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Editorial

Vitamin D deficiency: is it real? Need to re-evaluate in context to the latest research findings

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Till some two decade ago vitamin D was better known as 'anti-ricketic vitamin', and was known to cause rickets in children and osteomalacia in adults. But suddenly this sunshine vitamin has gained all the attention from internist, specialist to super specialist in the field of medical science.[1,2] At present even common men are more aware of vitamin D and its associated clinical conditions than what a medical practitioner knew some 20 years ago. Everyone is inquisitive about vitamin D.

Vitamin D (Vit D) an important fat soluble vitamin is synthesised in human body from cholesterol upon skin exposure to UVB (290-315 nm) sunlight or is available through dietary intake. The Vit D synthesised in the body is Vit D3 (cholecalciferol) and that availed from dietary sources are mainly Vit D2 (ergocalciferol) and some amount of Vit D3. Vit D on hydroxylation in the liver form 25(OH) Vit D, which becomes biologically active 1,25-(OH)2 Vit D (calcitriol) on further hydroxylation in the kidney.[1,2] Vit D metabolism and actions in concert with calcium and phosphorus metabolism are regulated by parathyroid hormone. Vit D metabolites circulate in the body bound to Vit D binding proteins (VDBP).[2,3] Although sunlight is a vital source of body Vit D, however, amount of sunlight exposure is important for Vit D synthesis, as production of vitamin D in the skin minimizes in winters. Latitudes and longitude also determines the amount of sunlight, reaching our skin. The unit of UV exposure is "1 standard vitamin D dose" (SDD), and is defined as the time required to obtain the recommended UV dose for adequate vitamin D synthesis.[4-6] The time duration for 1 SDD varies with latitudes and longitudes and with season of the year. Also important is the time of the day when exposure is taken; though there are a handful of recommendations, but almost all agrees that mid day or solar noon is the optimal time for exposure and adequate Vit D synthesis. Weather conditions such as cloud cover and pollution, ozone layer, surface reflection etc., also determines the amount of sunlight exposure. Further the trend of using sunscreen greatly reduces the sun exposure and hence decreases Vit D synthesis. Besides these, dark colored people, people living indoors on most time of the day, over covering with clothes due to religious or other reasons have less sun exposure and consequently less Vit D synthesis. Dietary deficiency of Vit D can result from either decrease intake of food rich in Vit D or decrease intake of foods fortified with Vit D. Even after adequate intake of Vit D; the same may not be absorbed properly or may not be activated to 1, 25-(OH)2 Vit D or calcitriol.

Vit D deficiency or insufficiency has been reported worldwide as per the present cut off defining Vit D deficiency or insufficiency. Such deficiency or insufficiency has been reported from every continent-the United States, South America, Canada, the Middle East, Australia, South Asia, Europe, and Africa.[7-14] Studies from India have reported a deficiency ranging from 30% to as high as 100%.[13,15,16] Other parts of the world like the Middle East, China and South America have also reported alarmingly high incidence of Vit D deficiency. The question that comes to our mind is whether these alarming deficiency states are related to any disease conditions; the answer to which is controversial in the present scenario. Vitamin D deficiency has been linked to chronic diseases such as diabetes, cancer (breast, colon and prostate), cardiovascular disease, osteoporosis, osteomalacia and several autoimmune diseases among others.[2,17] Many of such studies however lacked sufficient statistical power to draw meaningful conclusions. But, Vit D is certainly

liked with enormous non-skeletal conditions resulting in increased number of Vit D estimation, and overzealous supplementation. However the consensus related to Vit D intervals and its association with various non-skeletal conditions does not exist at present, other than for the outcome of osteomalacia, which occurs only in individuals whose 25(OH)D is <10 ng/mL (25 nmol/L).[18] Various society have put forward cut off level of Vit D so that meaningful association between Vit D and various non-skeletal conditions and potential health benefits of Vit D supplementations can be ascertained. Many such recommendations were based on the fact that the PTH concentrations plateau when the 25(OH)D concentrations were at least 30 ng/mL (75 nmol/L).[18] However when, the Institute of Medicine's (IOM) report (2010) stated that vitamin D supplementation was unlikely to be beneficial for any condition other than bone health and that blood concentrations of 20 ng/mL (50 nmol/L) or greater were sufficient for maintaining bone health, several metaanalyses have failed to show that low 25(OH)D concentrations are associated with risk for any of the above-mentioned non-skeletal chronic conditions, with the possible exception of fractures.[19]

Estimation of Vit D also present challenges. Vit D is often considered a "difficult" analyte and there has been a considerable debate regarding the measurements of Vit D.[2,20,21] As per the present recommendations by various societies the total 25(OH) Vit D, i.e., 25(OH) D2 plus 25(OH)D3 should be estimated. There are immunoassays which does not have equal detection of 25(OH) D2 and 25(OH)D3 and hence, the estimated Vit D value is many a times less than the actual value. Also for proper interpretation of Vit D laboratory reports, it is essential that the treating clinician be aware of the various factors that may affect the Vit D assays. The methodology used for Vit D assays are not uniform and also different laboratories measures different metabolite of the sunshine vitamin. There are various confounders for Vit D assays as well. Lack of standardisation of Vit D assays is also a matter of concern. Hence the Vit D reports that is generated from the diagnostic laboratory should always be interpreted in context with the methods used, the metabolite estimated and with proper clinical correlation.[2]

Recently there has been detection of genetic polymorphisms in vitamin D binding proteins (VDBPs) that segregate well between blacks and whites, this may explain the fact that despite having high bone density blacks have low blood Vit D.[18] If we follow the concept of hormone metabolism we can infer that perhaps we should be looking at bioavailable 25(OH)D rather than total 25(OH)D. Several studies have suggested that polymorphisms in the VDBP gene account for >10% of the variation of 25(OH)D concentrations in population studies. There are 3 major variants of the VDBP (GC-1f, GC-1s, GC-2), which can be combined to form 6 diplotypes.[18] Presently there are very few assays for determination of VDBP and validity of such assays is controversial. Many Vit D experts believe that the recent findings about VDBP polymorphisms might affect interpretations about the association of Vit D concentrations with cancer, diabetes, and cardiovascular disease mortality. If this turns to be true the entire studies should be repeated!

From the foregoing discussion it can be assumed that the documented Vit D deficiency put forward by various studies are too good to be real. The deficiency suggested may be ascertained to the high cut off for Vit D deficiency, lack of standardisation of Vit D estimation and might also be due to not taking into account the genetic polymorphism of VDBP and receptors. The cut off defining Vit D deficiency needs to be readdressed. Clinicians and general people need to be educated regarding the various aspects of Vit D so that adequate intake and synthesis of Vit D is possible, unwanted economic burden by overzealous estimation and supplementation can be avoided and unnecessary apprehension for Vit D deficiency can be eased. So presently there is lack of consensus regarding the non-skeletal benefits of Vit D, and if there are any association it need to be reevaluated taking into account the latest findings like VDBP polymorphism. We still know too little of Vit D and near future is sure to unfold many novel facts of Vit D and till then we should not hype Vit D deficiency.

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