

The Vitamin D cutoff conundrum



Introduction

Vitamin D status is considered important for calcium balance and bone health as $1,25\text{ (OH)}_2$ vitamin D (calcitriol) promotes calcium absorption from the gut and has pleiotropic effects in bone. Vitamin D deficiency leads to hypocalcaemia and osteomalacia or rickets in adults and children respectively.

Vitamin D status was also brought under the spotlight owing to an apparent association with cardiovascular health and several other chronic disorders. These associations were noted in animal studies but the findings were not mirrored in humans. Vitamin D sufficiency or insufficiency is determined using quantitative analytical techniques, with results interpreted

against statistically-determined cutoffs.

The Controversies

Controversies exist due to the analytical methods as well as the methods to determine these decision limits. The analytical methods available to quantify vitamin D include immunoassays and HPLC or LC-MS/MS methods. The majority of labs use immunoassays to measure 25(OH) vitamin D (calcidiol), and a smaller group also measure calcitriol by immunoassay. Calcidiol occurs at higher concentrations in the serum and, in most cases, it better reflects the vitamin status than calcitriol, as 1-alpha-hydroxylase activity is modulated according to calcitriol and calcium status.

However, immunoassays are non-specific regarding metabolites of vitamin D and therefore results of calcidiol and calcitriol measurement may not be accurate due to cross-reactivity. LC-MS/MS is a much more accurate methodology to measure both calcidiol and calcitriol as well as other metabolites of interest, such as 24,25(OH)₂ vitamin D. One controversial point is, therefore, whether or not calcidiol and calcitriol measurements by immunoassay are accurate.

The second controversy lies in the determination of the decision limits for vitamin D repletion, sufficiency and insufficiency. Currently, there are two major sets of decision limits to choose from. The first were determined and recommended by the Endocrine Society based on recommended daily allowances (RDA) for the vitamin. It is argued that the concept of the RDA is misinterpreted and the methods for setting the RDA not understood. These decision limits are high, and by these limits some 50% of most populations are diagnosed with vitamin D insufficiency. This is also dangerous, as replacement of vitamin D may lead to hypervitaminosis D, which is not benign and may in fact increase the risk of falls and fractures. Another consequence

is the demand for testing vitamin D levels is very high, which is expensive for healthcare funders or individuals, with questionable health benefits.

The other popular set of decision limits were determined based on the risk of falls and fractures (Institute of Medicine) – a more functional approach. The result of using these limits is that the majority of the population will fall into the vitamin D sufficient or replete groups, and only individuals at high risk will have their status checked and/or monitored and receive supplementation as necessary. This is a more cost- and clinically-effective approach, but is yet to be globally adopted.

	Vitamin D Status				
Institute of Medicine	25-OH D (ng/ml)		Endocrine Society	Treatment*	Maintenance†
Deficient	<12	<20	Deficient	50,000 IU/week for 6-8 weeks	600–2,000 IU/day
Insufficient	12–19				
Sufficient	20–29	20–29	Insufficient	≥400 IU/day	
	30–49	≥30	Sufficient		
High	>50				

The final point to be made is perhaps what drives the interest in vitamin D status, and it may be suggested that it is the reagents and pharmaceutical industry as they stand to gain from increased testing and demand for supplements.