Review Article

The intestinal calcistat

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ABSTRACT

The main physiological function of vitamin D is maintenance of calcium homeostasis by its effect on calcium absorption, and bone health in association with parathyroid gland. Vitamin D deficiency (VDD) is defined as serum 25-hydroxy vitamin D (25OHD) levels <20 ng/ml. Do all subjects with VDD have clinical disease according to this definition? We hypothesize that there exist an intestinal calcistat, which controls the calcium absorption independent of PTH levels. It consists of calcium sensing receptor (CaSR) on intestinal brush border, which senses calcium in intestinal cells and vitamin D system in intestinal cells. CaSR dampens the generation of active vitamin D metabolite in intestinal cells and decrease active transcellular calcium transport. It also facilitates passive paracellular diffusion of calcium in intestine. This local adaptation adjusts the fractional calcium absorption according the body requirement. Failure of local adaptation due to decreased calcium intake, decreased supply of 25OHD, mutation in CaSR or vitamin D system decreases systemic calcium levels and systemic adaptations comes into the play. Systemic adaptations consist of rise in PTH and increase in active vitamin D metabolites. These adaptations lead to bone resorption and maintenance of calcium homeostasis. Not all subjects with varying levels of VDD manifest with secondary hyperparathyroidism and decreased in bone mineral density. We suggest that rise in PTH is first indicator of VDD along with decrease in BMD depending on duration of VDD. Hence, subjects with any degree of VDD with normal PTH and BMD should not be labeled as vitamin D deficient. These subjects can be called subclinical VDD, and further studies are required to assess beneficial effect of vitamin D supplementation in this subset of population.

Key words: Bone mineral density, calcium, phosphatase and parathormone, vitamin D

Introduction

Vitamin D deficiency (VDD) is defined as serum 25-hydroxy vitamin D (25OHD) levels <20 ng/ml. VDD has been documented in more than 90% across all age groups and both sexes from India.[1,2] Classical manifestations of VDD is described as rickets/osteomalacia, which manifest as bony deformity/pain, decreased bone mineral density (BMD), increased risk of fracture and is associated with raised alkaline phosphatase and parathormone (PTH). However, secondary hyperparathyroidism (SHPT) is observed in <50% of subjects in Indian and US population.[1,3,4] Subjects with same levels of serum 25OHD have varied clinical and biochemical abnormalities including some showing no abnormalities.[5] This raises logical question "Do all subjects with VDD have clinical disease according to this definition?"

The main physiological function of vitamin D is maintenance of calcium homeostasis by its effect on calcium absorption and bone health in association with parathyroid gland. Calcium is absorbed actively in the duodenum through transcellular (active transport-80%) process, which is vitamin D dependent, whereas passive absorption is a paracellular (passive diffusion-20%) process, which occurs throughout intestine independent of vitamin D and is dependent on concentration of calcium in the intestinal tract. Total fraction of calcium absorbed from total intake can vary from 20 to 80%. In the event of decreased calcium availability from intake, calcium is released from bone under the effect of vitamin D-PTH system to maintain its homeostasis. Calcium excretion is also dependent on calcium balance.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.119497

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Vitamin D and Calcium Absorption

As per the recent Institute of Medicine (IOM) statement [6] "The data currently suggest that fractional calcium absorption (FCA) reaches a maximum between 12 and 20 ng/ml in both children and adults."

In most of the studies reviewed by IOM, the baseline serum 25OHD was > 10 ng/ml and there was no correlation of serum 25OHD levels with calcium absorption. When we have plotted mean basal serum 25OHD levels in various studies and mean FCA, there was a significant inverse correlation ($r = -0.75$, $P = 0.001$).[7] There is only one study among elderly that has assessed the relation of calcium absorption and base line serum 25OHD levels ranging from 4 to 20 ng/ml.[8] This study has clearly shown that calcium absorption decreases in the ranges from 4 to 8 ng/ml and not >8 ng/ml. Similarly, in the most studies related to vitamin D supplementation, basal serum 25OHD levels were > 8 ng/ml. Only one study carried out in subjects with 25OHD level of 4 ng/ml showed an increase of 21% with change in 25OHD level to 24 ng/ml, whereas in those with the increase in 25OHD level from 8 to 28 ng/ml only 3% increase of calcium absorption occurred.[9] There is no correlation of mean change in FCA (increase or decrease) with either mean basal serum 25OHD levels ($r = -0.122$, $P = 0.754$) or increment in serum 25OHD levels.[7] These data clearly shows that the maximum calcium absorption capacity is reached when serum 25OHD levels are >8 ng/ml.

Logically to maintain calcium homeostasis in the face of VDD, the first body will try to absorb maximum available calcium, rather than affecting bone. Hence, calcium absorption is the first most important adaptive mechanism in patients with VDD. FCA is inversely related with calcium intake. High FCA (54-63%) has been reported from the region of China with low calcium intake (<500 mg) compared with 25-34% in US children with high intake of calcium (>900 mg).[10] This suggests that the body tries to adapt to the calcium availability to bodies requirement by adjusting FCA.

Intestinal Calcistat

The conventional explanation of homeostasis is by systemic adaptation, in which decreased calcium intake results in decreased calcium absorption, which leads to increase in PTH levels. The PTH up regulates the 1-α hydroxylase enzyme, leading to increase generation of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D) levels and increased calcium absorption and bone resorption. However, as deduced from the above discussion, the body has a tremendous reserve to increase the FCA in the face of decrease in calcium intake. This suggests that calcium absorption can be kept static over a wide range of calcium intake and serum 25OHD levels by local intestinal adaptation. What is the mechanism of this local adaptation?

We hypothesize that the first adaptive mechanism in calcium homeostasis is local rather than systemic. This can be called the "intestinal calcistat," which controls the calcium absorption independent of PTH levels. It consists of calcium sensing receptor (CaSR) on intestinal brush border, which senses calcium in intestinal cells and negatively affect vitamin D system in intestinal cells to decrease active transcellular calcium transport. It also facilitates passive paracellular diffusion of calcium in the intestine, which is less efficient process. On the contrary, when there is decreased calcium intake, this feedback inhibition is removed and vitamin D dependent active calcium absorption will increase, maintaining calcium homeostasis.

Furthermore, there may be some genetic or epigenetic alteration in genes of 1-α hydroxylase enzyme, which decreases efficiency of active vitamin D generation or vitamin D receptor (VDR) genotype affecting calcium absorption.[11] In subjects with efficient VDR genotype for calcium absorption, local adaptation will be maintained at lower levels of serum 25OHD and vice versa will also be true. The interaction between CaSR and vitamin D system in intestinal cells ("intestinal calcistat") will decide the level of serum 25OHD at which calcium absorption can be maintained according to the need of the body or becomes suboptimal in a given individual indicating failure of local adaptation.

Systemic adaptation will come into play when local adaptation fails. Failure of local adaptation can occur in various circumstances. Firstly, decrease in calcium intake <250 mg, which cannot be overcome by increasing FCA. This will manifest as calcium deficiency rickets on the face of normal vitamin D levels. Secondly, mutation in CaSR, if "activating," may lead to decreased calcium absorption and if "inactivating," increased calcium absorption. Thirdly, decreased supply of substrate below critical levels (serum 25OHD <8 ng/ml) will lead to VDD rickets. However, this level can vary according to interaction between CaSR and vitamin D system in an individual-"intestinal calcistat." Finally, genetic mutation in 1-α hydroxylase [vitamin D resistant rickets-I (VDRR-I)] or VDR (VDRR-II) will also lead to failure of local adaptive response. This will also explain the observation in VDRR-I and II, where high intake of

calcium can overcome most of the clinical manifestation of the disease.[12] With very high intake, CaSRs will get saturated and will enhance passive (paracellular) calcium absorption, which will be able to fulfill the requirement of body.

With increasing severity of VDD, there will be decrease in calcium absorption. This will lead to increase in PTH and generation of active vitamin D metabolites. The calcium levels will now be maintained by bone resorption, rather than increasing calcium absorption, which is currently believed. Hence, generally held belief that increase in PTH will increase calcium absorption through generation of active vitamin D metabolites, is wrong. This puts PTH as a marker for systemic VDD or failure of local adaptation by the "intestinal calcistat."

Explaining 25OHD Levels, PTH and BMD Paradigm in VDD

The above hypothesis of the "intestinal calcistat" explains the vide variation observed in literature about relation between serum 25OHD, PTH, calcium absorption and BMD. According to this hypothesis, subjects with low serum 25OHD who have normal "intestinal calcistat" will absorb required amount of calcium and will not mount systemic adaptive response in the form of increase in PTH and 1,25(OH) 2D levels, hence will have lower 1,25(OH) 2D levels than those with failure of adaptation and BMD will not be affected. Subjects with adaptive failure will have higher 1,25(OH) 2D levels and will have lower BMD. The same observation has been reported in the recent study.[13] This is further supported by observation that patients with similar low serum 25OHD levels (<10 ng/ml), BMD was lower in subjects with SHPT.[3] This will also explain the observation that about 50% of subjects with VDD don't mount PTH response because they have adequate local adaptation in "intestinal calcistat." This will also explains that why there is no substantial increase in calcium absorption in with vitamin D supplementation because basal level of serum 25OHD is sufficient to supple enough substrate for generation of active vitamin D metabolites. Substantial calcium absorption will increase only in subjects with substrate deficiency (25OHD).

Conclusions

This brings us to question that should we define VDD with a value of serum 25OHD in isolation? It is obvious from the above discussion that there are adaptive mechanisms to overcome low vitamin D levels, which can be operative over a wide range of serum 25OHD levels. Failure of adaptive mechanism will lead to clinical and biochemical evidence of VDD. Among them first will be the rise in PTH levels and then decrease in BMD. Hence, the subjects with VDD defined by low vitamin D levels (<20 ng/ml or <30 ng/ml) according to the current definition with normal PTH and BMD will not have any clinical and biochemical consequence of low vitamin D levels and vice versa subjects with similar levels of serum 25OHD with raised PTH or low BMD are likely to be VDD. What should we call subjects with low serum 25OHD levels without evidence of SHPT or low BMD? Should we call them subclinical VDD, compensated VDD, asymptomatic VDD or not call them VDD at all. This is an open question. Further studies are required to define adverse biological consequences of VDD in this group and effects of vitamin D supplementation and comparing them with the population who already had adverse biological effects of VDD.

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Cite this article as: Garg MK. The intestinal calcistat. Indian J Endocr Metab 2013;17:S25-8.

Source of Support: Nil, **Conflict of Interest:** None declared.