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Letters to the Editor

Vitamin D

The 2010 recommendations of the American Institute of Medicine for daily intakes of vitamin D

Madam

Late in 2010 the US Institute of Medicine (IOM) recommended that adults should have dietary intakes of vitamin D of 15 μg/d (20 μg/d in older adults), based on evidence that these intakes improve bone health[1]. In the UK, the only one of thirty-one European countries to have no daily intake recommendation for vitamin D for adults between 19 and 64 years old[2], where current recommended intakes for pregnant women are 10 μg/d but where intakes average less than 5 μg/d[3], the implementation of these recommendations would improve vitamin D repletion at the population level. The IOM found no evidence of other health benefits from the specifically delineated types of evidence that it reviewed. However, there is now a large body of evidence for associations of hypovitaminosis D with non-bony health disorders such as multiple sclerosis, diabetes types 1 and 2, CVD, wound healing, peridontitis, and bacterial, viral and tuberculous infections, as well as for many cancers[4]. There is also much mechanistic evidence demonstrating how activated vitamin D produces protective effects for such diseases[5]. But there is still a shortage of data from randomized controlled trials (RCT) giving supplemental vitamin D in doses of 20 μg/d or more for risk reduction of these disorders, so that causality has not been proven for each of these conditions. Despite this, the weight of evidence has led the WHO's International Agency for Research into Cancer to accept that hypovitaminosis D is causal for colonic cancer[6]. The IOM report recommendations are for minimal intakes but their report also states that vitamin D intakes of up to 100 μg/d can be regarded as safe for healthy adults. While this sounds inconsistent, this considered conclusion should facilitate approval of RCT comparing vitamin D supplementation at up to 100 μg/d with currently recommended intakes, for their effects on many health outcomes, in order to establish both optimal vitamin D status and the intakes necessary for it to be achieved.

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Vitamin D

Vitamin D, how much is enough and how much is too much?

Madam

The recent Institute of Medicine (IOM) report on vitamin D[1] underemphasizes the potential benefits of vitamin D to many individuals who have low levels, while overstating the evidence for potential harm associated with higher intakes. In describing studies of mortality, the report concludes: 'In general, these studies, as expected, indicated that low serum 25(OH)vitamin D levels akin to deficiency states (<20 nmol/l or 12 ng/ml) are associated with an increased risk of mortality. Further, as serum 25(OH)D levels increase – up to a point – mortality is lowered'. Assuming 'as expected' implies a causal relationship between some low level of 25-hyrdoxyvitamin D (25(OH)D) and total mortality, this statement is surprising because no other health effect for vitamin D was recognized besides skeletal health, which alone could not account for the increased mortality. Further, the report states: '…the committee emphasizes that, with few exceptions, all North Americans are receiving enough calcium and vitamin D'. The fact that numerous studies detect an inverse association between 25(OH)D level and mortality (in addition to various other health outcomes) would indicate that a substantial proportion of individuals must not be getting optimal vitamin D; if all received enough vitamin D, no association would be detectable. Even if a level as low as 50 nmol/l is required to eliminate excess risk, many people remain deficient. For example,

in a study based on the third National Health and Nutrition Examination Survey (NHANES III), levels below 50 nmol/l were associated with a substantially increased risk of total and cardiovascular mortality[2]. Approximately one-third of participants fell into this deficiency category and this proportion is a large underestimate because in northern states samples were collected only in the summer months. Levels in the winter months in northern latitudes are of most concern for vitamin D deficiency. For example, in the winter months in northern states in the USA, almost all African Americans have levels below 50 nmol/l[3].

In contrast to downplaying any potential beneficial non-skeletal role for vitamin D, any evidence of potential harm was magnified. The IOM report cited a few studies that demonstrated an apparent U-shape or inverse J-shape for some health outcomes, and the potential for harm was prominently stated, even reflected in its two sentence summary statement. Some of the selected examples require a stretch of the imagination to see the evidence for a U-shaped pattern. For example, the results of one study of 25(OH)D and CVD[4] were described as: …'there was no additional reduction in risk at levels greater than 75 nmol/L and that the dose–response relationship may be U-shaped above 75 nmol/L'. Upon inspection of the figure for this 'U-shaped' relationship, there was no credible statistical evidence for an increased risk – because only six cases had levels >75 nmol/l, the confidence intervals were extremely wide and essentially uninformative. A better description of the results from this study is that risk of CVD decreases with increasing 25(OH)D but the benefit levels off at about 50–60 nmol/l.

Why the report placed large emphasis on the potential harm of high levels rather than the potential benefits may reflect largely the general approach for reviewing data, which, while appropriate for evaluating drug efficacy on specific diseases, may not be ideal to evaluate a 'lifestyle' biological factor, which I consider vitamin D to be. If we think of vitamin D as a pharmaceutical agent, we implicitly assume zero as the 'default' level and would look carefully for any evidence of risk, even from observational studies, and require evidence of benefit largely if not exclusively from randomized trials. However, 'natural' levels of 25(OH)D from healthy individuals with relatively high sun exposure (reflecting most of human history) are typically in the 125 to 175 nmol/l range. Because sun exposure tends to be low in current society, the highest levels are typically in the range of 75–100 nmol/l. Benefits and risks associated with vitamin D can be considered bidirectionally – for example, using 75 nmol/l as a starting point, the question of whether levels lower than this are deleterious is as relevant as the question of whether higher levels are harmful. The vast majority of studies for various endpoints including some cancers, total mortality, CVD, hypertension, skeletal health and some autoimmune and infectious diseases find higher risk at levels below 75 nmol/l; sometimes the trend appears inversely linear up to this point and sometimes the threshold for no further benefit may be lower (for example, at 50 nmol/l), but the group in the range of 75–100 nmol/l is typically the lowest-risk group. A much greater body of observational evidence supports that levels of 25(OH)D below 75 nmol/l are deleterious *v.* levels of 75 nmol/l or higher, than supports deleterious effects at higher levels.

Excessive concern for potential adverse effects may also extend from the example of β-carotene, where randomized trials did not support hypothesized benefits and even indicated harm. However, β-carotene trials tested intakes about tenfold higher than would be consumed by those on a diet naturally high in β-carotene, so any supraphysiological effects could not be predicted by experience in human subjects. I would not consider a seemingly high vitamin D dose of 25 μg (1000 IU/d), for example, as supraphysiological, as this amount could be made though several minutes of sun exposure. Ongoing and future randomized trials will undoubtedly generate important information, but are unlikely to address all relevant issues. For example, for some diseases, the timing of the relevant exposure could be decades before the diagnosis of the disease[5]. Given our current state of knowledge, it is a larger concern that many people are not getting enough vitamin D rather than many are getting too much.

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Vitamin D

Vitamin D and the limits of randomized controlled trials

Madam

Important decisions are now being made by the public health community regarding applications of vitamin D for