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Is the Institute of Medicine Report on Calcium and Vitamin D Good Science?

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The Institute of Medicine (IOM) of the National Academies released its new *Dietary Reference Intakes for Calcium and Vitamin D* report on November 30, 2010 (IOM, 2011), which is summarized in Ross et al. (2010). The IOM report found that the only health benefit of vitamin D supported by the rigorous scientific studies they reviewed was for the bones. The report set recommended dietary allowances of 600 IU/day for those aged 1–70 years and 800 IU/day for those aged 71 or older, under conditions of minimal sun exposure. It also stated that a serum 25-hydroxyvitamin D (25[OH]D) level of 20 ng/ml was adequate. However, the authors noted that no adverse effects such as hypercalcemia or acute toxicity had been documented for oral intakes of up to 10,000 IU/day for adults; regardless, they set the upper-level intake at between 1,000 IU/day for infants (aged 0–6 months) and 4,000 IU/day for those older than 9 years. While this report is a step forward, it is disappointing that no nonbony benefits emerged from this review.

What Should Count as Good Evidence?

In other reviews of the evidence on the health benefits of vitamin D, authors have recommended higher serum 25(OH)D levels and oral intakes. Cannell and colleagues recommend serum levels of 40–70 ng/ml and oral intake of 2,000–7,000 IU/day (Cannell & Hollis, 2008). In a study that the IOM committee dismissed, Hollis and Wagner recommend up to 6,400 IU/day during pregnancy and lactation, finding benefits for the fetus/infant and no adverse effects for the mother (Hollis & Wagner, 2009). A panel of vitamin D experts meeting in Paris, in 2009, recommended a serum value of 30–40 ng/ml and an oral intake of 800 IU/day (Souberbielle et al., 2010). Michael Holick, editor of a comprehensive reference book on vitamin D (Holick, 2010), recommends 2,000 IU/day (Holick, 2011). In 2010, 34 international vitamin D researchers joined in issuing a call to immediate public health action on vitamin D, recommending intakes of up to 2,000 IU/day and serum levels of 40–60 ng/ml (Scientists' Call to D*Action, 2010). Thus, other researchers have concluded that higher serum 25(OH)D levels and higher oral intakes are indicated on the basis of their comprehensive reviews of the journal literature.

How could the IOM committee have set such low guidelines for vitamin D in light of the large body of evidence that vitamin D has important health benefits, affecting risks of many types of disease (Grant & Boucher, 2011)? The probable explanation lies in the evidence report prepared to guide the committee's deliberations by the Tufts Evidence-based Practice Center: "Federal sponsors defined the key questions, and a technical expert panel was assembled to refine the questions and establish inclusion and exclusion criteria for the studies to be reviewed" (Tufts Evidence-based Practice Center, 2009). The criteria included randomized controlled trials (RCTs) and prospective observational studies, but excluded case–control studies with serum 25(OH)D measured at time of disease diagnosis and studies considering nonoral routes of nutrient delivery, that is, solar and artificial ultraviolet B (UVB) irradiance, such as in ecological studies. Whereas these criteria are quite appropriate for pharmaceutical drugs—which by definition are artificial compounds with no history of being part of human experience—they are not appropriate for a substance such as vitamin D, for which solar UVB is the primary source for most people on Earth.

RCTs

While RCTs are useful, they have a number of limitations when applied to health effects of vitamin D, such as confounding by vitamin D from incidental oral intake and production from solar UVB irradiance.

The RCT was first suggested in the 1930s by the great British statistician Austin Bradford Hill (Hill, 1937, 1990). Hill never supposed, however, as some do, that the RCT was the only valid approach to responsible medical judgment. Applying Hill's criteria for causality is another way to evaluate the evidence for a specific agent being causal for a given disease (Hill, 1965). Hill's criteria are strength of association,

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consistency, temporality, biological gradient, plausibility (mechanisms), coherence, and experiment (RCT). Others have added ways to correct for confounding factors and remove bias. In fact, vitamin D from oral intake and/or UVB irradiance generally satisfies all these criteria for several types of cancer (Grant, 2009b) as well as for multiple sclerosis (Hanwell & Banwell, 2011).

Observational Studies

The IOM report omitted case–control studies that measure 25(OH)D serum level at diagnosis but included nested case–control studies (NCCS). For breast cancer, case–control studies show an inverse correlation between serum 25(OH)D and incidence of the disease, whereas NCCS using a single-serum 25(OH)D-level measurement at time of enrollment and then monitoring the cohort for 3–15 years seldom do (Yin et al., 2010). The problem with NCCS is that a single measurement of serum 25(OH)D level may not accurately represent levels during 3- to 15-year observation periods. A Norwegian study, in fact, reported a fall in the predictive value of a single measurement, versus serial data, of 50% over 14 years (Jorde et al., 2010).

Ecological Studies

Many ecological studies have found striking inverse correlations between geographical variations in solar UVB and disease outcome for cancer (Garland & Garland, 1980; Grant & Mohr, 2009) and temporal variations in disease outcome, as for epidemic influenza (Cannell et al., 2006). Other than vitamin D production, research has provided no other mechanism to explain the findings of observational and ecological studies of solar UVB and disease outcome.

Ecological studies are well suited for studying the UVB-vitamin D-cancer hypothesis (Garland & Garland, 1980) because solar UVB irradiance is the primary source of vitamin D for most people; it is possible for 45-year-olds to produce 1,500 IU/day in summer through casual sun exposure as far north as Great Britain (Hypponen & Power, 2007). In the United States, solar UVB doses in summer are highest in the southwest and lowest in the northeast due to differences in surface elevation and stratospheric ozone layer thicknesses. The asymmetry of summertime solar UVB doses in the United States serves as an excellent measure for vitamin D production in such studies (Grant & Garland, 2006), and most such studies have also controlled for other cancer risk-modifying factors such as smoking, alcohol consumption, and dietary factors (Grant & Mohr, 2009).

Findings From Other Recent Reviews

The International Agency for Research on Cancer (IARC), which assembled a panel concerned primarily about reducing the risk of skin cancer and melanoma, concluded—despite deciding not to evaluate much ecological and other evidence (Grant, 2009a), and unlike the IOM—that vitamin D does reduce the risk of colorectal cancer (IARC, 2008). In two subsequent reviews, authors also found a beneficial effect of vitamin D for breast cancer from case–control study data but not from most NCCS (Grant, 2010; Yin et al., 2010). Furthermore, a committee of 11 researchers in the Netherlands reported a higher level of exposure to the sun has been found to be related to a reduced chance of contracting cancer of the colon, prostate, and breast and non-Hodgkin lymphoma, as well as to a reduced mortality in cases of cancer of the colon, prostate, and breast. The working group concludes that these results, in combination with other relevant scientific data, constitute an "indication" of a causal relationship. Laboratory experiments have shown that these types of cancer are impaired by high vitamin D levels, and it is thus plausible that sun exposure, as the main source of vitamin D, has a beneficial effect (de Gruijl, 2010).

Conclusions

While the IOM report is a step forward, especially where intakes and guidelines are regularly below its recommendations as in the United Kingdom Vitamin D Consensus Statement (British Assoc. of Dermatologists, 2010), it was a smaller step than could be justified based upon a comprehensive review of the evidence for the health benefits of vitamin D.

Health agencies and organizations in the United States and elsewhere will review their vitamin D guidelines in light of the IOM report and make any changes they deem necessary. Many additional studies on the health effects of vitamin D in progress (there are currently 528 active vitamin D clinical studies in the United States and other countries listed by the National Institutes of Health [http://clinicaltrials.gov/]) will report, together with further research on mechanisms, safety of higher doses, and benefits for specific conditions.

Thus, I would hope that the IOM will reconvene a further review panel within 3–5 years. This panel should appoint several recognized experts on the epidemiology of vitamin D and disease and should consider all types of vitamin D studies with discussion of their strengths and limitations. It should also use an open review process, submitting the report to review by vitamin D researchers and addressing their comments in the report. A successful model for this approach is provided by the earlier Nobel prize-winning Intergovernmental Panel on Climate Change (www.ipcc.ch/), in which more than 600 scientists contributed to the report and 500 scientists acted as reviewers. If this model were to be followed for the next review although with fewer scientists involved, I am confident that the panel would find evidence that vitamin D had many more health benefits than just for bones, and the recommended daily reference intake and serum 25(OH)D levels would be much higher, in the ranges of at least 1,000–2,000 IU/day and 30–40 ng/ml, respectively.

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