



## Mini-Review

# Variable Responses to Vitamin-D Dosing

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## Introduction

**Background:** Vitamin D deficiency is recognized as a global public health problem, with deficiency states reported from various countries [1-3]. Acting as a Pro-Hormone; this is a unique endogenously synthesized vitamin. Besides its pivotal role in calcium homeostasis and bone mineral metabolism, the vitamin-D endocrine system is now recognized to sub-serve a wide range of fundamental biological functions in cell differentiation, inhibition of cell growth, and immunomodulation [3]. Vitamin-D deficiency affects not only musculoskeletal health but also a wide range of acute and chronic disease [4].

The metabolic product of vitamin-D is a potent, pleiotropic, repair and maintenance; secosteroid hormone that targets more than 200 human genes in a wide variety of tissues, meaning it has as many mechanisms of action on genes it targets [5]. Two related sterol compounds viz. Cholecalciferol [Vitamin-D3] and Ergocalciferol [Vitamin-D2] are grouped as 'Vitamin-D'. Cholecalciferol is of animal origin and the other Ergocalciferol [Vitamin-D2] is plant based. Interestingly, antirachitic properties of Vitamin-D2 and D3 are identical [6]. After oral administration; Vitamin-D3 is absorbed better than D2 in small intestine; and bile is essential for absorption [6].

## In animals

Under effects of Ultra Violet light 7-Dehydrocholesterol in skin is converted to Cholecalciferol [Vitamin-D3]. D2 and D3 are converted to 25-OH-cholecalciferol [25-OH-CC] in Liver. This is first hydroxylation. 25-OH-CC /25-OH-D or Calcifediol is the major circulating form of Vitamin-D and has a half life of 19 days; and serum concentrations are 15-50 nanograms/ml with steady state pharmacokinetics [6]. 25-OH-CC undergoes second hydrolysis to 1, 25-OH-CC, primarily in kidneys but to some extent in extra-renal sites as Macrophages and Keratinocytes [6]. Calcitriol or 1, 25-OH-CC is the final active form of Vitamin-D. Both 25-OH-CC and 1, 25-OH-C may undergo further hydrolysis in renal tubules to INACTIVE forms 24, 25-OH-CC and 1, 24, 25-OH-CC [6]. The optimal level of 25[OH] Vitamin-D should be 50 -100 ng/ml. Blood levels of 25[OH] Vitamin D exceeding 200ng/ml are considered potentially toxic. Vitamin D toxicity is very rare [7,8].

Serum 25-hydroxyvitamin-D [25(OH) D], Calcidiol, is the storage form of vitamin-D, and the most reliable indicator of the vitamin D stores of an individual. It is therefore the one tested for in routine assays to determine deficiency/adequacy of the vitamin. The production of 25(OH) D is not regulated, and therefore the concentration of the compound in serum reflects both cutaneous synthesis and absorption from the diet. The half-life of 25(OH)-D is about six weeks. Biochemically, levels of 25(OH)-D more than 30 ng/ml (to convert ng/ml to nmol/ml multiply by 2.5) are considered as 'normal'. Levels between 20 and 30 ng/ml are defined as 'insufficiency' and levels less than 20ng/ml are defined as 'deficiency' [3]. The best option for estimation of vitamin- D levels in laboratory is LCMSMS-Liquid Chromatography Tandem Mass Spectrometry [9].

## Suggestions to Treat the Deficiency State

Various clinical trials suggested different dose regimes to treat Vitamin-D deficiency. It was found that an intake of 400 IU/day oral vitamin D3 did not sustain circulating maternal 25(OH) D levels, and thus, supplied only extremely limited



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amounts of vitamin-D to the nursing infant via breast milk. Infant levels achieved exclusively through maternal supplementation were equivalent to levels in infants who received oral vitamin-D supplementation. Studies showed that a maternal intake of 4000 to 6400 IU/day vitamin-D elevated circulating 25(OH) D in both mother and nursing infant [10-12]. 'NO-OBSERVED ADVERSE-EFFECT LEVEL' (NOAEL) were noted with this dose schedule [12].

## Findings

In our study all the participants received 1200,000 IU of Vitamin-D and repeat levels were monitored over six months [13]. Yet in another study of ours, in spite of four mega- doses of Vitamin-D injections [of 600,000 IU]; only two third or 9/14= 64.3% showed good response and 5/14 =35.7% failed to achieve target serum levels of Vitamin-D [14]. Annual Single dose of Vitamin-D is one of the few options tested by some authors. In our study of Annual Single Mega-dose of Vitamin-D injection as Supplementation Therapy [15]; all eight members had normal serum levels of vitamin-d to start with and they received one mega-dose of 600,000 IU intramuscular injection as maintenance dose. It has been noted that a single dose of 600,000 IU of cholecalciferol rapidly enhances 25(OH)-D with vitamin D deficiency [16,17]. This satisfactory response to high dose vitamin-D was seen in Australian population [18]. We observed in all our Vit-d projects that the response even with high mega-dose Vitamin-D treatment is erratic and unpredictable. Few other authors have made similar observations in population with Asian Indian ethnicity [19,20] in India and United Kingdom. Probably this is multifactorial issue. Genetic factors seem more important than environmental ones. These studies from different geographic locations rule out environmental factors. So we are left with genetic factors to explain this odd phenomenon.

## We tried to reason it out

1. Vitamin D-binding protein is coded by Genes like TT, TK or KK. It has been shown that increments in serum 25(OH) D in response to treatment depend on the heritability/ genotype of vitamin D-binding protein carried by the individual. KK genotype shows highest increments followed by TK and then last on list is TT variant [this is more frequently found in people of Indian origin [21]. This may explain the variability or low levels in spite of good dosing.
2. Secondly, high 24-25 Hydroxylase activity is seen in Indians. This is also been proved in laboratory using tissue culture techniques. This may change active form 25-OH-D to inactive one viz. 24-25-OH-D [22]. This can be looked upon as a shunt operating to safeguard against the development of high levels of Vitamin-D. Is it an adaptive mechanism?
3. For obvious reasons, the Skin pigmentation factor cannot be counted. Melanin in the skin competes with 7dehydrocholesterol for UVB rays. The greater the amount of melanin in the skin, the lower is the efficiency of vitamin-D synthesis. Skin with darker pigmentation, like those of most Indians, requires a longer duration of sun exposure to synthesize an equivalent amount of vitamin-D as compared to Caucasian skin. Indians' skin comes under type V category.
4. After absorption, Vitamin-D3 circulates in association with Vitamin-D Binding Protein; specific Alpha Globulin. The Vitamin-D disappears from blood with half-life of 30 hours, but remains stored in fat depots for prolonged periods [6]. In our study; 47 participants showed poor responses and all of these had BMI higher than their counterparts who showed good response. Could it be that these POOR participants had Vitamin-D stored in fat depots?
5. Probably there few other genetic factors as well. Studies in Twins have confirmed role of genetic factors in determining bone resorption and formation, calcium excretion, and the hormones regulating these processes [23].

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