher, and they also received a letter of acceptance from the Archives with a reminder of our policy regarding duplicate publication. Their response to this Notice of Duplicate Publication follows.

I acknowledge the receipt of your letter regarding the duplicate publication in the Archives of Internal Medicine1 and Clinical Cancer Research.2 First, I sincerely apologize for our careless actions that resulted in duplicate publications. It was never our intention to produce a duplicate publication. This was a result of a misunderstanding and lack of communication between one of the coauthors and me.

This case report was submitted in the spirit of scientific conduct to raise awareness of potentially harmful ef-
ffects of over-the-counter supplements. As this is a sensitive topic, many journals were reluctant to consider our article. We went through various iterations and submissions. In this process, an error occurred that resulted in the duplicate publication. One of the coauthors at a different institution submitted the full article to Clinical Cancer Research and I submitted the research letter to the Archives of Internal Medicine without knowledge of each other’s submission. The oversight resulting in the duplicate submission is very regrettable.

As corresponding and first author of the Archives of Internal Medicine article, I assume full responsibility for this error. I place great emphasis on following the rules of conduct of science, because those rules make for effective science. As a reviewer and a member of other editorial boards, I know how important it is for research journals to guard against duplicate publication. For those reasons my error is especially regrettable to me, professionally as well as personally.

I would like to stress that all coauthors are deeply upset by this error. We ask you to accept our sincere apology for the publication of these articles. This will not happen again. We remain at your disposal for further information.

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