

## Review Article

**The Enigmatic Association between Vitamin D and Cortisol: A Review**Piyanka Sengupta<sup>1,2,3</sup>, Sandip Mukherjee<sup>1</sup> & Alok Chattopadhyay<sup>2\*</sup><sup>1</sup>Dept. of Physiology, Serampore College (UG & PG Section), Hooghly<sup>2\*</sup> Dept. of Physiology, Harimohan Ghosh College, Kolkata<sup>3</sup>Department of Food & Nutrition, Sister Nibedita Govt General Degree College for Girls, Alipore, Kolkata**(Received: 11-11-2025****Revised: 17-03-2026****Accepted: 19-03-2026)**Corresponding Author: **Alok Chattopadhyay** Email: [alokc1972@gmail.com](mailto:alokc1972@gmail.com)**ABSTRACT**

Vitamin D which is mainly designated as hormone, play numerous significant roles in our human body. They not only fall under bone health but other body systems which strongly get affected due to vitamin D deficiency. Especially In today's society due to faulty life style and improper food habit vitamin deficiencies are seen to manifest various chronic health disorders which are interplayed by their association with other endocrine factors specially hormones. The current review work shows the less elaborated relationship between Vitamin D and cortisol a highly relevant adrenal corticosteroid involved in stress response. This review work highlights the positive and negative correlation between these 2 hormones which may influence both mental and physical health of individual. Many studies have indicated that there may be an imperceptible possibility that these two bio molecules may possess some sort of inter-dependent association. Significant information obtained from this review focuses on generating awareness regarding the impact of vitamin D and Cortisol on combating serious health issues from their early inception.

**Keywords:** Vitamin D, Cortisol, Inter Relationship**1. INTRODUCTION**

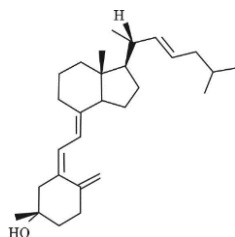
In today's hectic world especially, the young adults are prone to various life style disorders mainly non-communicable diseases or chronic degenerative diseases. Current modern lifestyle accompanied with chronic stress are causing severe oxidative damages (associated with increased inflammatory markers) in human body tissues as well as increasing the stress mediators and in turn leading to worsening of the situations. While assessing the vivid spectrum of causative factors which are behind the increment of the stress mediators or inflammatory markers, the role of VITAMIN D is becoming more prominent. Vitamin D is found to be important in mitigating not only physical health problems but also to various mental health issues, like depression, anxiety and chronic stress periods of one's life. vitamin D has also been linked with inhibiting the proliferation of pro inflammatory cells. These cells in future give rise to the onset of degenerative diseases or lifestyle disorders

(mainly due to chronic inflammation) like cardiovascular disease, pulmonary disorders, irritable bowel syndrome (IBS) Inflammatory Bowel Disease (IBD), kidney disorders, Liver diseases like Non-Alcoholic Fatty Liver Diseases, Metabolic Syndrome, Diabetes mellitus and others [1]. The active form of vitamin D, a well-known indigenous antioxidant, is related with various antioxidant properties to support physiological function and activity of various marker cells. It can be successfully applied for the treatment of conditions like rickets, osteoporosis, thyroid imbalance, and other adverse health effects mainly contributed by low levels of calcium or vitamin D. it is also witnessed that Vitamin D can be successfully related with the prevention of cancers. This fat-soluble vitamin is also essential for the generation of glutathione which is linked with the reduction of reactive oxygen level in the blood [2]. Cortisol is a steroid hormone which has vital role in the regulation of many important physiological processes including blood glucose

regulation, inflammatory response modulations, stress and blood pressure control maintaining general homeostasis and last but not the least stress response. As Addison's disease may occur due to low cortisol, simultaneously too much cortisol level cause Cushing's syndrome which in turn leads to high blood pressure, anxiety, stress disorders, reproductive problems including infertility etc. [3]. Studies have shown vitamin D a steroid hormone like Cortisol can effectively reduce the symptom or prevalence of high cortisol level in blood. This theory can help in formulation of vitamin D supplementation to reduce such current life style disorders [4].

### Chemical nature, Biochemistry & Synthesis of vitamin D

Vitamin D though known as vitamin in 20<sup>th</sup> century is now mainly known by the term prohormone and this is found mainly in 2 forms: ergocalciferol or Vitamin D<sub>2</sub> & cholecalciferol or vitamin D<sub>3</sub>. Vitamin D can be produced in the skin from 7-dehydrocholesterol mainly by exposure to sunlight & it can also be obtained through diet by including non veg food sources like fish oils, fish products and vitamin D<sub>2</sub> is mainly consumed from plant sources. Both forms of vitamin D perform the same function as a prohormone [5]. Vitamin D is fat soluble in nature and it has got the following characteristic structure as follows:



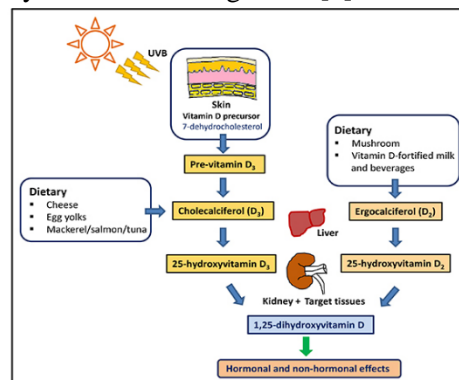
**Fig 1. Chemical structure of vitamin D**

Reference: <https://www.chm.bris.ac.uk/~paulmay/webprojects2002/schnepp/vitamind.html>

### Cutaneous production of Vitamin D

Vitamin D, is produced in the skin from **7-dehydrocholesterol (cholesterol-like precursor)** mainly due to exposure to sunlight and it can be provided by the diet. the form which is obtained from diet can be vitamin D<sub>3</sub> or a similar molecule of plant source known as vitamin D<sub>2</sub> and Vitamin D. From a nutritional perspective, both vitamin D<sub>2</sub> and Vitamin D<sub>3</sub> undergo similar metabolic pathway, both are

functionally active in similar manner. Researches have authenticated that vitamin D<sub>3</sub> is primarily metabolised in the liver to 25-hydroxyvitamin-D or Calcidiol & then from there finally 1,25-(OH)<sub>2</sub>D<sub>3</sub> cholecalciferol or calcitriol the biologically active form gets produced in the kidneys and acts on target cell [6].



**Fig 2: Schematic representation of synthesis of vitamin D in human body**

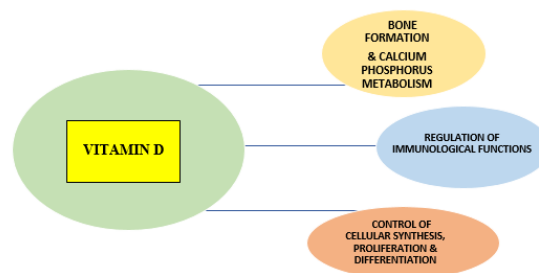
Reference: Wimalawansa SJ. "Controlling chronic diseases and acute infections with vitamin D sufficiency" *Nutrients*. [Internet] 2023; 15:3623.

The subcutaneous part of our body, pre vitamin D<sub>3</sub> is synthesised from 7 dehydrocholesterol (pro-vitamin D) while exposure to sunrays [7] exposure to UV radiation to even small section of body like face, hands arms about 1000 IU of vitamin D can be produced [8]. 15-20 minutes of sun exposure in the entire body specially in summer time 10,000 IU of cholecalciferol can be synthesised [9]. Various factors like age, race, colour of skin, seasonal changes, weather changes, body surface area, clothing, altitude, skin type, use of sunscreen may directly alter the rate of Vitamin D production. For example, it can be mentioned that ageing and melatonin content in the skin can directly influence the rate or level of Vitamin D production [10, 11]. Apart from the sub cutaneous production of vitamin D, this important steroid hormone can be also obtained from various food sources. The important food sources of Vitamin D are fatty fish, egg, mushroom, liver, milk & milk products, fortified cereal etc.

### General functions of Vitamin D in body

Whenever the mention of function of vitamin D is discussed, its role in skeletal system gets mostly highlighted. The influence of vitamin D on calcium phosphorus balance, are mainly

exerted by modulating gene expression in small intestine, kidney & bone. The active form of Vitamin D facilitates calcium and phosphate absorption from intestine, renal tubules and also mobilization of these minerals from the bone [3]. The mineral deposition in the bone is facilitated with the help of cholecalciferol by inducing mineral absorption upon the collagen protein matrix in the bone itself leading to its formation [7]. Vitamin D3 along with parathyroid hormone enhance bone resorption mainly stimulating the action of osteoclast cells [12]. This proves the strong inclination towards the role of Vitamin D3 in the bone formation, bone remodelling as well as mineral homeostasis. Vitamin D is known to be extremely important for its role as antioxidant, immune modulator, and essential regulator of various metabolic activity. Various studies have successfully showed that Vitamin D has an important contributory role in the prevention of various inflammatory diseases. There is a great body of work available which show that Vitamin D in the causation of various chronic diseases due to inflammation. As vitamin D initiates and improves the expression of cytokines with anti-inflammatory properties as well as various important antioxidants thus it was found to have active role in regulating the ROS (Reactive oxygen species) and prevents inflammation adversities. Studies show that cholecalciferol activates VDR (Vitamin D receptors), which influence our immune system, causing anti - proliferative, anti-metastatic effect on various cancerous cells, provide protective action against chronic diseases like cardio vascular disease, obesity & diabetes [13]. Apart from numerous physiological benefits, studies have highlighted that this vitamin is significantly associated with preventing the occurrence of anxiety, depression, schizophrenia, behavioral disorder & cognitive impairments [14]. Vitamin D Receptors play an important role in maintaining muscular health and also improves muscle functioning. It aids in the functioning of insulin hormone and also helps in its secretion. Vitamin D also regulate the growth of parathyroid glands, prevents the onset of diseases like dementia, inflammatory disease like multiple sclerosis and infections like tuberculosis [15].



**Fig 3: Schematic representation of main functions performed by Vitamin D in our body.**

### Consequences of Vitamin D Deficiency

Hypovitaminosis D has a wide spectrum of prevalence. There are many contributory factors like lack of sunlight exposure, sedentary lifestyle, obesity, more indoor activities, over use of sunscreen, ageing, liver or kidney disorders, smoking which aggravate the deficiency situation. In context to its availability in food, it is already known that Vitamin D generally is present in very limited amount (oily fish, fish liver oil, sundried mushrooms are known sources). Along with this, low consumption of Vitamin D fortified foods doesn't help in mitigating the problem. Thus, for fulfilling the majority of Vitamin D requirement, more exposure to sunlight is required as it is already established that sunrays synthesise active Vitamin D3 in skin. So, lack of exposure to sunrays remains most important cause of hypovitaminosis D [16]. The skeletal consequence of vitamin D mainly affects health and functioning of the bone. In children it causes bow shaped malnourished bones commonly resulting Rickets. In adult the deficiency is mainly characterised by Osteopenia and Osteomalacia which soften and weaken the bone. In later life the condition becomes severe as the bone turns porous and weak and can be easily fractured, commonly known as osteoporosis. All these conditions can greatly influence one's health and reduce the quality of life of individuals [17]. Also, another manifestation of vitamin D deficiency on skeletal system cause Paget disease. In this condition occurs a phenomenon which increases bone resorption, causing reduction in bone mass in turn leading to increased osteoblastic activity. The condition is characterized by osteoclastic activity which is

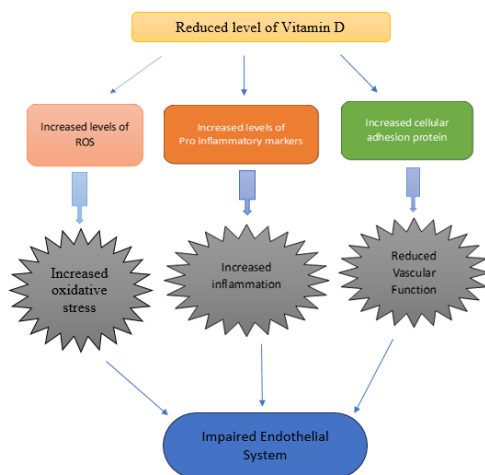
then subsequently followed by osteoblastic activity, causing the formation of less compact, mechanically weaker disorganized bone which are more prone to fracture. This bone disorder is often seen in elderly people similar to osteoporosis [18]. Research articles show that reduced levels of Vitamin D is related with oxidative stress and similarly it is crucially associated with endogenous oxidative markers like MDA (malondialdehyde), NO (Nitric Oxide) and the curtailing of GSH (glutathione), SOD (superoxide dismutase) activity, CAT(Catalase) activity and TAC (Total antioxidant capacity). Studies also claim that vitamin D reduces inflammatory disorders like systemic lupus erythematosus and familial Mediterranean fever. Vitamin D deficiency is mainly seen due to contributory factors like inadequate exposure to sunlight, inadequate intake of vitamin D rich foods, consumption of drugs which reduce vitamin D action, altered metabolism and malabsorption [19]. Vitamin D deficiency can be a contributory factor in onset of cancer. A study on women of reproductive age group has shown that a high blood level of provitamin D<sub>3</sub> in women can successfully reduce the chances of breast cancer to 50 %. [20]. Even High exposure to sunrays for a long time can reduce the occurrence of breast cancer in women by 60% [21]. Vitamin D along with calcium supplementation also reduce any form of cancer apart from reproductive tract and also improves various functioning of all important systems [22]. It is also well documented that Vitamin D plays a major role in reducing the risk of non-communicable diseases like Diabetes, heart disease, rheumatoid arthritis, auto immune disease, asthma etc. [23]. A study showed that post-menopausal women when received 2000IU/day of vitamin D, their risk of developing upper respiratory infection rate dropped to 10% in one year [17].

#### **Cortisol and Vitamin D Relationship: The Paradox**

Cortisol the steroid hormone has huge implication in human physiology. This hormone has significant control on regulation of various bodily function and metabolic activity. It not only regulates glucose metabolism but also affect

blood pressure, anxiety, inflammatory response, thyroid function etc. [24]. Just like physiological health influences, cortisol was found to be related with various mental health parameters. An increased cortisol level is seen in many mental disorders like anxiety, depression, bi polar disorders & schizophrenia. It is also observed that when cortisol levels are decreased patient's conditions have significantly improved. So, it can be stated that Cortisol strongly influences mental wellbeing [25]. Studies have showed that vitamin D just like cortisol is a steroid hormone. These 2 are equally important for health. Researches have pointed toward the possibility that cortisol changes the bioavailability of vitamin D. Many other researches indicated that glucocorticoid or cortisol in overdose can reduce levels of 25(OH)D by changing vitamin D receptor's expression in many tissues and cells [26]. A recent study was conducted to understand Vitamin D metabolism in patient with Cushing Disease where cortisol level generally remains high. The study also concluded that changed activity of vitamin D catabolism may influence the effectiveness of treatment with cholecalciferol [27]. Another study revealed that level of 25(OH)D is significantly lower in patient with high cortisol levels like in Cushing Disease [28]. Vitamin D strongly improves mitochondrial efficiency, prevents protein degeneration and lipid peroxidation and DNA denaturation due to higher levels of oxidative stress in the cellular level [29]. due to all these roles, vitamin D also delays the effects of ageing. Recent studies have highlighted that active vitamin D greatly reduce inflammation, oxidative stress and tissue damage. Also, it was found that Vitamin D<sub>3</sub> can greatly reduce the generation of proinflammatory cytokines like IFN $\gamma$ , IL-17, and IL-21 & T lymphocytes [30]. T-cell cytokines were found to be regulating vitamin D metabolism in macrophages. As an example, it can be stated that T-helper (Th)-1 cytokine like IFN $\gamma$  can lead to increased bioconversion of 25(OH)D<sub>3</sub> to its biologically active form – 1,25(OH)<sub>2</sub>D<sub>3</sub>. Opposite to this it is seen that Th2 cytokine like IL-4 helps in conversion of 25(OH)D<sub>3</sub> to its inactive form i.e.24,25(OH)<sub>2</sub>D<sub>3</sub> [31]. suggesting the role of vitamin D in various categories of

immune responses. Many clinical studies have highlighted that serum vitamin D levels can indicate the chances of developing Acute Respiratory Infection (ARI) and also it may significantly alter lung functions [32]. In vitamin D deficiency oxidative stress seems to get higher in proportion which may lead to the onset of chronic degenerative diseases like Type 2 Diabetes, cancers, and other inflammatory diseases [33].



**Fig. 4: Flow Diagram depicting impact of low vitamin D status on various endogenous system.** Vitamin D, steroid hormone, though mainly is popular for its effect on calcium-phosphorus homeostasis and having an impact on bone health, other than this has multiple profound health benefits. Vitamin D strongly not only regulate various bodily functions, but many works have highlighted the significant impact of vitamin D in managing or reducing oxidative stress and controlling the adversities of inflammation and also controlling cortisol the stress hormone. This review work tried to focus on the ambiguous relationship between cortisol and vitamin D and also the contribution of Vitamin D in preventing various chronic diseases which influence the quality of life of individual.

## Discussion

### Correlation between Cortisol Imbalance and Vitamin D

#### A. Vitamin D and Hypoactivity of Cortisol: Addison's Disease.

Addison's disease (AD) a rare endocrinal disorder, also often called primary adrenal insufficiency, is often occur due to autoimmune

adrenitis. Idiopathic adrenal insufficiency mainly denotes to a cluster of diseases that are clinically found in females. This complex endocrinal disorder has multiple causative factors like genetic predisposition, changes in immune system and adverse environmental factors. Recent findings show that the active form of vitamin D or 1,25 (OH)2D3 can also provide feedback repression of hydroxylase enzyme required necessary for adrenal hormone synthesis (mainly glucocorticoid and mineralocorticoid) [34]. Studies showed that vitamin D can be significantly metabolized by the adrenal gland which contribute toward its paracrine activity. Also, according to various findings, adrenocortical cells may secrete vitamin D metabolites [35]. This further strengthen the possibility of an adrenal specific vitamin D activation pathway. Research findings have often indicated that the active vitamin D3 suppress the generation of inflammatory cytokines and also increase the production of regulatory T cells. In addition to this, it is also found that vitamin D receptor and vitamin D activating enzyme 1-alpha-hydroxylase strongly influence the cytokine production mainly by the immune cells. Vitamin D deficiency can strongly influence the consequences of Addison's disease. As a result, immune dysfunction is observed, causing the release of inflammatory cytokines like Interleukin-1, Tumour Necrosis Factor (TNF) and Interferon  $\alpha$ . Studies have also established that increased proinflammatory cytokines activity and low serum Vitamin D level were witnessed in chronic degenerative diseases like multiple sclerosis, rheumatoid arthritis, insulin dependent diabetes mellitus and various types of colitis. Various experimental studies have also highlighted that patients with low adrenal functioning also developed symptoms associated with low vitamin D status. So, in many cases of Addisons disease vitamin D supplementation was found to be helpful specially by altering the situation through immune modulation [36]. There is great evidence that vitamin D status is found to be altered in Type 1 diabetes mellitus. Their study revealed that there is frequent occurrence of Addison's disease in people with low vitamin D status [37].

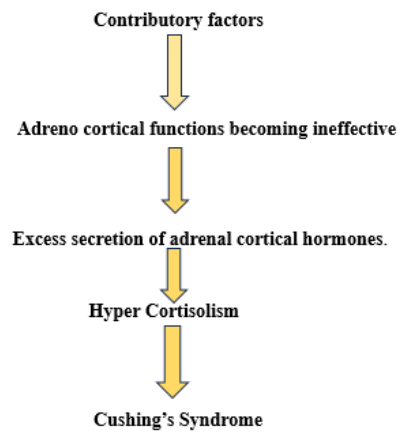
It may be due to deficiency of VD predispose AD by altering immune response and as a result the high inflammation in AD subsequently lowers vitamin D levels. Also, Addisons Disease may lead to suppression of the parathyroid hormone-vitamin D axis showing an association of vitamin D and adrenal steroidogenesis. Apart from these findings, it was also seen that low VD status was significantly co related with one of the characteristics of AD that is severe fatigue. It can be stated that VD plays crucial role in controlling functions of CNS and also the functioning of neurotransmitters like serotonin. Thus, it can be safely assumed that low level of Vitamin D can aggravate symptoms associated with Addisons Disease.

**B. Vitamin D & Hyperactivities of Cortisol: Cushing's Syndrome.**

Cushing’s Syndrome (CS) is an infrequent endocrine disease that is caused due to excessive secretion of cortisol. CS causes major complications which may increase mortality rates due to this condition. Cushing Syndrome is highly manifested by symptoms like malaise, mood changes, anxiety, irritability, poor muscle tone, impaired cognitive function, altered blood pressure, increased risk of infections, darkening of skin, loss of bone mass, increased risk of fractures, decreased libido, decreased fertility rate, erectile dysfunction, sudden weight gain, “moon face”, “buffalo hump”, striae mainly seen in body parts like abdomen, thighs, breasts etc. Hair thinning, easy skin bruising, poor wound healing, development of cardiovascular problems are also witnessed [37].

**Contributory factors**

The relationship between vitamin D and Cushing Syndrome should be stated as the most intricate and indefinite one. There were many investigations which highlighted the possible use of glucocorticoids in changing the serum levels of vitamin D possibly by reducing vitamin D receptors and their activity in many tissues of our system. Also, some research findings acknowledged that extensive use of glucocorticoids significantly reduces vitamin D levels which further only strengthen the idea that there may be an inverse co relation between these 2 important bio molecules of our system [42].



**Fig. 5. Pathophysiology of hyper activity of cortisol**

**Table: Few reviews of articles indicating relationship between Cushing Syndrome and Vitamin D:**

Study	Findings	Conclusion
Seeman (1980) [38]	Excess of Glucocorticoids causes smaller decreases in plasma concentrations of 25(OH)D.	Excess Glucocorticoids does not affect vitamin D status in human
Kugai (1986) [39]	In patients with Cushing syndrome, plasma levels of 25OH vitamin D and 24.25 (OH) vitamin D were significantly found to be lower.	The results indicated impaired absorption of calcium including abnormal vitamin D metabolism.
Povaliaeva (2021) [40]	Patients with Cushing’s Disease have lesser Vitamin D levels than healthy people without Cushing’s disease.	The study concludes that the altered activity of vitamin D catabolism which can be altered with the administration of cholecalciferol.
Guarnotta (2022) [41]	Patients suffering from Cushing’s Disease suffered from lowered Vitamin D levels rather than people with normal cortisol level.	Serum levels of vitamin D were found to be lower in patients suffering from Cushing’s disease rather than in control. Cholecalciferol administration was found to be beneficial in increasing insulin sensitivity and in general lipid profile.

**Conclusion**

Vitamin D and Cortisol both steroid hormones are extremely crucial for regulation of our essential metabolic process, controlling inflammation and managing stress. Though the exact nature of relationship between these two bio molecules are not clearly established yet, still it can be said that vitamin D may have an

association with the ever-changing levels of cortisol in human body thus may prevent the occurrences of stress induced health hazards though more extensive studies are required to support the finding specially in context to our society. It can be anticipated that more experimental studies on the influence of these two biomarkers will provide significant information which can be utilized for influencing overall human health.

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### Conflict of Interest

We wish to inform and confirm here that there are no known conflicts of interest associated with this publication and there has been no financial support for this review work that could have influenced the outcome of this article.

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