

Vitamin D and Its Implications in Various Diseases

Shubhangi Sharma¹, Shikhaa Mahajan², Suvarna Prasad³, Neeru Bhaskar⁴,
Sunita Manhas², Ritu Devi¹

¹MSc. Medical Student, ²Assistant Professor, ³Professor & Head, ⁴Professor,
Department of Biochemistry, MMIMSR, Maharishi Markandeshwar University, Ambala.

Corresponding Author: Shubhangi Sharma

ABSTRACT

Vitamin D is not just a vitamin and functions mainly as hormone. The functional form of vitamin D i.e. calcitriol functions through gene modulation and through extra genetical mechanisms through vitamin D receptors on the cell surface (VDR). There are various epidemiological as well as clinical data describing the beneficial role of vitamin D in the osteoporosis, cancer, immunity, diabetes, multiple sclerosis and rheumatoid arthritis. The main action of vitamin D is mediated through cell cycle regulation and modulation of the immune system.

Keywords: Vitamin D, Calcitriol, disease, diabetes, biochemical basis.

INTRODUCTION

Vitamin D functions in the body through both an endocrine mechanism (regulation of calcium absorption) and an autocrine mechanism (facilitation of gene expression). The former acts through circulating calcitriol, whereas the latter, which accounts for more than 80% of the metabolic utilization of the vitamin each day, produces, uses, and degrades calcitriol exclusively intracellularly. In patients with end-stage kidney disease, the endocrine mechanism is effectively disabled; however, the autocrine mechanism is able to function normally so long as the patient has adequate serum levels of 25(OH)D, on which its function is absolutely dependent. For this reason, calcitriol and its analogs do not constitute adequate replacement in managing vitamin D requirement of such patients. Optimal serum 25(OH)D levels are greater than 32 ng/mL (80 nmol/L). The consequences of low 25(OH)D status comprises elevated risk of various chronic

diseases, differing from hypertension to diabetes to cancer. The sound and most inexpensive way to ensure sufficient vitamin D status is to use oral administration of native vitamin D. Serum 25(OH)D can be expected to rise by about 1 ng/mL (2.5 nmol/L) for every 100 IU of additional vitamin D each day.

Study of the effects of vitamin D and its metabolites and analogs has increased in the past 10 yr, leading to revisions in understanding of both the mode of action of vitamin D and the extent of its role in the functioning of a still growing number of body tissues, systems, and organs. Figure 1 shows metabolism of vitamin D, it shows vitamin D input to the body (whether cutaneous or oral) resulted in conversion to 25-hydroxyvitamin D [25(OH)D] in the liver, with subsequent conversion of 25(OH)D to calcitriol [1,25(OH)₂D] in the kidney. Calcitriol functioned as a hormone, course in the blood to trigger the induction of various elements of the calcium transport

system in the intestinal mucosa. The net result was that active calcium absorption was elevated and the efficiency of calcium absorption, normally low, was expanded so as to permit the restrained adaptation to varying calcium consumption.

Vitamin D has indications of many diseases as discussed below:-

In some of the chronic disorders, vitamin D deficiency has been found to play a vital role. This has been proved either by epidemiologic studies or from hazardous, controlled trials of vitamin D interference. Table 1 below lists various disorders with magnitude of their indications. Four pluses denominate strong evidence including one or more randomized trials; three pluses denominate strong and consistent epidemiologic evidence, without, however, evidence from randomized trials; and one and two pluses denominate less strong evidence that is nonetheless

suggestive. Also, the lack of clinical trial data does not signify that there were null trials, so much as that the trials that are required to reaffirm a causal association have not been done. Moreover, it is worth observing that, in certain occasions, such trials might be quite difficult to conduct (e.g., with a rare disorder such as multiple sclerosis).

TABLE NO. 1 Disorders produced or aggravated by low vitamin D status

DISORDER	STRENGTH OF EVIDENCE
Osteoporosis	++++
Type I diabetes	++
Cancer	++++
Autoimmune diseases	++
Periodontal disease	++++
Multiple Sclerosis	++
Susceptibility /poor response to infection	++++
Osteoarthritis	++

'++++'denominate strong evidence including one or more randomized trials;'+++ 'denominate strong and consistent epidemiologic evidence, without, however, evidence from randomized trials; '++' and '+' denominate less strong evidence that is nevertheless suggestive.

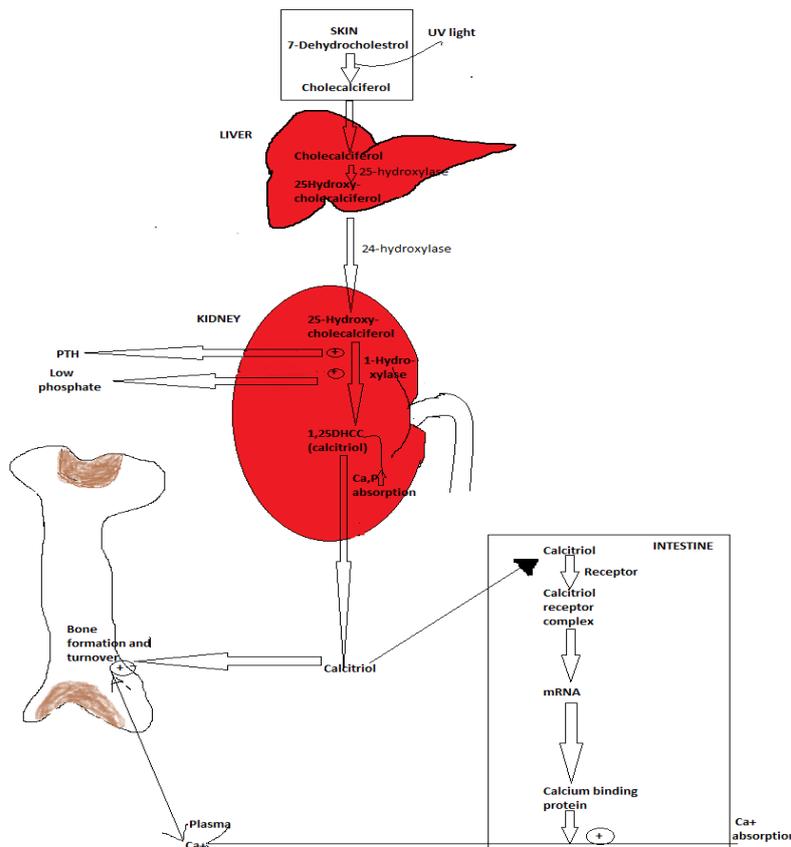


Figure no. 1 Shows metabolism of vitamin:-

Metabolism and biochemical functions of vitamin D(1,25DHCC-1,25-Dihydroxycholecalciferol, also called as calcitriol is the active form of vitamin D; PTH- Parathyroid hormone). [1]

Osteoporosis

Canonical function and the autocrine activity both are required for the role of vitamin D in the pathogenesis and the course of osteoporosis. For the canonical function, furtherance of calcium absorption, it is inconvenient to dissect apart the particular roles of calcium and vitamin D and doubtless not relevant, in any case. This is plainly because one cannot assimilate ample calcium from conceivable diets unless one has fair normal vitamin D status, and, simultaneously, one cannot assimilate sufficient calcium, regardless the vitamin D status, if calcium intake itself is completely low. [2] Hence, given the generality of low consumption of both nutrients, it is not staggering that most of the clinical tryouts that have shown fracture prevention with calcium supplementation did necessitate treatment with vitamin D. All such experiments show security against age-related bone loss and, in many occasions, pruning in fracture risk as well. Where fractures have been reduced, the induced serum 25(OH)D level was in excess of 75 to 80 nmol/L, and dosages that failed to achieve such serum levels generally failed to show fracture reduction. [3] In addition, apparently through an autocrine pathway, vitamin D has been shown to reduce fall risk within only a few weeks of starting treatment, in some trials by as much as 50%. [4,5]

Biochemical basis:- Vitamin D increases intestinal absorption of calcium and phosphate. Vitamin D in low concentrations is associated with impaired calcium absorption, a negative calcium balance, and a compensatory rise in parathyroid hormone (PTH), which results in excessive bone reabsorption.

Cancer

There is a huge body of epidemiologic data showing an inverse interrelation between incident cancer risk and previously measured serum 25(OH)D. [6-9] This corroboration has been accumulated for such cancers as prostate,

colon, breast, lung, and marrow/lymphoma. Risk reduction for breast cancer, for example, is reported to be as much as 70% for the top quartile of serum 25(OH)D (>75nmol/L) relative to the bottom quartile (<45nmol/L). [9] Furthermore, there is an even larger body of animal data showing that vitamin D deficiency in experimental systems predisposes to development of cancer on exposure to typical carcinogens. [10,11] This has been demonstrated both for animals with knockout of the vitamin D receptor and for animals with generated, nutritional vitamin D deficiency. Limiting these lines of evidence is a contemporary randomized, controlled trial of postmenopausal women showing considerable reduction in all-cancer risk, amounting to from 60 to 75%.

Biochemical basis of how vitamin D deficiency causes breast cancer:-

In nearly all forms of breast cancer, vitamin D affects the structure of your epithelial cells. These cells are held together by a glue-like substance called E-cadherin, which provides structure to the cell. E-cadherin is made up of mostly vitamin D and calcium. If you don't have adequate vitamin D, that structure comes apart and those cells do what they are programmed to do in order to survive - they go forth and multiply. If this growth process (cell proliferation) gets out of control, you may end up with cancer.

If you have breast cancer in progress, the addition of vitamin D can help stop cancer cells in their tracks by replenishing E-cadherin. Once cancer growth is slowed, your immune system can begin to get ahead of the cancer cells, because it doesn't have to deal with gazillions of them.

Immunity/Response to Infection

In the days when rickets was unrestrained, children with this disorder frequently died of respiratory infections. Calcitriol in its autocrine role has been identified for approximately 20 years as playing a role in various aspects of the

immune response, [12] best illustrated in the study of Liu et al. [13] for innate immunity. Clinically, it has been noted in randomized, controlled trials that vitamin D co-therapy substantially improved response to standard anti-tubercular therapy in patients with advanced pulmonary tuberculosis [14] and, as a secondary outcome, reduced risk for influenza in postmenopausal black women who received vitamin D. [15] Also, phagocytic function of human macrophages is enhanced in individuals who received vitamin D supplementation. [16] So in nutshell, feedback to infection is hampered when vitamin D status is not so much as highest standard.

Biochemical basis of how vitamin D increases immunity and helps fight infection:-

Vitamin D has effects on the innate immunity. Macrophages recognize lipopolysaccharide (LPS) a surrogate for bacterial infection, through toll like responses (TLR). Engagement of TLR, leads to a cascade of events that produces peptides with potent bactericidal activity such as cathelicidin and beta defensin. These peptides co localize within phagosomes with ingested bacteria where they disrupt bacterial cell membrane and have potent anti-bacterial effects.

Diabetes

Both type 1 and type 2 diabetes have been associated with low vitamin D status, both current and antecedent. [17-19] For example, in a study based in the National Health and Nutrition Examination Survey (NHANES) data, participants without a known history and/or diagnosis of diabetes were much more likely to have high blood sugar values, both fasting and after a glucose challenge, when they had low vitamin D status. [17] Diabetes Mellitus Type 2. The generality of diabetes mellitus type 2 (DM type II) is expanding in children and adolescents. Thus, investigating the part of vitamin D and calcium in this population is of utmost importance. Obesity effects both diabetes and vitamin D status. DM type II is

prepondering in children with obesity and vitamin D is faultily absorbed and coursing in people with obesity. Many investigations has demonstrated that vitamin D and calcium effect pancreatic β -cell function, insulin sensitivity, and systemic inflammation. Furthermore, it has also been uncovered that patients with DM type II are advanced to have a lower serum 25-OH D concentration in contrast to controls without diabetes.

Biochemical basis:-

Vitamin D may be implicated in pathophysiology of diabetes through modulating mitogen-activated protein kinase (MAPK), phosphoinositide3-kinase inhibitor (P13K) and Smad signalling.

Hypertension and Cardiovascular Disease

The interrelation of vitamin D status and hypertension is specifically intense. Both controlled trials and meta-analyses have shown a protective effect of high calcium intake for both pregnancy-related and essential hypertension [20-23] although risk for incident hypertension is contrarily linked to previously calculated serum 25(OH)D concentration.

Biochemical basis:-

Vitamin D effect cardio-vascular disease by modulating mitogen-activated protein kinase (MAPK), phosphoinositide3-kinase inhibitor (P13K) and smad signalling.

Dry Eye Syndromes and Macular Degeneration

Many of the recent studies demonstrate that patients with vitamin D deficiency should be examined for dry eye syndromes. One could easily presume and say that anyone with dry eye syndrome would be recommended to get their vitamin D levels checked.

It was also noticed that premenopausal women who were not having enough of specified in vitamin D had considerable risk of dry eye and impaired tear function.

Vitamin D deficiency may also elevate the risk of age-related macular degeneration (AMD) if you are genetically susceptible to it.

Biochemical basis of how vitamin D inhibits occurrence of dry-eye:-

Occludin is a major tight junction protein in the cornea and is needed for proper wound healing and cell migration. A decreased expression of occludin leads to decreased rate in wound healing, decreases trans epithelial resistance and increases permeability. Vitamin D supplementation has shown in studies to enhance corneal barrier function, likely through increased expression of tight junction based protein occludin.

Vitamin D Deficiency and Multiple Sclerosis (MS)

It has been evaluated that the prevalence of MS increases the farther away you live from the equator, indicating lack of sun exposure increases the risk.

Furthermore, this elevated risk is maximized if one has insufficiency of sun exposure prior to 15 years of age.

MS is a persistent, neurodegenerative disease of the nerves in your brain and spinal column that is brought about through by the means of demyelization process. It has been from a very long time adjudged to be as "hopeless" disease with insufficient therapy options.

The usual prescription for multiple sclerosis, center the highly toxic immune repressing medications like prednisone and interferon. Although, the studies over the past few decades indicates that MS may be ameliorated using vitamin D.

Various experiments also states that vitamin D can work for in a protective capacity, and evidently it's advantageous to avert it rather than trying to treat it before it develops.

Biochemical basis: 1,25-(OH)₂D alters dendritic cell and T-cell function and regulates macrophages in experimental allergic encephalomyelitis (EAE). Interestingly, 1,25-(OH)₂D is thought to be

operating on CNS constituent cells as well. Subtle defects in vitamin D metabolism, including genetic polymorphisms related to vitamin D, might possibly be involved as well. Optimal 25OHD serum concentrations, throughout the year, may be beneficial for patients with MS, both to obtain immune-mediated suppression of disease activity, and also to decrease disease-related complications, including increased bone resorption, fractures, and muscle weakness.

Vitamin D's Role in Inflammatory Rheumatic Diseases

Chronic inflammatory rheumatic diseases, comprises but is not only confined to rheumatoid arthritis (RA); it refers to over 100 various conditions established in chronic inflammation impacting your joints. Broadly, CIRD is considered to be associated with autoimmune dysfunction.

It has also been hypothesized that with various types of arthritis found over 40 percent of the patients with rheumatoid arthritis were deficient in vitamin D, with a 25-hydroxyvitamin D level of 20 ng/ml or less. Almost 40 percent of those with ankylosing spondylitis, and nearly 41 percent of those with psoriatic arthritis were also vitamin D deficient. In contrast, less than 27 percent of the controls had vitamin D deficiency.

Biochemical basis:- Rheumatoid arthritis is a disorder that is mediated by Th1 cytokine. [24] By hampering Th1 responses, vitamin D assists in redirecting the T cell reaction in order to obtain immunosuppressive state.

Vitamin D deficiency common in those with Lupus

According to researchers in Cairo [25] most patients with systemic lupus erythematosus (SLE) have some level of vitamin D deficiency (defined as a level of 10 ng/ml or less) or insufficiency (a level between 10 and 30ng/ml). Those with depressed levels also tend to have problem controlling their disease.

On average, SLE patients had significantly lower serum 25(OH) D than the healthy participants -an average of 17.6ng/ml compared to 79ng/ml. More than 73 percent of lupus patients had inadequate vitamin D levels, and over 23 percent were deficient.

Biochemical basis:- Vitamin D receptors are found on the surface of a cell where they receive chemical signals. By attaching themselves to a receptor, these chemical signals direct a cell to do something. For example, to act in a certain way, divide or die. There are vitamin D receptors found on cells in the immune system, and vitamin D can bind to these receptors. This can cause the auto-antibodies to decrease and stop attacking the healthy cells in the body. Therefore, it is believed that vitamin D can help prevent lupus flares by reducing inflammation in the body.

Vitamin D for HIV/AIDS

The ability of vitamin D to combat infections and strengthen immune function is notable, many researchers now advise that vitamin D supplements may be an easy and budgeted way to combat even more serious infections like HIV.

A team of various researchers from different countries like U.S, U.K and South Africa enlisted 100 Cape Town residents between the ages of 18 and 24 to evaluate various factors i.e., the impact of sun exposure, dietary vitamin D, genetics and skin pigmentation on vitamin D levels in the blood. The study [26] also looked for signs of improved resistance to HIV.

After keeping in account various factors like diet, genes and skin color, sun exposure was found to be the strongest amongst them determining vitamin D blood levels. During winters, vitamin D deficiency was common among all participants regardless of skin tone. In regards, the consequences of the vitamin D had on HIV, it was found out that it reduces HIV replication and elevate white blood cell counts, advising it might help to repress disease progression.

Biochemical basis of action:- High-dosage oral vitamin D3 supplementation attenuated HIV-1 replication, increased circulating white blood cells and reversed winter-associated anemia," the researchers reported. "Vitamin D3 presents a low-cost supplementation to improve HIV-associated immunity

Hyperparathyroidism.

Sparse levels of serum vitamin D and calcium result in encouraging the release of parathyroid hormone (PTH). As deficiency advances, the parathyroid is overstimulated and results in secondary hyperparathyroidism. This release of PTH results an increase in the metabolism of 25-OHD to 1,25dihydroxyvitamin D, and this additionally aggravate vitamin D deficiency. This release of PTH also results in phosphatemia, reduced levels of serum phosphorus that cause decreased mineralization of the collagen matrix, resulting in osteomalacia, and in the due course osteoporosis.

Biochemical basis of action: A high serum phosphate, decreased levels of serum 1, 25 (OH)₂D and the subsequently low serum calcium are the major metabolic abnormalities in CRF, which lead to the secondary hyperparathyroidism. At the level of parathyroid hormone (PTH) secretion there is insensitivity to the ambient serum calcium. PTH mRNA levels are increased by a post-transcriptional mechanism that involves the binding of PT cytosolic proteins to the PTH mRNA 3'-untranslated region (UTR)

Low Bone Density:

Low bone density is prevalent in adults. The clinical basis for low bone density is a bone mineral density that is a t-score of more than 1 but less than 2.5 standard deviations (SDs) below the mean for young adults measured via dual-energy x-ray absorptionmetry (DEXA). To put this into perspective, osteoporosis is valued at a t-score of 2.5 SD or more below the mean for young adults. [26] Patients with low bone

mineral density are more prone to fractures, chiefly hip and vertebrae. Greater than 33.6 million Americans have low bone density, and 80% of those people are women. [26] A Meta analysis of 25 trials involving postmenopausal women showed that vitamin D supplementation (300-2000 IU daily) reduced the risk of vertebral fracture. [26] Supplementation of Vitamin D assist in reducing the incidence of low bone density and, in turn, fractures.

Biochemical basis of action:- Pathophysiology of low bone density regulation may be modulated by a single gene with pleiotropic transcriptional actions.

Periodontal Disease.

Periodontal disease is the principal cause of tooth loss in older adults. This inflammatory disease causes loss of periodontal attachment, including ligaments and alveolar bone. [27] Poor bone quality is thought to be a risk factor of periodontal disease, and it has been shown that vitamin D supplementation can reduce tooth loss. [27] Raised serum 25(OH)D levels through vitamin D and calcium supplementation has been demonstrated to decrease tooth loss and cut down periodontal disease.

Biochemical basis: Vitamin D produces cathelicidin and defensins, which have antimicrobial properties. These compounds reduce the number of bacteria in the mouth. Reduces matrix metalloproteinases (MMPs). MMPs are enzymes that are associated with periodontal disease.

Vitamin D and Non-alcoholic fatty liver disease (NAFLD)

NAFLD is a pathological clinical entity that includes a broad spectrum of liver conditions from steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis NAFLD is one of the primary causes of chronic liver disease in developed countries. Some NAFLD patients develop NASH and cirrhosis, while many others do not experience disease progression; however, the reason for these differences in progression is not known.

Vitamin D deficiency has been associated with systemic increase in inflammation markers, and systemic inflammation may play a chief role in the pathogenesis and progression of NAFLD. Increase in visceral adiposity encourages the release of fatty acids and pro-inflammatory cytokines and actuate inflammation pathways in the liver, prompting pro-inflammatory cytokine secretion that leads to liver damage. Furthermore, the obesity enhances the onset of NAFLD due to elevated hepatic lipid synthesis secondary to access free fatty acids; following association with oxidative stress on mitochondrial and with the increase of pro-inflammatory cytokines can surely activate a progression of steatosis to non alcoholic steatohepatitis (NASH) and cirrhosis. Studies in vivo and in vitro have clearly documented that steatosis reduces oxidative activity controlled by cytochrome P450. [28] These inflammatory processes may be blocked by increasing the levels of 25(OH)D, and the development and progression of NAFLD may stop. In fact, vitamin D supplements have been shown to decrease inflammation markers [29-32] and increase anti-inflammatory cytokines. [29] It is best-known that vitamin D's effect in the liver is not only exerted on the hepatocytes, given that these cells show minute VDR mRNA. In contrast, sinusoidal cells, Kupffer cells, hepatic stellate cells and immune system cells exhibits VDR mRNA that is functionally active. Therefore, vitamin D deficiency may influence the activity/expression of macrophages, dendritic cells and T and B lymphocytes by favoring oxidative stress and the production of pro-inflammatory cytokines that lead to subclinical inflammation. Moreover, fibrosis is evoked by TGF- β secretion that results from the elevated secretion of the matrix metalloproteinase 9 inhibitor (TIMP-1). [33] In fact, cell cultures demonstrate that vitamin D has an anti-inflammatory and an antifibrinolytic effect on hepatic stellate cells. Ultimately, animal models showcase that more severe histological lesions of

NAFLD are associated with high levels of mRNA of TLR2, 4 and 9, proinflammatory cytokines and oxidative stress markers in rats with a high-fat diet and deficient in vitamin D. [34] A recent study of experimentally NAFLD-induced rats showed that ultraviolet light exposure decreased hepatic stellate cell activity and TGF-β synthesis and stimulated the production of apolipoprotein E and adiponectin. Together, these findings translate into a beneficial effect on NAFLD, and a decrease in IR, steatosis, apoptosis,

inflammation and intra-hepatic fibrosis was hypothesized. [34] Therefore, it is concluded that extrahepatic signaling affects fibrosis and inflammation and that the vitamin D-VDR axis may play a role in the initiation and progression of NAFLD.

Therefore, while the operation of vitamin D's control over hepatic lipid homeostasis and its connection with inflammation are not well known, latest research lines aids in comprehending its immune modulation capacity and of current remedial interventions for NAFLD.

Table 2. Biological response and deficiency diseases because of vitamin D deficiency.

Summarizes the biological responses produced by vitamin D and disease produced in its deficiency.

S.NO	PHYSIOLOGICAL SYSTEMS	BIOLOGICAL RESPONSES	VITAMIN D DEFICIENCY ASSOCIATED DISEASES
1.	ALL CELLS	Cell cycle regulation ***** Cell proliferation inhibition	Cancer ***** Prostate, breast, colon cancer(prevention) Leukemia(treatment)
2.	CALCIUM HOMEOSTASIS	Intestinal calcium absorption and bone remodeling	Rickets, Osteomalacia, Osteoporosis, low bone density.
3.	IMMUNE SYSTEM INNATE ***** ADAPTIVE	Stimulating synthesis of antimicrobial peptides ***** Dendritic and T-cell function	Increased prevalence of infection ;e.g tuberculosis ***** Increased autoimmune diseases :e.g. type 1 diabetes, HIV/AIDS, multiple sclerosis, inflammatory bowel disease, psoriasis.
4.	PANCREAS-β Cells	Facilitate insulin secretion	Impaired glucose tolerance and type-II diabetes
5.	HEART AND CARDIOVASCULAR	Renin-angiotensin regulation, Coagulation, Fibrinolysis, heart muscle function.	High rennin hepertension:increased Cardiovascular risk factor; increased thrombogenesis.
6.	MUSCLE	Promote normal skeletal muscle development; improve muscle strength	Muscle myopathy;increased falls
7.	BRAIN	In progress brain has VDR and 1α-Hydroxylase	Vitamin D deficiency in-utero may contribute to developmental problems.
8.	INFLAMMATORY CYTOKINES	Cause antibodies to decrease and stop attacking healthy cells in body and reduces inflammation	Systemic lupus erythematosus: mouth and nose ulcers, inflammation of pleura, fatigue
9.	OCCLUDIN	Enhance tear film parameters and reduce ocular surface inflammation	Dry eye and macular degeneration: impaired tear function.
10.	CALCIUM SUPPLEMENTATION	Exerts its anti-inflammatory effects and reduces pathogenic bacteria.	Periodontal disease: bacterial driven inflammation (tooth loss in elderly)
11.	PARATHYROID GLAND		Hyperparathyroidism, parathyroid tumors.
12.	NON-ALCOHOLIC FATTY LIVER DISEASE	Anti-inflammatory and an anti-fibrinolytic effect on hepatic stellate cells	NAFLD-obesity, high TG levels and Type 2 DM, patients with metabolic syndrome,insulin resistance.

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