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Vitamin D: In Health and Clinical Practice

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INTRODUCTION

Kurt Huldschinsky, a century ago, concluded from his experiments that exposure to UV radiation was an "infallible remedy" for rickets in children. The factor whose deficiency was linked to the development of rickets, was later in 1919 found to be cholecalciferol. In the past few decades, painstaking work by researchers worldwide has convincingly demonstrated that vitamin D apart from its calciotropic actions also mediates extra-skeletal effects across a wide range of homeostatic functions.

VITAMIN D SYNTHESIS

Vitamin D_3 (cholecalciferol) is made from 7-dehydrocholesterol in the epidermal layer of the skin under the influence of UV (B) radiation (290-315 nm). It is also acquired from animal-based foods. Vitamin D2 (ergocalciferol) is derived from plant sources. Vitamin D is activated in two steps of hydroxylation reactions in liver and kidney to active hormone endogenously. The first hydroxylated compound, 25 hydroxy cholecalciferol (25-HCC) and the next 1,25 dihydroxy CC (1,25-HCC) are the well known metabolites of vitamin D. The renal 1α-hydroxylation is closely regulated, being enhanced by parathyroid hormone (PTH), hypocalcemia, and hypophosphatemia and inhibited by hyperphosphatemia, FGF-23 and 1,25-HCC itself. The biologically active form of vitamin D i.e. 1,25-HCC (aka calcitriol) performs many of its biologic functions by acting on high-affinity vitamin D receptor (VDR) located primarily in the nuclei of target cells, which further binds to sites in the DNA called vitamin D response elements (VDREs). Later, a variety of co-regulators attach to this complex resulting in either up- or down-regulation in the expression of vitamin D-responsive genes in a cell specific fashion.

ACTIONS OF VITAMIN D

A. Classical calciotropic actions: Calcitriol facilitates intestinal calcium absorption and bone formation. It also interacts with VDR in osteoblasts to stimulate osteoclastogenesis. The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. In the kidneys calcitriol together with PTH stimulates calcium reabsorption from the glomerular filtrate. As serum calcium levels rise, PTH secretion drops and vice versa. Calcitriol suppresses parathyroid gene expression and parathyroid cell proliferation, providing important feedback loops that reinforce the direct action of increased serum calcium levels.

B. Non-calciotropic actions: VDRs are found fairly ubiquitously throughout the body in tissues viz., in the small intestine, colon, osteoblasts, activated T and B lymphocytes, pancreatic islet cells, and most organs in the body including brain, heart, skin, gonads, prostate, breast, and mononuclear cells. The innate ability of the above tissues to convert 25-HCC to calcitriol suggest an autocrine or paracrine role of calcitriol not related to calcium metabolism. The three important modes of non-classical actions of vitamin D are:

a. Regulation of hormone secretion- Vitamin D is shown to enhance insulin secretion, growth hormone and TSH release, physiological significance of some are yet to be established.

b. Regulation of immune function- It modulates innate and adaptive immunity, enhances chemotactic and phagocytic responses of macrophages and transcription of antimicrobial proteins such as cathelicidin and defensin and downregulates pro-inflammatory cytokines. It regulates differentiation of CD4+T cells, and favors less development of self-reactive T-cells and autoimmunity.

c. Regulation of cellular proliferation and differentiation- Vitamin D causes marked inhibition of cell proliferation, and allow differentiation of epithelial cells including keratinocytes which proves its effectiveness in therapy of psoariasis. It is shown to slow or prevent tumorogenesis by promoting cellular differentiation, stimulating apoptosis, and reducing angiogenesis.

SOURCES OF VITAMIN D

More than 90% of the vitamin D requirement is met from casual exposure to bright sunlight (between 10 am-3 pm) just for 5 min/day. Sources of vitamin D are mentioned in Table 1.

FACTORS CAUSING LOW VITAMIN D LEVELS

1. Lesser duration of exposure and odd timing (low ambient UVR level), ageing, chronic hospitalisation, high melanin content in the skin especially among African-americans, extensive clothing cover, decreased dietary intake, winter season, higher latitudes, use of sunscreen, low socio-economic status, exclusive breast feeding.

Table 1: Sources of Vitamin D

Sources of Vitamin D
1. Natural UV (B) radiation Cod liver oil (excellent source) Fish- Salmon, mackerel, sardine Egg yolk (variable)
2. Fortified foods Milk, orange juice and other juice products Some breads and cereals Irradiated mushrooms

2. Malabsorption syndromes and gastric bypass
3. Adiposity - low amount of vitamin D presented to the liver for 25-hydroxylation
4. Renal dysfunction, hepatic disease or some familial enzyme deficiency disorders
5. Drugs like anticonvulsants, glucocorticoids, rifampicin, ketoconazole, and few antiretroviral drugs

DEFINING VITAMIN D STATUS

The most accurate method of evaluating a person's vitamin D status is to measure the level of serum 25-HCC. Majority of the groups define vitamin D status as follows:

Table 2: Recommendations of IOM and Endocrine Society Clinical Practice Guidelines

	Age (yrs)	0-0.5	0.5-1	1-3	3-8	8-13	13-18	18-30	30-50	50-70	>70
IOM recommendations	RDA (IU/d)	← 400[b] →		← 600 →							800
	UL [a] (IU/d)	1000	1500	2500		3000	← 4000 →				
ESCPG Recommendations	RDA (IU/d)	400-1000 [c]		← 600-1000 →				← 1500-2000 →			
	UL [a] (IU/d)	← 2000 →		← 4000 →				← 10000 →			

a – UL is upper limit which indicates the level above which there is risk of adverse events

b – reflects adequate intake reference value than RDA, RDA has not been established for infants

c – mother's intake for infant requirement is 4000-6000 IU/d (if infant is not receiving 400 IU/d)

Table 3: Additional recommendations for special groups and deficiency correction

RECOMMENDATIONS AS PER ENDOCRINE SOCIETY PRACTICE GUIDELINES

a. Dietary requirements of vitamin d in special groups:
Pregnant and lactating women - at least 600 IU/d
Obese children and adults
All patients on anticonvulsant medications, glucocorticoids, antifungals such as ketoconazole, and medications for AIDS

} at least 2-3 times the recommended vitamin D for their age group

b. Daily dose for deficiency correction:
0-1yr - 2000 IU/d OR 50k IU once weekly of vitamin D2 or vitamin D_3 for 6wks f/b maintenance Rx of 400-1000 IU/d
1-18yrs - 4000IU/d OR 50k IU once weekly for 6wks f/b maintenance Rx of 600-1000 IU/d
>18yrs - 6000 IU/d OR 50k IU once weekly for 8wks f/b maintenance Rx of 1500-2000IU/d
Special groups:
In obese patients, patients with malabsorption syndromes, and patients on medications affecting vitamin D metabolism require 2-3 times the recommended doses (for both initial and maintenance) for their age

c. Monitoring the response to therapy:

i. In case of deficiency correction, monitoring blood levels of 25-HCC three months after beginning treatment is recommended so as to allow dose adjustments.

ii. In patients with extrarenal production of 1,25-HCC, serial monitoring of serum 25-HCC and calcium levels is suggested during treatment with vitamin D to prevent hypercalcemia

Table 4: Vitamin D linked disorders and role of vitamin D

Vitamin D linked disorders	Comments
Musculoskeletal disorders Rickets osteomalacia osteoporosis myopathy, risk of falls, risk of fractures	Vitamin D (calcitriol, cholecalciferol) used in therapy
Skin disorders Psoariasis Atopic dermatitis	 Vitamin D analogs viz., calcipotriene, 1,24-HCC, and maxacalcitol approved Vitamin D supplementation shown to suppress inflammatory responses, enhance antimicrobial peptide activity and ameliorate clinical signs of the disease
Endocrine disorders a. Parathyroid 2° hyperparathyroidism (due to severe vitamin D deficiency/ CKD) Hypoparathyroidism b. T2 DM	 Vitamin D (calcitriol) and its analogs including calcifediol, paricalcitol, doxercalciferol, maxacalcitol and falecalcitriol approved for treatment Cholecalciferol or calcitriol approved for treatment Experimental studies suggest that vitamin D may preserve glucose tolerance by enhancing insulin secretion and sensitivity
Cancer	1,25-HCC keeps cell growth in check and possibly prevents neoplasia. Positive association of low vitamin D status and increased risk of colorectal, breast, prostate and pancreatic cancer in observational studies
Autoimmune disorders a. T1 DM b. SLE c. Crohn's disease d. Multiple Sclerosis	 4 case-control studies revealed a significant 29% risk reduction for type 1DM among vitamin D-supplemented infants compared with controls; No RCTs A recent RCT concluded that vitamin D supplementation for 12 months showed significant improvement in levels of inflammatory and hemostatic markers, and disease activity Low vitamin D is inversely correlated to disease activity documented by clinical scores and surrogate markers of inflammation(CRP and fecal calprotectin), probably because of low cathelicidin and defensin, and dysregulated mucosal defense A RCT showed that vitamin D_3 supplementation in optic neuritis and Clinically Isolated Syndrome (CIS) patients with low serum 25-HCC may prevent or delay the onset of a second clinical attack and the subsequent conversion to MS
Respiratory Conditions a. Tuberculosis b. Cystic Fibrosis (CF)	 An experimental study said that serum low in 25-HCC could not up-regulate induction of cathelicidin leading to ineffective killing of intracellular M. tuberculosis. One RCT gave positive results with vitamin D supplementation on antimycobacterial responses in healthy adult tuberculosis contacts CF patients with vitamin D supplementation pre-emptive to pulmonary exacerbation returned to their baseline lung function much earlier with better clinical outcome than placebo group
Mental disorders Depression	 Vitamin D is believed to directly up-regulate tyrosine hydroxylase, the rate limiting enzyme for brain monoamine synthesis and increase monoamine levels

Serum concentration of 25-HCC

i. < 20 ng/mL (50 nmol/L) - deficiency

ii. 20-30 ng/mL (50 to 75 nmol/L) - insufficiency

iii. > 30ng/mL (75 nmol/L)- sufficiency

iv. 40-60 ng/mL is ideal and that up to 100 ng/mL is safe

v. > 150ng/mL may cause toxicity (hypervitaminosis D)

[Note: Conversion from ng/mL to nmol/L, multiply by 2.496]

DIETARY RECOMMENDATIONS

Dietary recommendations made by Institute of Medicine (IOM) and Endocrine Society Clinical Practice Guidelines (ESCPG) on vitamin D intake are mentioned in Table 2. Additional recommendations made by Endocrine society for special groups and deficiency correction are given in Table 3. The ICMR, 2009 report gives no suggestions for age-specific vitamin D intake, but mainly emphasizes on adequate exposure to sunlight.

[Note: 1mcg (40 IU)/day of Vitamin D_3 on a routine basis increases circulating 25-HCC by 1-4 nmol/L (0.4-1.6 ng/Ml]

Vitamin D linked disorders and the proposed therapeutic role of vitamin D are explained in Table 4**.**

CONCLUSION

Vitamin D deficiency is a common under-diagnosed condition that has recently been receiving increasing attention in the world. The US Endocrine Society and the IOM recommend screening only in populations who are at specific risk for vitamin D deficiency and patients of hypovitaminosis D. The observation that a multitude of genes may be directly or indirectly regulated by 1,25-HCC in a cell-specific fashion has provided a rationale for the non-skeletal health benefits of vitamin D. However, there remains skepticism due to lack of randomized controlled trials to support these benefits. Vigilance in maintaining a normal vitamin D status, i.e., serum 25-HCC concentration > 30ng/mL, should be a high priority for overall health and well-being. The effective strategy to prevent vitamin D deficiency as advocated by Expert committees is to obtain sensible exposure to sunlight by outdoor physical activity, ingest foods that contain vitamin D and take vitamin D supplements if necessary.

REFERENCES

1. Hossein-nezhad A, Holick MF. Vitamin D for health: A global perspective. *Mayo Clin Proc* 2013; 88:720–755. doi: 10.1016/j.mayocp.2013.05.011
2. Grant WB, Holick MF. Benefits and requirements of vitamin D for optimal health: a review". *Altern Med Rev* 2005; 10:94–111.
3. Martineau AR, Wilkinson R, Wilkinson K, Newton S, Kampmann B, Hall B, Packe G, Davidson R, Eldridge S, Maunsell Z, et al. A single dose of vitamin D enhances immunity to mycobacteria. *Am J Respir Crit Care Med* 2007; 176:208–13.
4. Burkiewicz CJ[1], Guadagnin FA, Skare TL, do Nascimento MM, Servin SC, de Souza GD. Vitamin D and skin repair: a prospective, double-blind and placebo controlled study in the healing of leg ulcers. *Rev Col Bras Cir* 2012; 39:401-7.
5. Bergman P, Norlin A-C, Hansen S, Björkhem-Bergman L. Vitamin D supplementation to patients with frequent respiratory tract infections: a post hoc analysis of a randomized and placebo-controlled trial. *BMC Research Notes* 2015; 8:391. doi:10.1186/s13104-015-1378-3
6. Ganmaa D et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. *Am J Clin Nutr* 2012;96:391-6. doi: 10.3945/ajcn.112.034967. Epub 2012 Jul 3
7. Lehouck A et al. High Doses of Vitamin D to Reduce Exacerbations in Chronic Obstructive Pulmonary Disease (COPD): A Randomized Trial, *Ann Intern Med* 2012; 156:105-14. doi: 10.7326/0003-4819-156-2-201201170-00004
8. Von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. *Br J Nutr* 2010; 103:549-552012
9. Grossmann RE et al. Pilot study of vitamin D supplementation in adults with cystic fibrosis pulmonary exacerbation: A randomized, controlled trial. *Dermatoendocrinol* 2012; 4:191-7. doi: 10.4161/derm.20332
10. Khoraminya N, Tehrani-Doost M, Jazayeri S, Hosseini A, Djazayery A. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. *Aust NZ J Psychiatry* 2013; 47:271-5. doi: 10.1177/0004867412465022. Epub 2012 Oct 23