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Review Article

Hylonome

Vitamin D – The iceberg nutrient

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Vitamin D_3 has long been recognized as necessary for efficient absorption of dietary calcium, but until recently, ways of assessing vitamin D adequacy have been severely limited. Recommended intakes[1] (200 IU/d for adults up to age 50, 400 IU/d up to age 70, and 600 IU/d thereafter) are sufficient only to prevent rickets or osteomalacia, and the presumption had been that if an individual did not have these disorders, then he or she was getting enough vitamin D. Since 1997, with the publication of the DRIs for calcium and the bone-related nutrients[1], serum 25-hydroxy-vitamin D 25(OH)D has been recognized as the appropriate indicator for assessing vitamin D status, and a great deal of work has been done since then to define the serum 25(OH)D level that assures optimal functioning of the body systems dependent upon vitamin D.

Calcium absorption has been studied mainly in Caucasians, in whom it has been shown to rise with serum 25(OH)D levels up to about 80 nmol/L[2]. Consistent with this finding is the widely reported experience that serum parathyroid hormone (PTH), which rises when calcium absorption is inadequate, "bottoms out" at a serum 25(OH)D value of ~80 nmol/L[3]. Both observations suggest that a level of 80 nmol/L or higher is necessary for optimal functioning of the calcium economy. Supporting this conclusion are data from a randomized controlled trial showing that osteoporotic fracture risk drops by 33% as serum 25(OH)D rises from 50 to 75 nmol/L[4] and, from NHANES-III, that hip BMD rises in all races as a function of serum 25(OH)D[5]. The rise is steepest up to values of about 40 nmol/L, but BMD continues to rise to values well above 100 nmol/L. A very similar pattern is seen for lower extremity neuromuscular performance[6], when plotted as a function of serum 25(OH)D. Neuromuscular function is an important factor in preventing falls, and several randomized controlled trials have shown that supplemental vitamin D reduces fall risk to a clinically important extent[7].

Vitamin D is necessary for optimal functioning of many tissues unrelated to the calcium economy, and is now known to be involved as a part of the autocrine signaling system by which various tissues control cell reproduction, differentiation, and apoptosis. There are ~200 genes in the human genome with vitamin D response elements[8], most of which are unrelated to the canonical function of vitamin D in the calcium economy. The best worked out example of vitamin D's function in intracellular signaling comes from a study of the response of the innate immune system to an antigen such as that of tuberculosis[9]. Human monocytes bind the tuberculosis antigen to a toll-like receptor and ultimately produce a bactericidal peptide. But this response depends upon the medium concentration of 25(OH)D. The first genes to be expressed in this response are the 1-α-hydroxylase (Cyp27) and the VDR. In the effective absence of 25(OH)D nothing further happens. However, at normal serum concentrations of 25(OH)D [or when 25(OH)D is directly added to the medium], the monocytes convert the 25(OH)D to $1,25(OH)_2D$, which binds to the expressed VDR and then, with proteins connected to the activated toll-like receptor binds to the VDRE for cathelicidin, the bactericidal peptide[5] concerned. Both cathelicidin and the 24-hydroxylase (Cyp24) are expressed, the latter degrading the synthesized $1,25(OH)_2D$ and quickly turning off the signal. In this manner, vitamin D functions as a rapid on-off switch for the genes concerned. Cell-level abnormalities of this system have been identified in several cancer model systems. Not surprisingly, there is now a huge literature associating low vitamin D status with increased risk for a wide variety of disorders, from various epithelial cancers, to Type I diabetes, to multiple sclerosis[10].

These autocrine functions of vitamin D probably account for 75-95% of total vitamin D utilization every day (which current data suggest is on the order of 4000 IU)[11]. Serum 25(OH)D levels needed to ensure optimal functioning of these cell-cycle regulatory and immune processes are not known, but from preliminary data would appear to be at or above 80 nmol/L.

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Vitamin D is not a true nutrient for most mammals, as it is not considered to be present in most foods. In the human diet, only oily fish is generally recognized to contain appreciable amounts, though it is likely that the meat of animals grown outdoors may also contain nutritionally meaningful amounts. Milk, some orange juices, and some ready-to-eat cereals have been fortified to contain modest amounts of vitamin D. It is unusual, however, for diets of persons over age 50 to provide sufficient vitamin D to reach even the currently recommended intakes for that age group, let alone the amounts needed to ensure optimal functioning. Hence supplementation or more aggressive food fortification programs are necessary to ensure an adequate serum 25(OH)D level in older individuals.

Normally most of our vitamin D needs every day is met by vitamin D synthesized in the skin in response to sun exposure. However, several factors limit how much we can get that way – age, living at higher latitudes, working indoors, use of sunscreen, skin pigmentation, and cultural practices that preclude exposing skin when outdoors, all reduce the synthesis of this key vitamin. Individuals with one or more of these factors may need up to 4000 IU/d to maintain a serum 25(OH)D level of 80 nmol/L. For these individuals supplementation is the only feasible answer.

The Tolerable Upper Intake Level (TUIL – "upper limit") has been set by the Institute of Medicine at 2000 IU/d[1], but recent evidence has called that level into question[12]. Toxicity is essentially never seen at 25(OH)D levels below 400–500 nmol/L, and 2000 IU/d will not approach such 25(OH)D values even when taken by outdoor workers already 2 standard deviations above the population mean[13]. The best current evidence indicates that the no-observed-adverse-effect-level (NOAEL) is 10,000 IU/d[14].

There are two principal forms of the vitamin: cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2). Vitamin D_3 is the natural form in all animals, and is what is synthesized in the skin. Vitamin D_2 is derived from ergot mold formed on some plant products. The two were once thought to be equipotent and for that reason were measured in the same International Units (IU), but it is now known that vitamin D_2 is metabolized by the body much more rapidly than vitamin D_3[15], and hence exhibits substantially lower effective potency, unit for unit.

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