Available Online at: www.ijrpp.com

Print ISSN: 2278 - 2648
Online ISSN: 2278 - 2656

International Journal of Research in Pharmacology and Pharmacotherapeutics

(Review article)

Lacto-D3, The sunshine Vitamin provides Vitamin D3 optimum Strength

***[1]Govind shukla, [2]Sharathkumar, [3]C.J Sampath kumar**
LACTONOVA INDIA, Habsiguda, Hyderabad, A.P, India.

ABSTRACT

Supplementation of cholecalciferol (vitaminD$_3$) significantly reduces all-cause mortality emphasizes the medical, ethical, and legal implications of promptly diagnosing and adequately treating VitamnD3 deficiency. Not only are such deficiencies common, and probably the rule, VitamnD$_3$ deficiency is implicated in most of the diseases of civilization. Vitamin D3's final metabolic product is a potent, pleiotropic, repair and maintenance, seco-steroid hormone that targets more than 200 human genes in a wide variety of tissues, meaning it has as many mechanisms of action as genes it targets. One of the most important genes VitamnD$_3$ up-regulates is for cathelicidin, a naturally occurring broad-spectrum antibiotic. Natural VitamnD$_3$ levels, those found in humans living in a sun-rich environment, are between 40-70 ng/mL, levels obtained by few modern humans. Assessing serum 25-hydroxy-VitamnD$_3$ (25(OH)D) is the only way to make the diagnosis and to assure treatment is adequate and safe. Three treatment modalities exist for VitaminD3 deficiency: sunlight, artificial ultraviolet B (UVB) radiation, and VitamnD$_3$ supplementation. Treatment of vitamin D deficiency in otherwise healthy patients with 2,000-7,000 IU VitamnD$_3$ per day should be sufficient to maintain year-round 25(OH)D levels between 40-70 ng/mL. In those with serious illnesses associated with VitamnD3 deficiency, such as cancer, heart disease, multiple sclerosis, diabetes, autism, and a host of other illnesses, doses should be sufficient to maintain year-round 25(OH)D levels between 55-70 ng/ mL. Vitamin D 3-deficient patients with serious illness should not only be supplemented more aggressively than the well, they should have more frequent monitoring of serum 25(OH) D and serum calcium. Vitamin D3 should always be adjuvant treatment in patients with serious illnesses and never replace standard treatment. Theoretically, pharmacological doses of VitamnD$_3$ (2,000 IU/kg/day for three days) may produce enough of the naturally occurring antibiotic cathelicidin to cure common viral respiratory infections, such as influenza and the common cold, but such a theory awaits further science. The present paper Reviews the role of VitamnD$_3$ in preventing different human disorders.

Keywords: lactoD3, VitaminD3, VitaminD$_3$ deficiency, VitaminD$_3$ metabolism

INTRODUCTION

A recent meta-analysis of 18 randomized controlled trials (RCT) found that cholecalciferol (VitamnD$_3$) significantly reduced total mortality.1. This discovery is all the more remarkable because of the relatively low doses of VitamnD$_3$ used (mean dose 528 IU (13 mcg)) and because the finding persisted across a number of subgroup analyses. In spite of the low doses used and the short duration of the trials, VitamnD$_3$'s mortality reduction was seven percent.2. Indeed, the recent discovery that statins significantly increase 25-hydroxy-VitamnD3$_3$ (25(OH) D) levels raise the possibility that some – or all – of the mortality reduction of statins may be mediated through increases in VitamnD$_3$ levels. [3,4] Lappe et al recently reported the first RCT of VitamnD3 in preventing internal cancers and found a 60-percent reduction in such cancers by increasing baseline

*** Corresponding author:**
Govind Shukla,
Asst. Product Manager
LACTONOVA INDIA (Makers of LactoD3)
2-25/1 street no.3, Kakathiya nagar, (Above Mahesh Bank)
Habsiguda, Hyderabad
A.P. India
E-mail address: info@lactonova.com

25(OH)D levels from 29 ng/mL to 38 ng/mL with 1,100 IU (28 mcg) per day.5. Baseline and treatment induced serum 25(OH)D levels were strong and independent predictors of cancer risk. Lappe et al's study left open the possibility that higher doses and higher treatment-induced 25(OH)D levels might prevent even more cancers. (Note that 25(OH) D levels are reported in the literature as either ng/mL or nmol/L; 1.0 ng/mL equals 2.5 nmol/L.) Besides cancer, VitamnD_3 deficiency is associated with cardiovascular disease, hypertension, stroke, diabetes, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, osteoporosis, periodontal disease, macular degeneration, mental illness, propensity to fall, and chronic pain.6-10.

A recent review presented considerable evidence that influenza epidemics, and perhaps even the common cold, are brought on by seasonal deficiencies in antimicrobial peptides (AMP), such as cathelicidin, secondary to seasonal deficiencies in VitamnD3.11. Results of an RCT support the theory, finding 2,000 IU of VitamnD_3/day for one year virtually eliminated self-reported incidence of colds and influenza [12]Even the current triple childhood epidemics of autism13, asthma, [14] and type 1 diabetes, [15] all of which blossomed after sun-avoidance advice became widespread, might be the tragic and iatrogenic sequela of gestational or early-childhood VitamnD3 deficiencies brought on by medical advice to avoid the sun. Claims that VitamnD_3 may help prevent such a wide variety of diseases seem incredible until one realizes VitamnD_3 is not a vitamin; rather, it is the only known substrate for a potent, pleiotropic, repair and maintenance, seco-steroid hormone with a single endocrine function, but multiple autocrine functions. Previously, many practitioners thought VitamnD_3's activity was principally its endocrine function – the regulation of serum calcium – and was thus mainly involved in bone metabolism. Indeed, the classic endocrine function of VitamnD_3 begins when the kidney hydroxylates 25(OH)D into 1,25(OH) D, which then acts, both directly and indirectly, to maintain serum calcium. However, in the last ten years, it has become clear the VitamnD_3 steroid hormone system includes more than the classic endocrine pathway used to preserve calcium economy.16. The enzyme that further hydroxylates 25(OH)D to 1,25(OH)2D (activated VitamnD3, the steroid hormone) is present in a wide variety of human tissues other than kidney. 1,25(OH)2 D is autonomously made in tissues and directly affects numerous cells via its autocrine, and presumed paracrine, functions. [17]

VitaminD3 hormones, 1,25(OH)2 D acts as a molecular switch, activating more than 200 target genes, thereby regulating gene expression. Thus, locally produced 1, 25(OH) 2 D exists in most tissues of the body, is under autonomous autocrine control, and has as many mechanisms of action as genes it targets. This explains why the same substance may have a role in preventing cancer, influenza, autism, asthma, multiple sclerosis, and cardiovascular disease, not just curing rickets and osteomalacia. Such claims leave practitioners with understandable skepticism and multiple questions. Is VitamnD_3 a cure-all? When should I recommend VitamnD_3? How much should I prescribe? What form of VitamnD3 should I use? How much did children need? How much did pregnant or breastfeeding women need? Is it appropriate to use higher doses of VitamnD_3 as adjuvant treatment for any of the above diseases? How do I interpret VitamnD3 blood tests and which tests should I order? What is the risk of toxicity? Another way to ask many of these questions is, "What is an ideal 25(OH)D level?" Levels needed to optimize intestinal calcium absorption (34 ng/mL)[19] are lower than those needed to optimize neuromuscular performance (38 ng/mL).[20] Recent pooled meta-analyses estimate 25(OH)D levels of 52 ng/mL are needed to effect a 50-percent reduction in the incidence of breast cancer.21. Although some experts believe the lower limit of adequate 25(OH)D levels is in the low 30s, [22,23] others recommend a lower limit of 40 ng/mL;[24,25] 24,25 24,25 there is certainly no scientific consensus. Ideal levels are unknown but are probably close to levels present when the human genome evolved in sub-equatorial Africa. Natural levels, such as those found at the end of summer in 30 young men who spent the summer working outdoors, were around 50 ng/mL;[26] 26, 26, however, these levels are obtained by only a small fraction of people. [27,] Furthermore, despite such summertime levels, at the end of winter 25(OH)D levels in 50 percent of these men dropped to less than 30 ng/mL, indicating a sun-induced level of 50 ng/mL at the end of summer is inadequate to maintain such a level during wintertime.

Another way to ask the "ideal 25(OH) D" question involves understanding VitamnD3's unique pharmacokinetics. Unlike any other steroid hormone system, the substrate concentrations for the liver production of 25(OH)D is absolutely rate limiting. This means the liver enzymes that initially hydroxylate VitamnD3 to form 25(OH)D and the enzyme in tissue that generates 1,25(OH)2 D operates below their Michaelis-Menten constants throughout the full range of modern human substrate concentrations; i.e., the reactions follow first order mass action kinetics.28. The more quantity of VitamnD3 that is ingested, the more quantity is converted into 25(OH) D, and the more is converted into 1,25(OH) 2 D in the tissues. The reaction appears to be uncontrolled; an aberrant, totally unique, and potentially dangerous situation for a steroid hormone system. Imagine, for example, if cortisol, testosterone, progesterone, or estradiol levels were entirely dependent on the intake of their substrate, cholesterol. Hollis et al recently explained this conundrum and concluded very few humans obtain enough VitamnD3 even if they take several thousand units per day.29. Hollis et al studied the pharmacokinetics of the parent compound, VitamnD3, and its first metabolic product, 25(OH)D, in two groups; Hawaiians with significant sun

exposure and lactating women receiving 6,400 IU of supplemental VitamnD3 per day. They found 25(OH)D levels had to exceed a minimum of 40 ng/mL, and often 50 ng/mL, to begin to detect the parent compound in the blood and begin to normalize the kinetics of 25(OH)D production. In other words, when 25(OH)D levels > 40 ng/mL were achieved, the parent compound began to be detectable in the blood, the reactions became saturable and controlled (like other steroid hormone systems), and thus levels above 40 ng/mL appear to represent the lower limit of "normal" 25(OH)D levels. This implies virtually everyone has a chronic 25(OH)D substrate deficiency, at least in the winter, and the absence of the parent $VitamnD_3$ compound (cholecalciferol) in the blood means all available vitamin D is used for metabolic needs, and none of it is stored. Because of this, most individuals have chronic substrate starvation, functional $VitamnD_3$ deficiency, and thus, perhaps, higher risk for the "diseases of civilization." The ideal 25(OH) D level continues to be debated in scientific circles, and consensus awaits further science. However, do we wait for science to complete its work with highly seasonal 25(OH)D levels that reflect sunlight deprivation, levels where $VitamnD_3$ steroid pharmacokinetics is aberrant, or is it safer to wait with levels normally achieved by humans in a sun rich environment, levels where $VitamnD_3$'s kinetics are normalized (>40 ng/mL)? Once a practitioner is comfortable with ideal 25(OH) D levels being above 40 ng/mL, the answers to the questions posed above become fairly simple. Healthy humans should be supplemented with enough vitamin D3 or exposed to enough ultraviolet B (UVB) radiation to achieve natural 25(OH) D levels (40-70 ng/mL) year-round, whether they are infants, children, pregnant women, lactating women, healthy young adults, or the elderly. What role $VitamnD_3$ has in treating – rather than preventing – disease is largely unknown, but given $VitamnD_3$'s genetic mechanism of action, it may have a significant role. For example, $VitamnD_3$ reduces cellular proliferation, induces differentiation, induces apoptosis, and prevents angioneogenesis, each a laudable goal in cancer treatment. A simple risk-versus-benefit analysis suggests patients with a potentially fatal cancer. It is wise to maintain 25(OH) D levels in the high end of natural ranges (55-70 ng/mL), ranges that assure $VitamnD_3$'s kinetics are normalized. While the RCTs needed to clarify $VitamnD_3$'s role in the treatment of disease are being conducted, a strong case already exists for adequately diagnosing and aggressively treating VitamnD3 deficiency.22, 25, and 30.

Incidence of Vitamin D3 Deficiency

Adult Vitamin D3 deficiency is the rule rather than the exception in industrialized nations. [31-33] High numbers of otherwise healthy children and adolescents are also VitamnD3 deficient. [34,35] Rickets, a disease of the industrial revolution, is being diagnosed more frequently, [36] especially in breast-fed infants. [37] Alarmingly, given mounting animal data that gestational $VitamnD_3$ deficiency causes subtle but irreversible brain damage in mammalian offspring, [38, 39] severe deficiencies are common in newborn infants and pregnant women, especially African-Americans. [40] A population-based study of 2,972 U.S. women of childbearing age found 42 percent of African-American women had 25(OH) D levels below 15 ng/mL, and 12 percent had levels below 10 ng/mL. [41] Furthermore, the definition of VitamnD3 deficiency changes almost yearly as research shows the low end of ideal 25(OH)D ranges are higher than were previously thought. The aforementioned prevalence studies used outdated reference values for low-end 25(OH) D ranges and therefore, underestimate the incidence of VitamnD3 deficiency. Obviously, the higher the low end of the 25(OH)D cutoff point, the higher the percentage of the population defined as deficient. Only 10 percent of the subjects in any of the above studies had 25(OH) D levels > 40 ng/mL.

Vitamin D3 Metabolism and Physiology

Perhaps because the term "Vitamin D3" contains the word "vitamin," most people wrongly assume they can obtain adequate amounts by eating a healthy diet. The natural diets most humans consume, however, contain minimal $VitamnD_3$, unless those diets are rich in wild-caught fatty fish, sun-dried Shitake mushrooms, or wild reindeer meat. Small amounts of $VitamnD_3$ are contained in fortified foods, such as fortified milk, some orange juices, and cereals, but such sources are minor contributors to $VitamnD_3$ stores. Traditionally, the human $VitamnD_3$ system began in the skin, not in the mouth. Vitamin D3 normally enters the circulation after UVB from sunlight strikes 7-dehydro-cholesterol in the skin, converting it to Vitamin D3 or cholecalciferol (VitamnD3). When taken by mouth, the body metabolizes VitamnD3 similarly to that generated in the skin. No matter how it arrives in the circulation, the liver readily hydroxylates Vitamin D3 to 25(OH) D, the circulating form of $VitamnD_3$. Hundreds of tissues in the body use 25(OH)D as a substrate to make the end-product, 1,25(OH) 2 D, known as activated $VitamnD_3$, a pleiotropic seco-steroid. If enough 25(OH)D substrate is available, multiple tissues are free to autonomously produce and locally regulate the amount of steroids needed for any particular disease state. The skin's manufacture of VitamnD3 is extraordinarily rapid and remarkably robust; production after only a few minutes of sunlight easily exceeds dietary sources by an order of magnitude. Incidental sun exposure, not dietary intake, is the principal source of VitamnD3 stores and is a function of skin surface area exposed. [42,43]. For example, when fair-skinned people sunbathe in the summer (one, full-body, minimal erythemal dose of UVB), they produce about 20,000 IU of $VitamnD_3$ in 30 minutes, 44 the equivalent of drinking 200 glasses of milk (100 IU/8 oz. glass) or

taking 50 standard multivitamins (400 IU/tablet) to obtain the same amount orally. The fact that 20,000 IU VitamnD3 can be produced in the skin in 30 minutes of sun exposure, combined with VitamnD_3's basic genomic mechanism of action, raises profound questions. Why did nature develop a system that delivers huge quantities of a steroid precursor after only brief periods of sun exposure? Would natural selection evolve such a system if the remarkably high input that system achieved were unimportant? As humans evolved in a sun-rich environment (sub-equatorial Africa), is modern sunlight deprivation – and the resultant routinely low levels of this repair and-maintenance steroid in tissues – a possible common cause of the diseases of civilization?

Factors Affecting Vitamin D3 Levels

Factors that can affect UVB exposure, and thus the skin's production of VitamnD_3, include latitude, season of the year, time of day, air pollution, and cloud cover, melanin content of the skin, use of sunblock, age, and \the extent of clothing covering the body. When the sun is low on the horizon, ozone, clouds, and particulate air pollution deflects UVB radiation away from the earth's surface. Therefore, cutaneous VitamnD_3 production is effectively absent, early and late in the day and for the entire day during several wintertime months at latitudes above 35 degrees, and impaired anytime the skies are polluted or cloudy. Thus, VitamnD_3 deficiency is more common for the further pole ward the population. For example, Boston, Massachusetts (latitude 42 degrees), has a four month "VitamnD_3 winter" centered around the winter solstice, when insufficient UVB penetrates the atmosphere to trigger skin production. This becomes an even longer period when the fall and late winter months are included, when sufficient UVB only penetrates around solar noon. In northern Europe and Canada, the "VitamnD3 winter" can extend for six months. Furthermore, properly applied sunblock, common window glass in homes and cars, and clothing all effectively block UVB radiation – even in the summer. Those who avoid sunlight – at any latitude – are at risk of VitamnD3 deficiency any time of the year. For example, a surprisingly high incidence of VitamnD3 deficiency exists in Miami, Florida, despite its sunny weather and subtropical latitude. [45] African-Americans, the elderly, and the obese face added risk. Because melanin in the skin acts as an effective and ever-present sunscreen, dark-skinned people need much longer UVB exposure times to generate the same 25(OH)D stores as fair-skinned individuals. [46] The elderly make much less VitamnD3 than 20-year olds after exposure to the same amount of sunlight.[47] Body fat absorbs VitamnD3, thus obesity is a major risk factor for deficiency, with obese African-Americans at an even higher risk.[48] Anyone who works indoors, lives at higher latitudes, wears excessive clothing, regularly uses sun block, is dark-skinned, obese, aged, or who consciously avoids the sun is at high risk for VitaminD3 deficiency.

Diagnosis of Vitamin D3 Deficiency

In the absence of a metabolic bone disease such as rickets, osteomalacia, or osteoporosis, most practitioners assume Vitamin D3 deficiency is asymptomatic, although that may be changing. Complaints endemic to every practitioner's office, such as muscular weakness, a feeling of heaviness in the legs, chronic musculoskeletal pain, fatigue, or easy tiring may be symptoms of vitamin D deficiency. [49]

Such complaints are extremely common, difficult to treat, and easy to dismiss, but they may indicate symptomatic VitamnD3 deficiency. Physical examination is usually unremarkable but may reveal undue pain on sternal or tibial pressure if deficiency is severe. The vast majority of cases appears normal on the exam, although frequent infections, autoimmune illness, diabetes, cancer, heart disease, major depression, and a host of other "diseases of civilization" may be warning signs that deficiency has been present for many years. [22, 25]

The aged may be wheelchair-bound secondary to Vitamin D3 deficiency-induced myopathy, yet they typically recover mobility after treatment.[50] The recent strong association of low mood and cognitive impairment in the aged with VitamnD3 deficiency [51] suggests depressed mood and/or impaired cognition may be presenting symptoms. A blinded intervention trial found 4,000 IU VitamnD3 per day improved the mood of endocrinology outpatients, [52] but there is no interventional study of its effects on cognition. Even without physical signs or symptoms, the physician should screen those at risk. Obtaining and properly interpreting a serum 25(OH)D level is the only way to make the diagnosis. A 25(OH)D level should be obtained at least twice yearly on any patient at risk, once in the early spring for the nadir and once in the late summer for a peak level. [53] We recommend 25(OH) D levels be kept above 40 ng/mL year round.

It is crucial to remember that serum 1,25(OH) 2 D levels play no role in diagnosing VitamnD_3 deficiency. The kidney tightly controls serum 1, 25(OH) 2 D levels, which are often normal or even elevated in VitamnD3 deficiency. Therefore, a patient with normal or high 1, 25(OH) 2 D serum levels but low 25(OH) D levels is VitamnD_3 deficient despite high serum levels of the active hormone. Practitioners who rely on serum 1, 25(OH) 2 D levels to make the diagnosis of VitamnD3 deficiency will routinely miss it. [25]

Treatment of Vitamin D3 Deficiency

Three options exist for treatment of VitamnD3 deficiency: sunlight, artificial UVB light, and Vitamin D3 supplements. An exposure of 10-15 minutes of full body summer noon-day sun or artificial UVB radiation (such as tanning beds) will input more than 10,000 IU of VitamnD_3 into the systemic circulation of most light skinned adults. One or two such exposures per week should maintain 25(OH) D levels in an ideal range, but adequacy should be assured by

25(OH) D blood levels. Those who choose UVB light for VitamnD_3 repletion, from either sunlight or artificial sources, should avoid sunburn, which is associated with malignant melanoma. Furthermore, they should understand that regular UV exposure ages the skin and increases the risk of nonmelanoma skin cancers. The treatment of choice for VitamnD_3 deficiency is VitamnD_3, cholecalciferol, also known as VitamnD3. Oral VitamnD_3 treatment is more challenging than treatment with UVB light for several reasons. First, unexpectedly high doses of VitamnD_3 are usually needed to achieve adequate serum 25(OH)D levels. One of the problems with VitamnD_3 terminology is the archaic method used to express does, international units or IU. One thousand IU of VitamnD_3 sounds like a lot; in fact, it is only .025 mg or 25 micrograms; i.e., one mcg is 40 IU. Second, the amount of VitamnD_3 needed varies with body weight, body fat, age, skin color, season, latitude, and sunning habits. Third, unlike sun exposure, toxicity is possible with oral supplementation – although it is extraordinarily rare. Cholecalciferol is available over-the-counter and via the Internet in 400, 1,000, 2,000 and (recently) 5,000, 10,000, and 50,000 IU capsules. Supplementation with 1,000 IU per day will usually result in about a 10-ng/mL elevation of serum 25(OH)D when given over 3-4 months. Therefore, a normal weight, healthy adult with an initial level of 10 ng/mL would generally require about 2,000 IU per day to achieve a level of 30 ng/mL in the absence of cutaneous UVB exposure. However, its kinetics are not linear; 1,000 IU per day will substantially raise low baseline levels, but a similar dose will not increase higher baseline levels by a similar increment (that is, 2,000 IU per day may not raise 30 ng/mL to 50 ng/mL). In the absence of significant UVB exposure, input from diet and supplements of approximately 1,000 IU (25 mcg) per day for every 15 kgs of body weight may be needed; i.e., an obese 150-kg adult may require up to 10,000 IU per day to achieve a 25(OH)D level of 50 ng/mL. Patients with serious diseases may need more if the metabolic clearance of 25(OH)D is increased.

Grey at al treated 21 Vitamin D3-deficient patients with 50,000 IU cholecalciferol weekly for four weeks, then 50,000 IU monthly for one year. [57] Blood levels rose from a mean of 11 ng/ mL at baseline to 30 ng/mL at six months and to 31 ng/ mL at one year, indicating monthly doses of 50,000 IU of VitamnD_3 do not achieve natural 25(OH)D levels, and such levels do not continue to rise after six months of such treatment. If such intermittent high doses of cholecalciferol are used, maintenance requirements are probably 50,000 IU every 1-2 weeks in most adults, although such supplementation studies have not been done.

Cod liver oil contains a variable amount of VitamnD_3, but usually contains high amounts of vitamin A. Consumption of pre-formed retinols, even in amounts consumed in multivitamins, may be causing low-grade, but widespread, bone toxicity. [58]

Vitamin A antagonizes the action of VitaminD3, [59] and high retinol intake thwarts VitamnD_3's protective effect on distal colorectal adenoma.[60] The authors do not recommend cod liver oil. Neither the regular consumption of officially recommended amounts of VitamnD3 (e.g., 400 IU in a multivitamin), nor the regular consumption of vitamin D fortified foods (e.g., 100 IU per 8 oz. glass of milk), effectively prevent VitamnD3 deficiency. [61,62] Furthermore, 2,000 IU/day for one year failed to achieve a 32 ng/mL target 25(OH)D concentration in 40 percent of 104 African-American women studied. [63] The administration of 4,000 IU/day for more than six months to middle-age Canadian endocrinology outpatients resulted in average 25(OH) D levels of 44 ng/mL and produced no side effects other than improved mood. [52] Heaney estimates 3,000 IU/day is required to assure that 97 percent of Americans obtain levels greater than 35 ng/mL. [23] Healthy adult men utilize up to 5,000 IU of VitamnD_3 per day, if it is available. [64]. In general, the more a patient weighs, the more VitamnD3 will be required and large amounts of body fat further increase requirements. Not only are baseline 25(OH)D levels lower in the obese, the obese require higher doses of oral supplements or UV radiation than lean individuals in order to obtain the same increases in 25(OH)D blood levels.[65] Fat malabsorption syndromes may increase oral requirements or necessitate the use of ultraviolet radiation. Advancing age impairs the skin's ability to make VitamnD_3, so older persons generally need higher supplemental doses than younger ones. Therefore, dark-skinned, large, obese, or older patients often require higher maintenance doses than fair skinned, small, thin, or younger ones. Loading doses of 50,000 IU (1.25 mg) of cholecalciferol per day for a week, or at the most two, are safe to use before beginning maintenance therapy. Cytochrome P-450 enzymes are responsible for both the initial metabolism and subsequent catabolism of VitamnD3. Therefore, drugs dependent on cytochrome P-450 enzymes – and there are many – may affect VitamnD3 metabolism. What clinically relevant interactions these substances – including cardiac drugs, erythromycins, psychotropics, and even grapefruit juice – have on the metabolism of VitamnD3 is an area awaiting further research. Of the research done on drug/VitamnD3 interactions, anticonvulsants, corticosteroids, cimetidine, anti-tuberculosis agents, theophylline, and orlistat may lower 25(OH) D levels, while thiazide diuretics and statins increase 25(OH)D levels. [66, 67]. Patients on medications of any kind should have frequent testing of 25(OH) D levels when being treated with doses above 2,000 IU per day.

VitamnD_3 deficiency in pregnancy is an ongoing epidemic, [68] and animal evidence continues to accumulate that maternal VitamnD_3 deficiency permanently injures fetal brains. [38,39,69] Pregnant women – or women thinking of becoming pregnant – should have 25(OH)D levels checked every three months and be adequately treated, often with 5,000 IU or more per day, as outlined above. [70] Lactating

women require even more, up to 7,000 IU per day, to ensure breast milk is a rich source of VitamnD_3. [71] Infants being breast fed by supplementing mothers will not require additional supplementation, but will require adequate supplementation during and after weaning.

Treatment of Disease By far the most common reason to treat with VitamnD3 is osteoporosis, but the dose needed remains controversial because the lowest effective dose (800 IU/ day) is known, but the ideal dose is not. [72]

Currently, virtually all the evidence that VitamnD_3 is an effective adjuvant for the treatment of other serious medical conditions is anecdotal, implied by epidemiological studies, from open trials, or inferred from VitamnD_3's mechanism of action. For example, there is an anecdotal report that pharmacological doses of VitamnD_3 are effective in treating – not just preventing – viral respiratory infections. [73]
Doses of 2,000 IU/kg body weight for three days (200,000 IU per day for three days for a 100-kg adult) may seem excessive to those unfamiliar with VitamnD_3's pharmacology and toxicity. In fact, such doses are common in many parts of the world simply to prevent or treat VitamnD3 deficiency. For example, single injections of 600,000 IU (15 mg) VitamnD3 raised 25(OH)D levels from 2 ng/ mL to 22 ng/mL at two weeks and to 27 ng/mL at six weeks in 10 elderly subjects, with no evidence of toxicity. [74]
Indeed, a single injection of 600,000 IU of VitamnD_3 is not only safe; such doses were recently recommended in the autumn for the elderly, simply to prevent wintertime VitamnD_3 deficiency. [75] Likewise, there was no evidence of toxicity in young men taking 50,000 IU of VitamnD_3 per day for six weeks (although such a dose would become toxic if taken over a longer period). [76]

In 32 severely VitamnD3-deficient elderly patients, 50,000 IU/day for 10 days showed no evidence of toxicity and only raised 25(OH)D levels by an average of 5 ng/mL three months after administration. In no patient did levels increase more than 11 ng/mL at three months. [77]

Treatment of colds and influenza with pharmacological doses of VitamnD3 may only be the tip of the infectious disease iceberg. As Aloia and Li-Ng have pointed out, 12 it is intriguing that VitamnD3-sensitive antimicrobial peptides (AMP) inhibit the HIV virus there is evidence that VitamnD3 plays a role in HIV. [78] Invasive pneumococcal disease, meningococcal disease, and group A streptococcal disease are more common when VitamnD_3 levels are lowest (winter)[79-81] and all three bacteria are sensitive to AMP, [82-84] raising the possibility that pharmacological doses of vitamin D would be an effective adjuvant treatment. In fact, the dramatically increased production of AMPs by vitamin D and the broad spectrum of action of AMP make it reasonable to hypothesize that pharmacological doses of VitamnD_3 are effective adjuvants in treating a large number of infections. In a recent report, 12 patients in active phases of multiple sclerosis were treated with progressively increasing weekly doses of VitamnD_{33} (the equivalent of starting with 4,000 IU per day and increasing to 40,000 IU per day) and calcium. [85] Mean serum concentrations of 25(OH) D initially was 31ng/mL and rose to a mean of 154 ng/mL at the end of 28 weeks, with no abnormalities in serum or urine calcium detected in the 12 subjects. The number of MS lesions per patient on brain scans decreased from an initial mean of 1.75 at the beginning to a mean of 0.83 (p=0.03) at the end of the study. However, doses of 40,000 IU per day may cause toxicity if given for longer periods; certainly, such doses flirt with toxicity. Doses of 10,000 IU per day may well have achieved the same result without the risk of toxicity. Both epidemiological evidence and VitamnD_3's mechanism of action suggest it may have a treatment effect in early cancer. For example, a study of recurrence free survival in early-stage, non-small-cell lung cancer patients found those with the highest VitamnD_3 input had double the five-year recurrence-free survival and much better overall survival than those with the lowest. [86] This strongly implies a VitamnD_3 treatment effect, i.e., untreated VitamnD_3 deficiency in non-small-cell lung cancer patients is a risk factor for early death. Season of diagnosis has a survival effect on numerous cancers; i.e., cancer patients live longer if the diagnosis is made in the summer rather than the winter. [87, 88] Although no one has proven VitamnD_3 causes this summer-season treatment effect, Vitamin D3's anticancer mechanism of action is basic to all cancers. Thus, it is reasonable to hypothesize a general cancer treatment effect, at least in cancer's early stages, when aberrant cells are more likely to retain both the VitamnD_3 receptor, and the enzyme needed to activate VitamnD_3. Treatment of type-2 diabetic or hypertensive patients with physiological doses of VitamnD_3 should be prepared for the possibility of either hypoglycemia or hypotension, especially after several months of treatment. Theoretically, such doses of VitamnD_3 should eventually lower both blood sugar and blood pressure, although blood sugars may worsen for several weeks after initiation or increase of VitamnD_3. Should either hypoglycemia or hypotension occur, the diabetic and/or hypertensive medication should be lowered, not the VitamnD_3. Although modern science knows little or nothing about the metabolic clearance of VitamnD_3 in different disease states, it is reasonable to predict that vitamin D is cleared more rapidly in some disease states. For example, patients with diabetes, HIV, or cancer may rapidly use 25(OH) D as a substrate to make large amounts of 1, 25(OH) 2 D to fight their disease. Therefore, a patient with cancer may require significantly higher doses of VitamnD_3 to maintain 25(OH) D levels of 55-70 ng/ mL than a healthy adult of similar weight and body fat. Such patients should be supplemented (assuming they are not hypercalcemic) to high natural levels, even if it means taking 10,000 IU or more per day. Frequent

monitoring of 25(OH) D and calcium levels should guide dosing in patients with cancer and other serious illnesses, and such treatment should be adjunctive and never take the place of standard treatment.

Recent studies show a high incidence of VitamnD3 deficiency in patients undergoing treatment for cancer. [89] Even at the end of summer, 48 percent of cancer patients in Boston had levels less than 20 ng/mL. [89]. In another study, 72 percent of 60 cancer patients had 25(OH) D levels less than 30 ng/mL, and virtually none had natural levels. [90]

Vitamin D3 Toxicity

Vitamin D3 toxicity is exceedingly rare toxicity is secondary to the unbridled effects of hypercalcemia. In chronic toxicity, first urine calcium and then serum calcium will begin to gradually increase when 25(OH) D levels exceed some level above 150 ng/mL. Such levels must be associated with hypercalcemia in order to indict VitamnD_3. Chronic VitamnD_3 toxicity results when hypercalcemia goes undetected and calcifies internal organs, especially the kidneys. In order to produce hypercalcemia, most adults would have to take in excess of 10,000 IU per day for many months or even years. Most patients with VitamnD_3 toxicity recover fully by simply stopping the VitamnD_3 and practicing strict sun-avoidance. Credible evidence of VitamnD_3 toxicity in those chronically consuming 10,000 IU of supplemental cholecalciferol daily is absent in the literature. In fact, the literature contains few cases of cholecalciferol toxicity from supplement use; virtually, all the reported cases of hypercalcemia are from faulty industrial production, labeling errors, dosing errors, and patients treated medically with pharmacological doses of ergocalciferol. The current Adequate Intakes and Upper Limits are for medically unsupervised intake by adults and children, set by the Institute of Medicine's Food and Nutrition Board (FNB) in 1997, and do not apply to medically supervised treatment. Surprisingly, the FNB says Adequate Intake is the same 200 IU/day for the smallest infant as it is for the largest pregnant woman. Likewise, the FNB's Upper Limit for both one-year-old children and forty-year-old adults is 2,000 IU/day, a limit based on old and faulty literature. [93]

The only absolute contraindication to Vitamin D3 supplementation is VitamnD_3 toxicity or allergy to VitamnD_3, although no reports in the literature were found of acute allergic reactions to VitamnD_3 supplements. Contraindications to sunlight or artificial UV radiation include a number of dermatological conditions (porphyrias, xeroderma pigmentosum, albinism), as well as various photosensitizers (sulfonamides, phenothiazines, tetracyclines, psoralens). Previous skin cancers, especially cutaneous melanoma, are contraindications to excessive UV exposure, although a recent study found reduced mortality in melanoma patients who continued exposure to sunlight. [94]

Nevertheless, oral treatment is recommended for patients who have had any type of skin cancer. Although the liver initially metabolizes vitamin D, liver disease is not a contraindication to treatment of deficiency. The liver conserves the ability to hydroxylate VitamnD3 despite advanced liver disease. [95]

A recent study of patients with advanced noncholestatic chronic liver disease recommended treatment of concomitant VitamnD3 deficiency after finding serum 25(OH)D levels of less than 10 ng/mL predicted coagulopathy, hyperbilirubinemia, hypoalbuminemia, anemia, and thrombocytopenia.[96] VitamnD3 hypersensitivity syndromes – often confused with VitamnD3 toxicity – occur when extrarenal tissues produce 1,25(OH) 2 D in an unregulated manner, causing hypercalcemia. [97] These syndromes are diagnosed by measuring serum calcium (elevated), 25(OH) D (normal or low), and 1, 25(OH) 2D (elevated). VitamnD3 hypersensitivity syndromes can occur in some of the granulomatous diseases (especially sarcoidosis and tuberculosis), and in some cancers (especially non-Hodgkin's lymphoma and oat cell carcinoma of the lung). Such conditions may be unmasked by VitamnD3 treatment; for example, sarcoidosis may become clinically evident after summer sun exposure. Therefore, hypercalcemia is a relative contraindication to VitamnD3, sunlight, and artificial UVB radiation.

Pharmacodynamic properties

Strong evidence that supplemental calcium and VitamnD_3 can reduce the incidence of hip, and other non-vertebral fractures derives from an 18 month randomised placebo controlled study in 3270 healthy elderly women living in nursing homes or apartments for elderly people. A positive effect on bone mineral density was also observed.

In patients treated with 1200mg elemental calcium and 800IU VitamnD_3 daily, i.e. the same dose delivered by two tablets of Vitamin-D_3, the number of hip fractures was 43% lower (p=0.043) and the total number of non vertebral fracture was 32% lower than among those who received placebo. Proximal femur bone mineral density after 18 months of treatment increased 2.7% in the calcium/Vitamn$D3_3$ group and decreased 4.6% in the placebo group ($p < 0.001$). In the calcium/Vitamn$D3_3$ group, the mean serum PTH concentration decreased by 44% from baseline at 18 months and serum 25-hydroxy-VitamnD_3 concentration had increased by 162% over baseline.

Analysis of the intention-to-treat results showed a decreased probability of both hip fractures (p =

0.004) and other fractures ($p < 0.001$) in the calcium/VitamnD_3 treatment group. Analysis of the other two populations (active treatment and those treated and followed for 18 months) revealed comparable results to the intention-to-treat analysis. The odds ratio for hip fractures among women in the placebo group compared with those in the calcium/VitamnD_3 group was 1.7 (95% CI 1.0 to 2.8) and that for other non vertebral fractures was 1.4 (95% CI 1.4 to 2.1). In the placebo group, there was a marked increase in the incidence of hip fractures over time whereas the incidence in the calcium/Vitamn$D3_3$ group was stable. Thus, treatment reduced the age-related risk of fracture at 18 months ($p = 0.007$ for hip fractures and $p = 0.009$ for all non-vertebral fractures). At 3-years follow-up, the decrease in fracture risk was maintained in the calcium/VitamnD_3 group.

Pharmacokinetic properties

Vitamin D3 is absorbed in the small intestine and bound to specific alpha globulins, and is transported to the liver where it is metabolised into 25-hydroxy-cholecalciferol. A second hydroxylation to 1,25-dihydroxy-cholecalciferol takes place in the kidneys. This metabolite is responsible for the effect of VitamnD_3, i.e. increase of calcium absorption. Non-metabolised VitamnD_3 is stored in tissues, e.g. in fat and muscle. Vitamin D3 is excreted by the faeces.

Contra-indications:

The product is contraindicated in patients with a Histroy of Hypersenstivity to any of its ingredients.

The following medications increase the metabolism of VitamnD3 and may decrease serum D levels:

Phenytoin (Dilantin), fosphenytoin (Cerebyx), phenobarbital (Luminal), carbamazepine (Tegretol), and rifampin (Rimactane).

The following medications should not be taken at the same time as VitamnD3 because they can decrease the intestinal absorption of Vitamin D3:

Cholestyramine (Questran), colestipol (Colestid), orlistat (Xenical), mineral oil, and the fat substitute Olestra. The oral anti-fungal medication, ketoconazole, inhibits the 25(OH)D3-1-hydroxylase enzyme and has been found to reduce serum levels of 1,25(OH)D in healthy men. The induction of hypercalcemia by toxic levels of VitamnD3 may precipitate cardiac arrhythmia in patients on digitalis (Digoxin)

Side Effects

During pregnancy and lactation treatment with Vitamin D3 should always be under the direction of a physician. During pregnancy and lactation, requirements for calcium and Vitamin D3 are increased but in deciding on the required supplementation allowances should be made for availability of these agents from other sources. If Vitamin D3 and iron supplements are both required to be administered to the patient, they should be taken at different times.

Overdoses of Vitamin D3 have shown teratogenic effects in pregnant animals. However, there have been no studies on the use of this medicinal product in human pregnancy and lactation. In humans, long term hypercalcaemia can lead to physical and mental retardation, aortic stenosis and retinopathy in a new born child. Vitamin D3 and its metabolites pass into the breast milk.

Acknowledgement

We thank our company Lactonova India for providing required support for completing this review work successfully. LACTONOVA INDIA, a Hyderabad based Indian multinational company founded in the year 2000, is a manufacturer and supplier of nutraceutical raw materials, ethical formulations, phytonutrients, cosmeceuticals, minerals and specialty fine (comes under under the sub-category of products) chemicals. A vertically integrated bio-technology based research, manufacturing and marketing company. Lactonova India has R&D tie-ups and two patent pending molecules and 20 product registrations in the CIS countries. The company has manufacturing facilities in Hyderabad and Himachal Pradesh to cater to its own product manufacturing and to other companies across the country. The company leads in the manufacturing and sales Lycopene and other carotenoids in the country and has the distinction of launching many new molecules for the first time in India.

REFERENCES

1. Autier P, Gandini S. VitamnD3 supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med 2007;167:1730-1737.
2. Studer M, Briel M, Leimenstoll B, et al. Effect of different antilipidemic agents and diets on mortality: a systematic review. Arch Intern Med 2005;165:725-730.
3. Perez-Castrillon JL, Vega G, Abad L, et al. Effects of Atorvastatin on VitamnD3 levels in patients with acute ischemic heart disease. Am J Cardiol 2007;99:903-905.
4. Aloia JF, Li-Ng M, Pollack S. Statins and VitamnD3. Am J Cardiol 2007;100:1329.
5. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk:

results of a randomized trial. Am J Clin Nutr 2007;85:1586-1591.
6. Holick MF. High prevalence of VitamnD3 inadequacy and implications for health. Mayo Clin Proc 2006;81:353-373.
7. Peterlik M, Cross HS. VitamnD3 and calcium deficits predispose for multiple chronic diseases. Eur J Clin Invest 2005;35:290-304.
8. Holick MF. Sunlight and VitamnD3 for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80:1678S-1688S.
9. Zittermann A. VitamnD3 in preventive medicine: are we ignoring the evidence? Br J Nutr 2003;89:552-572.
10. Peterlik M, Cross HS. Dysfunction of the vitamin D endocrine system as common cause for multiple
11. malignant and other chronic diseases. Anticancer Res 2006;26:2581-2588.
12. Cannell JJ, Vieth R, Umhau JC, et al. Epidemic influenza and VitamnD3. Epidemiol Infect 2006;134:1129-1140.
13. Aloia J, Li-Ng M. Re: epidemic influenza and vitamin D. Epidemiol Infect 2007;135:1095-1096; author reply 1097-1098.
14. Cannell JJ. Autism and VitamnD3. Med Hypotheses 2007; Oct 24 [Epub ahead of print]
15. Litonjua AA, Weiss ST. Is VitamnD3 deficiency to blame for the asthma epidemic? J Allergy Clin Immunol 2007; 120:1031-1035.
16. Hypponen E, Laara E, Reunanen A, et al. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 2001; 358:1500-1503.
17. Heaney RP. Long-latency deficiency disease: insights from calcium and VitamnD3. Am J Clin Nutr 2003;78:912-919.
18. Lips P. VitamnD3 physiology. Prog Biophys Mol Biol 2006;92:4-8.
19. Dusso AS, Brown AJ, Slatopolsky E. VitamnD3. Am J Physiol Renal Physiol 2005;289:F8-F28.
20. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyVitamnD3. J Am Coll Nutr 2003;22:142-146.
21. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. Higher 25-hydroxyVitamnD3 concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. Am J Clin Nutr 2004;80:752-758.
22. Garland CF, Gorham ED, Mohr SB, et al. VitamnD3 and prevention of breast cancer: pooled analysis. J Steroid Biochem Mol Biol 2007;103:708-711.
23. Holick MF. VitamnD3 deficiency. N Engl J Med 2007; 357:266-281.
24. Heaney RP. The VitamnD3 requirement in health and disease. J Steroid Biochem Mol Biol 2005;97:13-19.
25. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of
26. 25-hydroxy VitamnD3 for multiple health outcomes. Am J Clin Nutr 2006;84:18-28.
27. Cannell JJ, Hollis BW, Zasloff M, Heaney RP. Diagnosis and treatment of VitamnD3 deficiency. Expert Opin Pharmacother 2008;9:107-118.
28. Barger-Lux MJ, Heaney RP. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 2002;87:4952-4956.
29. Vieth R. What is the optimal VitamnD3 status for health? Prog Biophys Mol Biol 2006;92:26-32.
30. Vieth R. The pharmacology of VitamnD3, including fortification strategies. In: Feldman D, Pike JW, Glorieux FH, eds. VitamnD3. San Diego, CA: Elsevier; 2005:995-1015.
31. Hollis BW, Wagner CL, Drezner MK, Binkley NC. Circulating VitamnD33 and 25-hydroxyVitamnD3 in humans: an important tool to define adequate nutritional VitamnD3 status. J Steroid Biochem Mol Biol 2007; 103:631-634.
32. Heaney RP: The case for improving VitamnD3 status. J Steroid Biochem Mol Biol 2007;103:635-641.
33. Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of VitamnD3 insufficiency in an adult normal population. Osteoporos Int 1997;7:439-443.
34. Lamberg-Allardt CJ, Outila TA, Karkkainen MU, et al. VitamnD3 deficiency and bone health in healthy adults in Finland: could this be a concern in other parts of Europe? J Bone Miner Res 2001;16:2066-2073.
35. Rucker D, Allan JA, Fick GH, Hanley DA. VitamnD3 insufficiency in a population of healthy western Canadians. CMAJ 2002;166:1517-1524.
36. Roth DE, Martz P, Yeo R, et al. Are national VitamnD3 guidelines sufficient to maintain adequate blood levels in children? Can J Public Health 2005;96:443-449.
37. Gordon CM, DePeter KC, Feldman HA, et al. Prevalence of VitamnD3 deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004;158:531-537.
38. Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. Am J Clin Nutr 2004;80:1697S-1705S.
39. Ladhani S, Srinivasan L, Buchanan C, Allgrove J. Presentation of VitamnD3 deficiency. Arch Dis Child2004; 89:781-784.

40. Almeras L, Eyles D, Benech P, et al. Developmental vitamin D deficiency alters brain protein expression in the adult rat: implications for neuropsychiatric disorders. Proteomics 2007; 7:769-780.
41. Feron F, Burne TH, Brown J, et al. Developmental Vitamin D3 deficiency alters the adult rat brain. Brain Res Bull 2005;65:141-148.
42. Bodnar LM, Simhan HN, Powers RW, et al. High prevalence of VitamnD3 insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr 2007;137:447-452.
43. Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2002; 76:187-192.
44. Poskitt EM, Cole TJ, Lawson DE. Diet, sunlight, and 25-hydroxy VitamnD3 in healthy children and adults. Br Med J 1979;1:221-223.
45. Holick MF. Photosynthesis of VitamnD3 in the skin: effect of environmental and life-style variables. Fed Proc 1987;46:1876-1882.
46. Hollis BW. Circulating 25-hydroxyVitamnD3 levels indicative of VitamnD3 sufficiency: implications for establishing a new effective dietary intake recommendation for VitamnD3. J Nutr 2005;135:317-322.
47. Levis S, Gomez A, Jimenez C, et al. VitamnD3 deficiency and seasonal variation in an adult South Florida population. J Clin Endocrinol Metab 2005;90:1557-1562.
48. Willis CM, Laing EM, Hall DB, et al. A prospective analysis of plasma 25-hydroxyVitamnD3 concentrations in white and black prepubertal females in the southeastern United States. Am J Clin Nutr 2007;85:124-130.
49. Holick MF. McCollum Award Lecture, 1994: vitamin D – new horizons for the 21st century. Am J Clin Nutr 1994;60:619-630.
50. Yanoff LB, Parikh SJ, Spitalnik A, et al. The prevalence of hypovitaminosis D and secondary hyperparathyroidism in obese Black Americans. Clin Endocrinol (Oxf) 2006;64:523-529.
51. Erkal MZ, Wilde J, Bilgin Y, et al. High prevalence of VitamnD3 deficiency, secondary hyperparathyroidism and generalized bone pain in Turkish immigrants in Germany: identification of risk factors. Osteoporos Int 2006;17:1133-1140.
52. Gloth FM 3rd, Lindsay JM, Zelesnick LB, Greenough WB 3rd. Can VitamnD3 deficiency produce an unusual pain syndrome? Arch Intern Med 1991;151:1662-1664.
53. Wilkins CH, Sheline YI, Roe CM, et al. VitamnD3 deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry 2006;14:1032-1040.
54. Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the VitamnD33 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. Nutr J 2004;3:8.
55. Holick MF. The VitamnD3 epidemic and its health consequences. J Nutr 2005; 135:2739S-2748S.
56. Houghton LA Vieth R. The case against ergocalciferol (VitamnD32) as a vitamin supplement. Am J Clin Nutr 2006;84:694-697.
57. Trang HM, Cole DE, Rubin LA, et al. Evidence that VitamnD3 increases serum 25-hydroxy VitamnD3 More efficiently than does VitamnD32. Am J Clin Nutr 1998;68:854-858.
58. Armas LA, Hollis BW, Heaney RP. VitamnD32 is much less effective than VitamnD33 in humans. J Clin Endocrinol Metab 2004;89:5387-5391.
59. Grey A, Lucas J, Horne A, et al. VitamnD3 repletion in patients with primary hyperparathyroidism and coexistent VitamnD3 insufficiency. J Clin Endocrinol Metab 2005;90:2122-2126.
60. Penniston KL, Tanumihardjo SA. The acute and chronic toxic effects of vitamin A. Am J Clin Nutr 2006;83:191-201.
61. Rohde CM, DeLuca HF. All-trans retinoic acid antagonizes the action of calciferol and its active
62. metabolite, 1,25-dihydroxycholecalciferol, in rats. J Nutr 2005;135:1647-1652.
63. Oh K, Willett WC, Wu K, et al. Calcium and VitamnD3 intakes in relation to risk of distal colorectal adenoma in women. Am J Epidemiol 2007;165:1178-1186.
64. Vieth R, Cole DE, Hawker GA, et al. Wintertime vitamin D insufficiency is common in young Canadian women, and their VitamnD3 intake does not prevent it. Eur J Clin Nutr 2001; 55:1091-1097.
65. Brot C, Vestergaard P, Kolthoff N, et al. VitamnD3 status and its adequacy in healthy Danish perimenopausal women: relationships to dietary intake, sun exposure and serum parathyroid hormone. Br J Nutr 2001; 86:S97-S103.
66. Aloia JF, Talwar SA, Pollack S, Yeh J. A randomized controlled trial of VitamnD33 supplementation in African American women. Arch Intern Med 2005;165:1618-1623.
67. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol

response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003; 77:204-210.
68. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of VitamnD3 in obesity. Am J Clin Nutr 2000; 72:690-693.
69. Valsamis H, Arora SK, Labban B, McFarlane S. Antiepileptic drugs and bone metabolism. Nutr Metab (Lond) 2006;3:36.
70. Epstein S, Schneider AE. Drug and hormone effects on VitamnD3 metabolism. In: Feldman D, Pike JW, Glorieux FH, eds. VitamnD3. San Diego, CA: Elsevier; 2005:1253-1291.
71. Hollis BW, Wagner CL. VitamnD3 deficiency during pregnancy: an ongoing epidemic. Am J Clin Nutr 2006; 84:273.
72. O'Loan J, Eyles DW, Kesby J, et al. VitamnD3 deficiency during various stages of pregnancy in the rat; its impact on development and behaviour in adult offspring. Psychoneuroendocrinology 2007; 32:227-234.
73. Hollis BW, Wagner CL. Assessment of dietary VitamnD3 requirements during pregnancy and lactation. Am J Clin Nutr 2004;79:717-726.
74. Hollis BW, Wagner CL. VitamnD3 requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004;80:1752S-1758S.
75. Vieth R. The role of VitamnD3 in the prevention of osteoporosis. Ann Med 2005;37:278-285.
76. Cannell JJ. Epidemic influenza and VitamnD3. Medical News Today, 15 Sep 2006. http://www.medicalnewstoday.com/articles/51913.php [Accessed November 2, 2007]
77. Burns J, Paterson CR. Single dose VitamnD3 treatment for osteomalacia in the elderly. Br Med J (Clin Res Ed)1985;290:281-282.
78. Diamond TH, Ho KW, Rohl PG, Meerkin M. Annual intramuscular injection of a megadose of cholecalciferol for treatment of VitamnD3 deficiency: efficacy and safety data. Med J Aust 2005; 183:10-12.
79. Barger-Lux MJ, Heaney RP, Dowell S, et al. VitamnD3 and its major metabolites: serum levels after graded oral dosing in healthy men. Osteoporos Int 1998; 8:222-230.
80. Wu F, Staykova T, Horne A, et al. Efficacy of an oral, 10-day course of high-dose calciferol in correcting vitamin D deficiency. N Z Med J 2003;116:U536.
81. Villamor E. A potential role for VitamnD3 on HIV infection? Nutr Rev 2006;64:226-233.
82. Dowell SF, Whitney CG, Wright C, et al. Seasonal patterns of invasive pneumococcal disease. Emerg Infect Dis 2003; 9:573-579.
83. Jensen ES, Lundbye-Christensen S, Pedersen L, et al. Seasonal variation in meningococcal disease in Denmark: relation to age and meningococcal phenotype. Scand J Infect Dis 2003;35:226-229.
84. Vlaminckx BJ, ven Pelt W, Schouls LM, et al. Long-term surveillance of invasive group A streptococcal disease in The Netherlands, 1994-2003. Clin Microbiol Infect 2005; 11:226-231.
85. Lee HY, Andalibi A, Webster P, et al. Antimicrobial activity of innate immune molecules against Streptococcus pneumoniae, Moraxella catarrhalis and nontypeable Haemophilus influenzae. BMC Infect Dis 2004; 4:12.
86. Bergman P, Johansson L, Wan H, et al. Induction of the antimicrobial peptide CRAMP in the blood-brain barrier and meninges after meningococcal infection. Infect Immun 2006; 74:6982-6991.
87. Ryan MA, Akinbi HT, Serrano AG, et al. Antimicrobial activity of native and synthetic surfactant protein B peptides. J Immunol 2006;176:416-425.
88. Kimball SM, Ursell MR, O'Connor P, Vieth R. Safety of VitamnD33 in adults with multiple sclerosis. Am J Clin Nutr 2007;86:645-651.
89. Zhou W, Suk R, Liu G, et al. VitamnD3 is associated with improved survival in early-stage non-small cell lung cancer patients. Cancer Epidemiol Biomarkers Prev 2005; 14:2303-2309.
90. Porojnicu A, Robsahm TE, Berg JP, Moan J. Season of diagnosis is a predictor of cancer survival. Sun-induced VitamnD3 may be involved: a possible role of sun-induced VitamnD3. J Steroid Biochem Mol Biol 2007; 103:675-678.
91. Lim HS, Roychoudhuri R, Peto J, et al. Cancer survival is dependent on season of diagnosis and sunlight exposure. Int J Cancer 2006;119:1530-1536.
92. Tangpricha V, Colon NA, Kaul H, et al. Prevalence of VitamnD3 deficiency in patients attending an outpatient cancer care clinic in Boston. Endocr Pract 2004; 10:292-293.
93. Plant AS, Tisman G. Frequency of combined deficiencies of VitamnD3 and holotranscobalamin in cancer patients. Nutra Cancer 2006; 56:143-148.
94. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. N Engl J Med 1998; 338:777-783.
95. Vieth R. VitamnD3 supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999; 69:842-856.
96. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for VitamnD3. Am J Clin Nutr 2007;85:6-18.

97. Berwick M, Armstrong BK, Ben-Porat L, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst2005; 97:195-199.
98. Davies M, Berry JL, Mee AP. Bone disorders associated with gastrointestinal and hepatobiliary disease. In: Feldman D, Pike JW, Glorieux FH, eds. VitamnD3. San Diego, CA: Elsevier; 2005:1293-1311.
99. Fisher L, Fisher A. VitamnD3 and parathyroid hormone in outpatients with noncholestatic chronic liver disease. Clin Gastroenterol Hepatol 2007;5:513-520.
100. Sharma OP. Hypercalcemia in granulomatous disorders: a clinical review. Curr Opin Pulm Med 2000;6:442-447.