

REVIEW

Importance of vitamin D in cancer management

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Abstract: Vitamin D is essential element for growth and development of bones. The receptor of the metabolite of vitamin D known as “nuclear calcitriol” have been identified in tissues and is responsible for playing a wide range of biological processes. Calcidiol [25(OH) D₃] corresponds to the storage space and the chief flowing metabolite of vitamin D₃. Calcitriol 1- α -25-dihydroxycholecalciferol is formed in the kidney. Deficiency of vitamin D and lack of sun exposure has been found to cause unceasing illnesses together with various lethal cancers. At cellular level the mechanism of anticancer action of vitamin D has not been entirely implicated. For the setting off and regulation of particular genes, calcitriol-VDR-RXR complex attach to definite DNA fragments called as vitamin D response elements (VDREs). After binding with VDR, calcitriol performs its function by regulating the function of over and above 60 genes providing direction for antiproliferative, prodifferentiating and antimetastatic effects on cells to result in antiangiogenic property. Vitamin D deficiency is evaluated as level of calcidiol less than 20ng/mL, shortage to the level of 21-29 ng/mL, and adequacy level is 30ng/mL.

Keywords: Vitamin D, calcidiol, calcitriol, angiogenesis, apoptosis, cancer, cell proliferation.

INTRODUCTION

Vitamin D is renowned as being vital for healthiness of bones (Giovannucci *et al.*, 2006). Vitamin D plays a role of true hormones, as it belongs to a set of prohormones that are actually fat soluble and in the body they form a number of biologically active metabolites, which circulate in the blood and modify the activities of various cell types - both calcemic and noncalcemic (Stolzenberg-Solomon *et al.*, 2009). The receptors of the metabolite of vitamin D known as nuclear calcitriol have been identified in both tissues which when get activation signals not only have the power over calcium metabolism, besides this they elicit a broad range of biological responses, which interns controls growth of cells as well as their proliferation, apoptosis, and execution of immune system. Recently, this growth modulating property of calcitriol is subject mattered to extreme research in the ground of cancer preclusion and reserve (Angwafo *et al.*, 1998).

History

Over the past 5 years, a noticeable boost in the quantity of high-dose vitamin D prescriptions in the United States has been observed. Vitamin D has an elongated and attention-grabbing account which is intimately associated with rickets, the childhood bone disease. Since the middle of 17th century, the subsistence of vitamin D had been supposed but in reality it was not revealed before 1920s and the chemical structure was explicated after 1932 (McCollum *et al.*, 1922; Stolzenberg-Solomon *et al.*, 2010; Holick *et al.*, 2007).

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Physiology

Vitamin D fit in to the foursome of fat soluble vitamins (A, D, E and K). This accounts for its allocation mainly in adipose tissue and its very measured yielding pace. It is a secosteroid with a ring structure comparable to cholesterol excluding the broken C-C bond in the B ring. Vitamin D exists in two major forms: vitamin D₂, is the first one also called as calciferol, formed by the irradiation of yeast (Masuda *et al.*, 2005; Kostner *et al.*, 2009). And the second is vitamin D₃ (cholecalciferol), which is most important and is a resultant obtained by photo conversion of 7-hydrocholesterol in the skin when exposed to sunlight or artificial ultraviolet rays and fish liver oil provides huge amounts of vitamin D₃. Lanolin also called wool fat act as the unprocessed starting material for commercial production of vitamin D₃. Certainly both D₂ and D₃ are accessible in pill form. Dietary sources of vitamin D₃ (Bid *et al.*, 2005) are given in table 1.

Biologically Vitamin D₂ is pathetic as compared to D₃, owning no more than 30% of vitamin D₃ activity. The two forms (D₂ and D₃), in the body track same metabolic pathways. Though, our center of attention in this evaluation will be largely on D₃ because it constitutes the main contribution and in humans it occurs naturally. Calcidiol [25(OH)D₃] corresponds to the storage space and the chief flowing metabolite of vitamin D₃. Clinically its level in the plasma is measured for reviewing the vitamin D dietary condition of the patient. Calcidiol, vitamin D₂, vitamin D₃ have practically no inherent

biological action at physiological concentrations (Webb *et al.*, 1998). A definite transporter protein acknowledged as a vitamin D-binding protein (DBP) circulates in the body and helps in travelling away of vitamin D and its mediators. Calcitriol 1- α ,25-dihydroxycholecalciferol [1,25(OH) $_2$ D $_3$] is formed in the kidney when a second hydroxyl group is attached to the molecule of calcidiol at position 1.1 α hydroxylase, is a cytochrome P450 enzyme (CYP27B1) which is responsible for the catalization of this feedback in the kidney. Serum level of calcitriol on average ranges between 15 and 75pg/mL (Larcombe *et al.*, 2008). Manufacturing of calcitriol and its circulating rank is based on a number of factors; the major one belongs to the functioning of 1 α -hydroxylase in the proximal tubule cells of the kidney. Action of this enzyme is improved via low calcitriol levels, high parathyroid hormone, low level of calcium and high level of phosphates (Eyles *et al.*, 2005; Fleet *et al.*, 1999). Though, additionally calcidiol an instant forerunner of calcitriol formation is an important determinant for the activity of 1- α -hydroxylase, whose build in is based on contact to UV radiation to skin along with ingestion of vitamin D $_3$ orally.

The vitamin D receptor (VDR) is a nuclear transcription factor for majority of the recognized actions of calcitriol. Retinoic acid x-receptor (RXR) in the cell nucleus causes the binding of calcitriol with VDR. For the setting off and regulation of particular genes, calcitriol-VDR-RXR complex attach to definite DNA fragments called as vitamin D response elements (VDREs) (Nemere *et al.*, 1998; Khanal *et al.*, 2007).

Actions & functions

In the decades which tagged along its finding, an irresistible body of medical and laboratory verification recognized its vital function in the persistence of skeletal health and calcium balance. Their acknowledged chief action is the upholding of plasma Ca $^{2+}$ concentration by means of mounting Ca $^{2+}$ absorption in the intestine, moving Ca $^{2+}$ from bone and decreasing its renal excretion. Hence, vitamin D is linked primarily and principally with these activities. Conversely, a rapid analysis of the modern journalism discloses that vitamin D is located at the midpoint of endocrine systems which is responsible for differentiation and also for the proliferation of cells, besides a broad variety of additional cellular actions, enlarging the function of vitamin D ahead of the skeleton to take account of the neuroendocrine cardiovascular and immune systems (DeLuca *et al.*, 2004; Chapuy *et al.*, 1992; Dusso *et al.*, 2005). A survey made in such manner would also be helpful in specifying that deficiency of vitamin D as well as the genetic changes in the receptors of vitamin D can take most important role in the etiology of a range of persistent disorders which counts cancer, diabetes, mycobacterium infections, cardiovascular diseases, and autoimmune diseases such as psoriasis,

multiple sclerosis, systemic lupus erythematosus, and rheumatic arthritis (Sullivan *et al.*, 2005; Heaney *et al.*, 2003; Dawson-Hughes *et al.*, 2005; Boonen *et al.*, 2006).

Actions of vitamin d on vital organs

Colon, prostate, brain and breast tissues, along with other organs, over and above the immune cells possess receptors for vitamin D and act in response to the dynamic type of vitamin D (1,25-dihydroxyvitamin D) (Liu *et al.*, 2006; Li *et al.*, 2003). May be direct or indirect way, calcitriol or 1, 25-dihydroxyvitamin D have power over above 200 genes, involving genes liable for the maintenance of production of insulin, synthesis of renin in kidney, cellular apoptosis, the development and profusion of muscular cells of heart and vessels, angiogenesis and cytokines discharge via T cells, and the assembly of macrophages against bacterial protein component cathelicidin (Chiu *et al.*, 2004).

Function of vitamin d in immune response

Though, it has been now by and large acknowledged that a powerful correlation is amid immune system and vitamin D subsists since it's been recommended by numerous conclusions: firstly the immune cells of humans, particularly those cells which are stimulated bear the existence of VDR. Secondly, their capacity to form calcitriol, and thirdly, the abundance of T cells is slowed down by calcitriol. Additionally, it has been progressively more clear in current days that calcitriol have a considerable function in varying the roles of the immune system as it reduces proliferation of normal body cells as well as cancerous cells by stimulating their terminal differentiation (Miller., 2010). When monocytes and macrophages are encountered with lipopolysaccharides they stimulate vitamin D receptor gene and therefore results in the augmented formation of vitamin which in turn, produces cathelicidin. This helps in wiping out infectious organisms. The monocyte or macrophage is prohibited from starting this instinctive immune reaction, when serum levels of 25-hydroxyvitamin D became lesser than 20ng per milliliter (Medzhitov *et al.*, 2007; Kindt *et al.*, 2007; Bartley *et al.*, 2010).

Vitamin d deficiency

Present are several causes of vitamin D deficiency, comprising of augmented catabolism, Reduced skin synthesis, Inadequate bioavailability, Liver failure, Breast-feeding having nutrient insufficient of vitamin D content and Hyperthyroidism - leading to increased metabolism of 25-hydroxyvitamin D, Nephrotic syndrome - counting for excessive release of vitamin D in urine, and Heritable disorders - rickets (Reid *et al.*, 1986).

Epidemiology

Now- a -days deficiency of Vitamin D is renowned as endemic mainly in the northern hemisphere where sun exposure is minimal and winter is of longer period.

Vitamin D distributes preferentially into the adipose tissue with a half-life of more or less 2 months as it is lipophilic. Vitamin D deficiency is evaluated as level of calcidiol less than 20ng/mL, shortage to the level of 21-29ng/mL and adequacy level is 30ng/mL. In recent therapeutic practice, these suggested ranges are progressively getting upward as vitamin D deficiency is more and more being concerned with the etiology of an intensifying catalog of diseases. Clear vitamin D toxicity marked as hypercalcemia and ectopic calcification does not arise, pending the calcidiol level is well greater than 150ng/mL. Though, it is to be decided the enduring safety of continued high levels (greater than 50ng/mol) given that the fashion of prescribing vitamin D mega-doses has become common in recent times. Consequently any advantage of vitamin D intake has to be balanced in opposition with the risk of known short-term and potential long-term toxicities (Zittermann *et al.*, 2006).

Table 1: Dietary Sources of Vitamin D₃ (Ecosh, 2020)

Food	Cholesterol per 100 g	Vitamin D per 100 g
Oysters	55 mg	640 IU
Sardines	145 mg	482 IU
Cod liver oil	560 mg	10,000 IU
Butter	217 mg	57 IU
Herring	13.0 mg	670 IU
Caviar	585 mg	230 IU
Salmon	87 mg	322 IU
Mackerel	94 mg	499 IU
Whole Egg	424 mg	48 IU
Catfish	82 mg	500 IU
Shrimp	172 mg	173 IU
All Plant Foods	0 mg	0 IU

The relationship between vitamin D & cholesterol content, definitely is not picture-perfect, however all of the diets comprising vitamin D hold significant quantity of cholesterol.

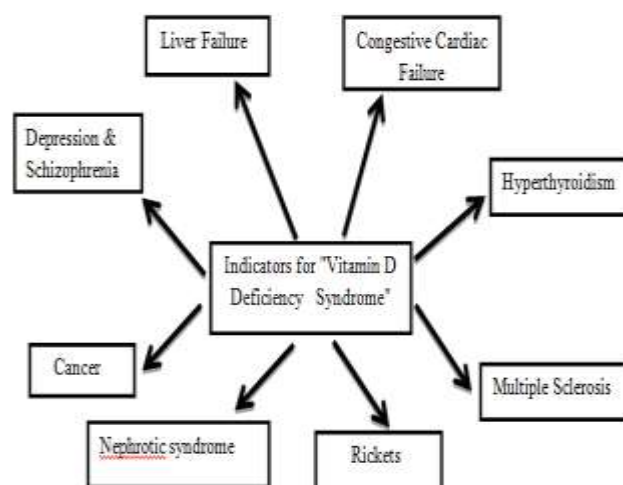


Fig. 1: Indicators for vitamin D deficiency syndrome

The survey made by 3rd National Health and Nutrition Examination (NHANES III) has exposed that a large division of the American population have low vitamin D levels; many other studies verified this fact. The phenomenon of has also been found in many other including .Middle East and North Africa are also included in the parts of the world where people suffer from vitamin D deficiency as their social customs state least skin spotlight. Causes of vitamin deficiency are numerous and comprise of the following like enclosed standard of living, dark skin, high latitude, skin area exposed to UVB is deficient, chronic kidney disease (CKD) , severe liver disease, obesity, aging (abridged capability for photosynthesis).

Besides, bone diseases in kids as well as adults, vitamin D deficiency has been coupled with a far-reaching diversity of unremitting circumstances with colorectal cancer, diabetes mellitus type II, infectious diseases, hypertension, and autoimmune diseases such as SLE and diabetes mellitus type I (Gorham *et al.*, 2005).

Depression and schizophrenia

Vitamin D deficiency has been interrelated to an augmented occurrence of schizophrenia and depression. Sustaining vitamin D levels in utero and throughout initial lifespan, maintains the transcriptional activity of the vitamin D receptor in brain, which is proven to be essential for development and progress of mental functioning in the future life (Zhang *et al.*, 2004).

Congestive cardiac failure

Vitamin D deficiency is related to congestive cardiac failure and also responsible for reducing levels of inflammatory factors in blood comprising interleukin-10 in addition to, C-reactive protein. Also living at upper leeway intensify the possibility of cardiovascular disease and hypertension (Berwick *et al.*, 2005; Jones *et al.*, 1998).

Vitamin d in relation with cancer

A Neoplasm or Cancer is “an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change.”

Latitude, sun exposure and chronic diseases

It has been experimentally determined that normal exposure to sun is linked with progressive lowering in death rates of certain cancer over and above with decrease in general cancer death rates, which may be correlated with metabolic pathway of vitamin D in the body. The initial indication about the probable connection between cancer and vitamin D deficiency is the study that both the occurrence of definite cancers and vitamin D deficiency show a discrepancy by latitude. This is referred to as the

geographic or ecological factor as it is found to be associated with the north-south sunshine gradient.

Epidemiological survey including 111 countries, a well-built and productive linkage flanked by latitude and the occurrence ratio of lung cancer was observed. All together there was a converse connection between lung rates cancer and the effectual contact to UVB rays. The instigators concluded that low levels of UVB irradiance are autonomously linked with higher incidence rates of lung cancer in addition with factors such as cigarette smoking (Hanchette *et al.*, 1992). About more than 60 observational studies based on exposition investigation were made in U.S proposes that insufficient vitamin D levels may be allied with a privileged occurrence of cancer in common (Grant, 2002; Holick, 2006; Ahonen *et al.*, 2000; Li *et al.*, 2007).

Some biological studies suggest that sunlight may shield from ovarian, colorectal, prostate and female breast cancers. A number of systematic researches also propose a defensive concern between prostate plus colorectal cancer and circulating vitamin D (Wactawski *et al.*, 2006). Current epidemiological facts revealed a tough correlation between meager vitamin D status and privileged risk for unending diseases of different etiology (Lappe *et al.*, 2007).

Deficiency of vitamin D and lack of sun exposure has been found to cause unceasing illnesses together with various lethal cancers (Boscoe *et al.*, 2006). It is now renowned that certain types of cancer as well as softening of bones, cardiovascular diseases and autoimmune diseases can be avoided in case of retaining calcifediol concentration in serum of about 32ng/ml or a little greater. A theory was held up in the middle of 1970-2007 which was based on investigation of crucial and appraisal medical literature printed and suggested that calcitriol has a noteworthy shielding result against cancerous growth. Epidemiological investigations have shown an opposite link between serum concentration of calcifediol /sun exposure/ vitamin D intake and risk of developing and/ or existing cancer (Grant., 2007). It seems to be effective to use supplements of vitamin D and levelheaded sun exposure and use of vitamin D supplements in avoidance of vitamin D insufficiency (Tuohimaa *et al.*, 2007). Additionally it has also been found by many members of staff that were searching on it that vitamin D is useful in bringing on death of cancerous cells both in vitro and in vivo, except prevention (Feskanich *et al.*, 2006).

In extra cloudy northern latitudes of US, a prostate, breast and colon cancer belt has been recognized to arise 2-3 times more frequently than the sunnier areas (Luscombe *et al.*, 2001).

An analysis has been made among the people living at higher latitudes and lower latitudes as people with higher

latitudes have greater possibility for Hodgkin's lymphoma. People living at higher latitudes are at increased possibility for Hodgkin's lymphoma in addition to ovarian, breast, colon, pancreatic, prostate, and other cancers and are further expected to expire from these cancers, in comparison to lower latitudes (Chang *et al.*, 2005; Mantell *et al.*, 2000; Cantorna *et al.*, 2004). According to the future and displayed epidemiologic studies specify that levels of 25-hydroxyvitamin D lower than 20ng per milliliter are related to 30 to 50% greater hazard of episode of breast, colon, prostate cancer, together with high death rates from these cancers. An investigation made by Nurses' Health Study cohort showed that study of vitamin D ingestion and the peril of colorectal cancer in 1954 men demonstrated a straight correlation. An observation survey made tells that the male individuals suffering from prostate cancer who worked in open air has been caught by the disease 3 to 5 years afterward in comparison with the men who performed their jobs indoors (Ponsonby *et al.*, 2002). Collective statistics from 970 women proved that the maximum vitamin D intake is associated with a 50% lesser hazard of breast cancer in contrast with the lowest (Van *et al.*, 2004). Kids and young mature people who are exposed to the largest part of sunlight have a 40% abridged risk of death from malignant melanoma once it develops and a lower risk of Hodgkin's lymphoma in comparison with the people who slightly expose to sunlight (Munger *et al.*, 2006).

Anticancer actions of vitamin D

Anticancer property of vitamin D has been deliberated in a large range of frequently encountering cancers (both in vitro and in vivo) of which the actions on prostate, colorectal and breast cancers have been considered to be strong potentially (Sato *et al.*, 2005; Chel *et al.*, 1998; Tangpricha *et al.*, 2004).

Mechanism of action

The enzyme 1-OHase is used for changing of calcifediol into calcitriol and this has been experimentally determined that calcitriol is synthesized by some tissues of the body involving colon, breast and prostate as they possess the genes on them for the expression of enzyme 1-OHase, in addition to the synthesis of calcitriol from its predecessor in the kidney.

At cellular level the mechanism of anticancer action of vitamin D has not been entirely implicated. As it has been explained above that all normal cells along with cancerous cells possess on their surface VDRs for conversion into calcitriol, the dynamic metabolite. These receptors fit in the super family of nuclear receptors, which comprise receptors for steroid/ thyroid hormone (Smolders *et al.*, 2008). A conformational change is occurred when the agonist calcitriol binds with VDR for its activation which in order dimerizes with the nuclear

retinoic X receptor. The binding of heterodimer with vitamin D response elements (VDREs) in the promoters of objective genes and endorses their transcription causing adjustments in differentiation, phosphocalcic metabolism or maintenance of cell division, and cell death (Ascherio *et al.*, 2010). After binding with VDR, calcitriol performs its function by regulating the function of over and above 60 genes providing direction for anti-proliferative, pro-differentiating and anti-metastatic outcomes on cells to effects anti-angiogenic property as the vitamin D is known to cause interference in the transduction pathway of receptor tyrosine kinases (growth factor(s)-activated receptors) which modulates transcription thereby changing genomic functions providing disability of angiogenesis, apoptosis and cell differentiation (Lo *et al.*, 1985; Aris *et al.*, 2005).

Thus differentiation, angiogenesis, apoptosis and cellular proliferation are linked with the non-calcium mobilizing functions of vitamin D. It also raises the intensity of Cystatin D an endogenous protein, which owned the antitumor and antimetastatic activity, as it is coded with the gene of expression. As the angiogenesis inhibitor action withdraws the cancer cells of their nutrients and oxygen for development and endurance. However not as a main anticancer agent, this vitamin can be utilized for the deterrence of cancer and incorporated as an adjuvant in combination chemotherapy for the management of cancer. Furthermore, the immature and eternal cancer cells on no account become adult, full-grown and become extinct and derivatives of vitamin D are acknowledged to encourage maturation and development of normal cells that is opposite to the character of the cancerous cells (Tangpricha *et al.*, 2004).

Management of cancer and vitamin D

The most important processes used of management and cure of cancer comprise of surgical treatment, irradiation and chemotherapy, generally provided in combination based on the form and phase of the illness. However in most of cancers the intimate management is curative. Because of the fact that untimely judgment is not achievable in common cases and the disease still continues untreatable in addition to all genuine and reasonable techniques for treatment. Furthermore, the outcomes of radiation therapy and surgical procedures in conjunction with severe undesirable results of chemotherapy auxiliary bound the commencement and prolongation of treatment (Van *et al.*, 2004).

The problem of resistance and tolerance to the existing drugs has created a decreased efficacy of these drugs in use. This problem has been tried to be overcome by increasing the drug delivery to the target site by the use of polymers (Khalid *et al.*, 2009; Hussain *et al.*, 2011) or through nanotechnology (Naz *et al.*, 2012; Ehsan *et al.*, 2012), synthesis of new drugs, either by the use of

proteomics (Qadir, 2011), or synthesis from lactic acid bacteria (Masood *et al.*, 2011), or marine microorganisms (Javed *et al.*, 2011). However, now a days, the trend is also being changed to the use of natural products or to control the diseases. Large numbers of natural constituents are constantly being screened for their possible pharmacological value particularly for their anti-inflammatory (Qadir, 2009), hypotensive (Qadir, 2010), hepatoprotective (Ahmad *et al.*, 2012), hypoglycaemic, amoebicidal, anti-fertility, cytotoxic, antibiotic (Amin *et al.*, 2012), Spasmolytic, bronchodilator, antioxidant (Janbaz *et al.*, 2012) and anti-cancer properties. Vitamin D may prove a strong candidate as anti-cancer agent in near future.

Recent approaches

The quickly rising consideration of biological processes which leads production of cancer has facilitated to utilize biological derangements exclusive to cancerous cells and to recognize new cellular targets for drugs used as anticancer agents. A few of the drugs consist of - matrix metalloproteinase inhibitors to retard attack and put off metastasis, antiangiogenic, which avert fresh development of blood vessels that is crucial for cancer growth, inhibitors of signal transduction pathways to disrupt the staid signaling pathways important for cellular enlargement and abundance, differentiation mediators to stay away the neoplastic cells in a phase where they contain minute or rebuff proliferative prospective, designer molecules, devised to restrain unbalanced tyrosine kinase overexcited action and proapoptotic means which have straight deadly outcome for cancer cells or augment the cellular breaking actions of anticancer agents (Dijkstra *et al.*, 2004).

Chemoprevention

In view of the fact that several cancers at present are untreatable, efforts may be done to check their incidence, if achievable. In this case to minimize the risk of incidence of definite forms of cancer the way of living must be change most importantly. Likewise, chemoprophylaxis may be regarded for each and every inhabitant or for crowd of people having greater hazard for a particular cancer. Ingestion of some vitamins and derivatives and dietary micronutrients like alpha-tocopherol, ascorbic acid, beta-carotene, isotretinoin and folic acid may restrain the growth of cancer. Big level assessments in this deference are steps forward (Wactawski *et al.*, 2006). Because of their antitumor activities, a few investigators suggest that vitamin D supplementation may be valuable in the cure and anticipation of some categories of cancer (Zittermann, 2006).

Daily dose of vitamin D

Presently, there are no recognized recommendations for medicating vitamin D in the several patient inhabitants

(nurslings, teenagers, youngsters, adults and old age people, expecting women, or nourishing mothers). Nevertheless, an estimation of lately issued literature advises that the presently indorsed daily stipends are perhaps too short and that advanced doses are mandatory to attain the finest results as a minimum in relations to colorectal cancer plus healthiness of bones. Youngsters with age 10-18 years and elders greater than 60 years might have need of advanced doses greater than 2,000 IUs/day. For new born in the first initial year, require regular vitamin D₃ dose of approximately 2,000 IUs (Zhang *et al.*, 2004; Zhou *et al.*, 2006).

CONCLUSION

A person devoid of eating oily fish regularly, then it becomes very challenging to acquire that quantity of vitamin D₃ from nutritional basis. Level headed sun contact in addition to the use of supplements is required to justify the body's vitamin D prerequisite. Undiagnosed vitamin D deficiency is not rare and 25-hydroxyvitamin D is the indicator for vitamin D level in the body. Serum 25-hydroxyvitamin D is not only a prognosticator of bone strength and also an autonomous analyst of hazard for cancer and other long-lasting diseases. Radio immuno assay quota total 25-hydroxyvitamin D, including levels of both 25-hydroxyvitamin D₂ plus 25-hydroxyvitamin D₃ with the help of tandem mass spectroscopy and liquid chromatography which gives the assessment values individually. In case if the person keeps 30ng/ml or greater, then his vitamin D level is appropriate.

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