events and cognitive decline.[2] Differential vulnerability of the brain in different patient populations is a probable source of these discrepancies, as has previously been noted in children with type 1 diabetes mellitus, whose developing brain may also be more vulnerable to the adverse effects of hypoglycemia.[7] In older people, hypoglycemic events are not likely to cause dementia by themselves. Nevertheless, hypoglycemic events may modulate dementia risk by accelerating subclinical neurodegenerative changes or cerebrovascular damage in the brain, or by drawing on cerebral reserve capacity. The observations from Bruce *et al.* suggest that once cognitive decline sets in, hypoglycemic events may become even more frequent, and lead to a vicious circle.

While all patients and physicians are aware that hypoglycemic events should be prevented, the present studies highlight the need for extra caution in older individuals.

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doi:10.1038/nrendo.2009.182

Competing interests
The author declares no competing interests.

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NUTRITION

US recommendations fail to correct vitamin D deficiency

Bruce W. Hollis

Vitamin D deficiency is widespread among women with breast cancer. Guidelines currently recommend daily supplementation with 400 IU vitamin D_3; however, attainment of a circulating level of 25-hydroxyvitamin D defined as sufficient (that is, ≥75 nmol/l) might not be possible with this level of supplementation, according to data published in the *Journal of Clinical Oncology.*

One might reasonably assume that, if followed correctly, a dietary recommendation made by the US Institute of Medicine (IOM) would ensure a sufficient circulating level of a given nutrient.[1] However, a report by Crew and collegues[2] has provided further evidence that the current IOM recommendation for vitamin D intake is completely inadequate. Crew *et al.* demonstrated a high prevalence of vitamin D deficiency among a group of premenopausal women who received daily supplementation with 400 IU vitamin D_3 for 1 year while undergoing chemotherapy for early-stage breast cancer. Although shocking, this finding was totally predictable given the data derived during the past decade. Nevertheless, the problem is still not fully appreciated by the medical community as a whole.

Crew and co-workers studied 103 premenopausal women who were diagnosed as having stage I to III breast cancer; all of the women were participants in a 1-year, randomized, placebo-controlled, intervention trial of zoledronic acid. The women each received four to eight cycles of chemotherapy during the study period. In addition, 67 of the participants received adjunct hormonal therapy (for example, tamoxifen). Regardless of chemotherapeutic regimen, all patients were prescribed daily supplementation with vitamin D_3 (400 IU) and calcium carbonate (1 g). The main outcome measure was the serum level of 25-hydroxyvitamin D, which was assayed at baseline and after 6 months and 12 months of supplementation.

The median age of the study group was 43 years and 51% of the women were non-Hispanic whites. The 6-month and 12-month evaluations were completed by 96 and 85 women, respectively. Compliance with study supplementation, dietary intake of vitamin D and levels of exposure to sunlight were unknown; however, 34 of the participants reported previous use of vitamin D_3 supplements. At baseline, the median circulating level of 25-hydroxyvitamin D was 42 nmol/l and 74% of the women were classified as vitamin-D-deficient (circulating 25-hydroxyvitamin D level <50 nmol/l). The 25-hydroxyvitamin D level remained low even after 12 months of supplementation (median 47 nmol/l); however, the number of women classified as vitamin-D-deficient had dropped to 60% at this time point. Vitamin D deficiency was more common among black and Hispanic women than non-Hispanic white women; furthermore, none of the black women enrolled in the study attained vitamin D sufficiency (defined as a circulating 25-hydroxyvitamin D level ≥75 nmol/l) in response to supplementation.

The results presented by Crew and colleagues are clearly disturbing; however, they were not entirely unexpected given the previously published data. Indeed, Crew *et al.* postulated that a standard dose of vitamin D_3 would not elevate serum 25-hydroxyvitamin D to levels considered 'sufficient'. In 2000, Vieth *et al.*[3] published data that demonstrated the effects of administering vitamin D_3 at doses of up

Practice points

- Vitamin D deficiency is common among patients with cancer
- The current Institute of Medicine (IOM) daily recommended intake of 400 IU vitamin D_3 is ineffective for correction of this deficiency
- The true vitamin D_3 requirement for patients with cancer could easily exceed the current IOM upper limit of 2,000 IU per day

to twice the lowest observed adverse effect level currently recommended by the IOM (2,000 IU daily).[1] Vieth *et al.*[3] found that a 4,000 IU daily intake of vitamin D_3 for a period of several months only increased the circulating 25-hydroxyvitamin D levels to 95 nmol/l, which is slightly above what is considered sufficient by today's standards.[4] In fact, a study in postmenopausal African American women demonstrated that daily supplementation with 2,000 IU vitamin D_3 for 1 year left more than half the women below the 80 nmol/l minimal level of circulating 25-hydroxyvitamin D defined by the study investigators.[5]

A landmark dose–response study published by Heaney *et al.*[6] in 2003 evaluated the effect of 5 months of vitamin D_3 supplementation (up to 10,000 IU daily) on the circulating levels of 25-hydroxyvitamin D in adult men (Figure 1). From this data, Heaney and colleagues calculated that for every 10 µg (400 IU) of vitamin D_3 intake, the circulating level of 25-hydroxyvitamin D would increase by around 7 nmol/l.[6] With this assumption in mind, therefore, the results published by Crew *et al.* were entirely predictable in that they observed a mean increase in serum 25-hydroxyvitamin D levels of 5 nmol/l during the 1-year study period.

I am frequently asked to do media interviews when scientific studies are published that link vitamin D deficiency with various disease states, such as cancer. The finding usually implicates vitamin D deficiency with the pathology of the disease and, as the interview ends, the interviewer will ask me how much vitamin D_3 is required to achieve an acceptable level of circulating 25-hydroxyvitamin D. My response is always 2,000–6,000 IU per day, a value derived from my own studies, as well as those I have already referenced here. However, when the interview is published or broadcast, I often find that my recommendation has been replaced by the IOM recommendation of 200–400 IU vitamin D_3 daily. This situation is very frustrating, as this level of supplementation has no effect on any pre-existing vitamin D deficiency. Clinicians should, therefore, familiarize themselves as to how the adult dietary vitamin D requirement was established some five decades ago, and how the value of 200–400 IU daily (along with the 2,000 IU per day lowest observed adverse effect level) has been perpetrated since the IOM recommendations were first published in 1997.[4] Medical professionals need to keep up to date with the literature to ensure their patients are provided ample vitamin D_3 to promote optimum health.

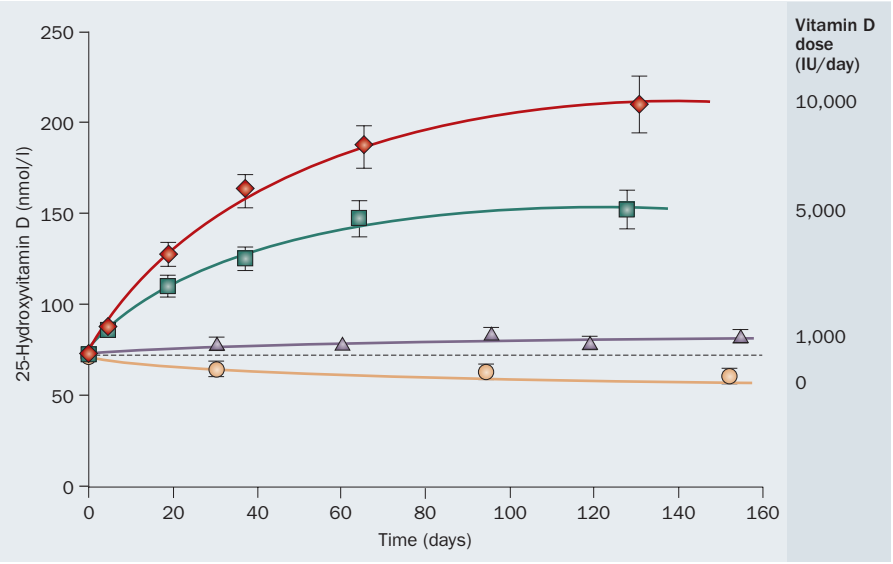

Figure 1 | Dose–response analysis of serum 25-hydroxyvitamin D levels after vitamin D_3 supplementation. The effects of vitamin D_3 supplementation on the circulating levels of 25-hydroxyvitamin D were assessed in adult men for a period of 160 days.[6] The graph shows the time course of serum 25-hydroxyvitamin D levels after administration of increasing amounts of oral vitamin D_3 (up to 10,000 IU daily). The points represent the mean values at each time point (±1 SEM); the horizontal dashed line indicates no change from baseline. Permission obtained from the American Society for Nutrition © Heaney, R. P *et al.* Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am. J. Clin. Nutr.* **77**, 204–210 (2003).

Finally, I would like to mention an important piece of research from the Women's Health Initiative (WHI) concerning vitamin D supplementation and the risk of colorectal cancer, which was published in the *New England Journal of Medicine* in 2006.[7] In this study, thousands of women received either placebo or 400 IU of vitamin D_3 each day for several years. At the conclusion of the study, all of the women probably remained vitamin-D-deficient but we don't know for sure because the poststudy blood samples were never assayed for 25-hydroxyvitamin D content. Nevertheless, the WHI investigators concluded that vitamin D_3 supplementation exhibited no protective effect on the development of colorectal cancer. I believe, however, that the proper conclusion should have been that protective effects are unlikely to be observed when a dose of vitamin D_3 is given that has no effect on the circulating or systemic levels of 25-hydroxyvitamin D. The current data of Crew *et al.* clearly expose the absurdity of the WHI conclusion in that a daily intake of 400 IU vitamin D_3 in an adult is essentially worthless for influencing the systemic levels of 25-hydroxyvitamin D.

Much evidence exists that adequate vitamin D status is a protective factor against various cancers (although most of the available data is epidemiological).[8,9] However, a randomized controlled trial of vitamin D_3 supplementation at a dosage of 1,100 IU per day demonstrated that increased circulating levels of 25-hydroxyvitamin D conferred some protection against the development of neoplasia.[10] Whether vitamin D is truly protective against cancer must be determined by future large, randomized controlled trials. In the meantime, the study of Crew and co-workers gives us some guidance on the dose of vitamin D_3 that should not be tested.

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doi:10.1038/nrendo.2009.178

Competing interests
The author declares an association with the following company: DiaSorin. See the article online for full details of the relationship.

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