|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2019: 79.34
Volume 5, Issue 9; September: 2021; Page No.225-239

Review Article

ANALYSIS OF VITAMIN D WITH INTRACTABLE DISEASES- A REVIEW.

Chelsea Rumao[1], Chitranshi Puranik[2], Diksha Garg[3], Reema Deshwal[4]

[1]Sophia College - Mumbai, Dr D.Y. Patil Institute of Biotechnology and Bioinformatics- Pune

[2]Manav Rachna International Institute of Research and Studies- Haryana

[3]Deenbandhu Chhotu Ram University of Science and Technology- Haryana

[4]Kalinga Institute of Industrial Technology- Bhubaneswar

Article Info: Received 04 August 2021; Accepted 10 September 2021
DOI: https://doi.org/10.32553/ijmbs.v5i9.2219
Corresponding author: Chelsea Rumao
Conflict of interest: No conflict of interest.

Abstract
Vitamin D is a fat-soluble, steroid hormone responsible for the phospho calcium mechanism. Mainly vitamin D encompasses a group of steroid compounds, namely the VitD2 (ergocalciferol) and the VitD3(cholecalciferol). It is an important requirement for normal functioning of the skeletal muscles, organs and normal metabolism. Providing Vitamin D supplementation to people with Diabetes (Type 1 and 2), Covid-19 positive and people with Thyroid problems showed improved glycaemic controls and regularized blood sugar levels, increase in immune response and regulating the Thyroid levels in the body. Vitamin D also adds to the innate immune system and also plays a major role in zinc metabolism which becomes a major reason for decreasing the symptoms of COVID-19 in the human body.
Keywords: Vitamin D, Type 2 Diabetes Mellitus, Type 1 Diabetes Mellitus, Covid-19, Diabetic Neuropathy, Diabetic Nephropathy, Thyroid, Hypovitaminosis.

Introduction

Vitamins are organic substances that are generally classified as fat soluble or water soluble and are of vital importance for normal growth and development. Vitamin D's traditional role is to maintain calcium homeostasis and help regulate bone metabolism. A few other studies elaborate on the functions that include cardiovascular homeostasis, modulation of inflammation and tuning of the innate and adaptive immunity systems. Altered levels of Vitamin D exacerbate other diseases as well, some of them being Diabetic Neuropathy (DN), Chronic Kidney Disease (Chronic Kidney Disease), Diabetic Foot Ulcer (DFU), Type 1 Diabetes Mellitus (T1DM) which will be discussed in this paper. There is an epidemic of vitamin D deficiency, with over one billion people affected worldwide. Vitamin D3 is a steroid hormone produced in the skin after sun exposure (cholecalciferol). UVB light of wavelengths between 280 and 315 nm is adequate for 7-dehydrocholesterol conversion to pre-vitamin D3, which is further converted to vitamin D3 in the skin. Vitamin D production is reduced in darker-skinned, older, and obese individuals. Vitamin D status is defined by measuring the levels of 25(OH)D in the blood owing to its longer half-life in plasma, where it forms a circulating reservoir of Vitamin D. Usually, dietary contribution is not more than 20% of total, unless food is fortified with Vitamin D. Cholecalciferol is biologically inert and requires two sequential hydroxylation reactions. One in the liver on the C25 position, to form 25- hydroxyvitamin D3 [25(OH)D3, or calcidiol]. Second in the kidney, at the α position of C1, to form 1,25-dihydroxyvitamin D3 [1,25-dihydroxyvitamin D3, or calcitriol].

Synthesis and metabolism of 1α,25-dihydroxyvitamin D3.
Deficiency - <20 ng/mL

Insufficiency -< 21–29 ng/mL

Satisfactory -< 30–100 ng/mL

Significant risk factors for vitamin D deficiency

1. Increasing age
2. Use of sunscreen >Pigmented skin >House-bound patients >Obesity
3. Medication (antiepileptic/antiretroviral drugs) >renal disease
4. Liver disease
5. Malabsorption syndrome

Vitamin D and the Vitamin D Receptor

Activated vitamin D acts through its cognate vitamin D receptor (Vitamin DR) that has two subtypes: membrane-located mVitamin DR, and nuclear-located nVitamin DR which are expressed majorly in mesenchymal derived cells; mVitamin DR regulates the non-genomic effects, exerted within seconds to minutes after its activation. It has a role in secondary signalling mechanisms, adipocyte metabolism, insulinotropic effects, and antiapoptotic pathways. While nVitamin DR regulates the genomic effects, showing its effects within hours to days after its activation.

25(OH)D concentration should exceed 30 ng/mL, to maximize its effect on calcium, bone, and muscle metabolism. Vitamin D insufficiency which is not low enough to cause bone disease is significantly associated with cardiovascular disease. Vitamin DR is present in many tissues, implying its multiple functions beyond calcium homeostasis. 1,25-dihydroxyvitamin D3 bound to Vitamin DR, interacts with retinoid X receptor (RXR) forming a heterodimer that binds to Vitamin D responsive elements. The action of Vitamin D in a cell depends on the Vitamin D-mediated gene activation, transcriptional response, and protein formation. Vitamin D stimulates intestinal calcium and phosphate absorption, 1,25-dihydroxyvitamin D3/ Vitamin DR-RXR and also regulates the expression of genes in non-calcemic tissues. This mechanism allows the concerted genomic and rapid actions of 1,25-dihydroxyvitamin D3 to have an interplay in varied diseases such as osteoporosis, cancer, diabetes, atherosclerosis, vascular disease/calcification, and infection. Furthermore, the Vitamin DR gene is expressed within developing neurons of rodent dorsal root ganglia, which may suggest a role for Vitamin D in PNS development and nociception. The recognition of receptors for 1α,25-dihydroxyvitamin D3 (1,25-dihydroxyvitamin D3) in cells of the immune system led to experiments in animal models of T1DM. Absence of a functional Vitamin D receptor (Vitamin DR) or its ligand, 25-

hydroxyvitamin D-1, in mice, created a bone and growth plate phenotype that mimics severe Vitamin D deficiency. Vitamin DR rescue in the intestine restores normal bone and growth plate phenotype. For example, Vitamin DR-deficient mice develop total alopecia, also seen in humans. The immune system of Vitamin DR- or Vitamin D–deficient mice show increased sensitivity to autoimmune diseases like inflammatory bowel disease or TIDM. Vitamin DR-deficient mice are prone to oncogene or chemo carcinogen-induced tumors. They also develop high renin hypertension, cardiac hypertrophy, and increased thrombogenicity.

Patients with advanced chronic kidney disease (chronic kidney disease) with creatinine clearance of <35 ml/min, and presence of renal osteodystrophy and were treated with either vitamin D3 or 1,25-dihydroxyvitamin D (1,25(OH)2D) along with calcium after a 6-month observation period. The group treated with 1,25(OH)2D, some patients developed hypercalcemia that required a reduction in dosage. The fall in creatinine clearance was greater during treatment than before treatment in all patients who were on 1,25(OH)2D.

Vitamin D can also be described as a neurotrophic hormone, displaying neuroprotective effects through upregulation of vitamin D receptor (Vitamin DR) expression and downregulation of L-type calcium channel expression. In vivo studies illustrate that Vitamin D improves axonogenesis, sensory neural response in peripheral nerves and improves electrophysiological recovery. A study found lower serum Vitamin D in patients with DN than those without DN. DN is linked with reduced Nerve Growth Factor (NGF) expression in human nerve cells and Vitamin D increases NGF production in human cells. Vitamin D deficiency triggers hyperglycemia and inflammation which is associated with DN progression. Vitamin D deficiency may also be correlated with increased pain sensitization. Vitamin D supplementation has been reported to have beneficial effects on neuropathic pain and prevents neuronal degeneration. DN patients have a disturbed balance as compared to healthy subjects and diabetic individuals without neuropathy. Recent studies have shown a relationship between Vitamin D and balance. A possible mechanism, -the association of Vitamin DR receptor in muscle tissue and CNS. Based on all these findings, Vitamin D replacement therapy in patients with DN may resolve neuropathic pain to some extent and improve balance.

The world is facing a pandemic of coronavirus infection, the disease called COVID-19. COVID-19 is caused by the SARS-CoV-2 that causes lower respiratory symptoms in the human body and is a cause of death for about 745000 people worldwide. COVID-19 big global pandemic creates a hypothesis that there is the relation between vitamin D levels and mortality causes of COVID- 19. Vitamin D treatment becomes the key aspect to prevent COVID -19. According to this research, COVID-19 is more prominent in African American individuals because of vitamin D deficiency due to less sun exposure.

Overall, Vitamin D levels and its supplementation can be linked to the treatment and management of various incurable diseases. This review paper focuses majorly on the role of Vitamin D in Covid-19 infection, Diabetes and Thyroid.

Methods:

The study was conducted using four databases Google Scholars SAGE, DOAJ and PubMed. The selection of papers was done based on keywords and themes relevant to this review. Further, the published papers from these databases were arranged in systematic order with respect to the year of publication.

Results:

Role of Vitamin D in Covid- 19 infection.

Covid-19 or SARS-2 is the deadliest disease recently. It spreads worldwide because of its rapid transfer from one person to another. It spreads through respiratory droplets, close contact, or even through tears. Its earlier strain SARS-1 or MERS is not deadliest like this strain. On January 30 it was declared by the WHO as a public health emergency on March 11 pandemic started because of its rapid spread all over the world. It is so challenging to find its exact symptoms as most of the cases are asymptomatic. Some mild cases are found with a nonspecific system like fever, cough, fatigue, headache, diarrhoea, sore throat. Most of the deaths are observed in the age category of above 60 years. The rate of death was higher in older individuals, specifically those who have hypertension and diabetes mellitus. The Chinese data reported that 2% of cases of COVID-19 were children. Vitamin D plays a very important role in all age groups. The infection by COVID -19 can be reduced by vitamin D because vitamin D immune the response of anti-inflammatory cytokines and that prevents lung damage in the human body. Vitamin D agonist calcitriol is used as a protective agent against lung injury by regulating the expression of ACE2 (angiotensin-converting enzyme 2) in lung tissues. A randomized trial from China reported the beneficial effects of vitamin D are acceptable for the prevention of seasonal influenza as proved by rapid relief from symptoms.

Due to the widespread of COVID-19 in 2020 scientists have found some of the asymptomatic, mildly symptomatic, and severe disease patients and concluded the hypothesis that vitamin D plays a vital role in finding the severity of COVID-19. For the hypothesis confirmation, they measured the vitamin D levels of all the COVID-19 patients.

RT-PCR was used to conform to COVID-19 patients. Then further they are divided into 2 groups named Group A and Group B. Group A were asymptomatic at the time of admission and remained asymptomatic till discharge (12th day) whereas Group B patients were admitted to ICU due to severe COVID diseases. Then Serum 25 (OH)D estimation was performed along with another routine blood test so the patients below the serum 25(OH)D level of <20ng/ml were considered to be vitamin D deficient. The research aims to explain that the majority of COVID-19 patients have a low vitamin D level, which may decrease immunity.

Mechanism of Vitamin D and Covid-19

Vitamin D was considered as a steroid hormone but now the outbreak of fast-spreading covid-19 is the reason for vitamin D when immune system acute respiratory disease syndrome. Vitamin help in the immunomodulation role increases innate immunity by secreting antiviral peptides. Some of the hypotheses state that vitamin D deficiency leads to the high risk of COVID-19 severity and mortality. So the mechanism used by vitamin D FOR COVID -19 infection was lymphopenia. Vitamin d helps to secrete the antimicrobial peptides and plays the role of protector for interstitial pneumonitis. To reduce the lung function vitamin D helps to secrete the renin-angiotensin system which leads to chronic cardiovascular diseases. But some hypotheses state that vitamin D helps to maintain immune homeostasis.

As COVID-19 is one of the deadliest diseases of the year 2020, this particular hypothesis focuses on finding the increased risk of testing positive covid-19 with deficient vitamin D status and this study fails to accurately reflect any particular effect of vitamin D on outcomes. A person on vitamin D treatment has low chances to come under the contact of viral infections but not a guaranteed outcome. Test low cost of vitamin D support argument for population-level supplements but a wide group of low-level vitamin D deficiency becomes a major issue for this particular treatment.it is still a question that vitamin D treatment decreases the covid 19 incidents just reduce the transmission of COVID-19 or just strength over the immune system although vitamin D also helps to increase the metabolism of zinc which decreases is the replication of coronavirus.

According to another report, COVID-19 mortality is high in adults who were admitted to respiratory intensive care unit it is about 50%, and then that rate was about 5%.CRP levels are used to determine cytokine storm and the severity of covid- 19 cases different relations and studies were agreement that 84.6% were ICU patients whereas 51.71 WERE NON- ICU have vitamin D insufficiency.

Role of Vitamin D in Thyroid

Vitamin D certainly influences autoimmune disease -namely Autoimmune Thyroid Disease(AITD). AITD is an organ-specific autoimmune disease (AID) when the immune system does not recognize the self thyroid cells and starts attacking them. Various studies have been carried out to explore the new pleiotropic roles of vitamin D. Most of the molecular and cellular mechanisms liable for the cardiovascular effects of the hormone are clarified. Thyroid hormone is known for deploying both genomic and non-genomic effects on cardiac myocytes. Studies have confirmed T3 as the active sort of hormone that accounts for the overwhelming majority of thyroid effects including stimulation of tissue thermogenesis, alterations within the expression of varied cellular proteins, and action on the heart and vascular smooth muscle cells. Vitamin D is studied to modulate thyroid neoplastic and autoimmune diseases. It investigated the role of the vitamin D receptor (Vitamin DR) in normal thyroid development and function (thyrocytes and C cells). 1,25-dihydroxy vitamin D3 [1,25(OH) 2 D3], the active form of vitamin D, is importantly studied for its effects on calcium and phosphate homeostasis with bone, intestine, and kidney as principal target organs/tissues. However, 1,25(OH)2 D3 has pleiotropic effects which include the following properties of antiproliferative, anti-inflammatory, and differentiating effects.

Low levels of vitamin D have also been related to thyroid disease, such as Hashimoto's thyroiditis. Similarly, patients with new-onset Graves' disease were found to possess decreased 25-hydroxyvitamin D concentrations. Impaired vitamin D signaling has been reported for the encouragement of thyroid tumorigenesis. A prevalence of vitamin D deficiency has been estimated to start at 20 to 100% of Western countries' elderly men and women. The same trends have been reported in children, teens, and young and middle-aged adults worldwide. In particular, low vitamin D concentrations, certain vitamin D receptor (Vitamin DR) gene polymorphisms, and pathologies of vitamin D-binding proteins and their genes may favor the event of Hashimoto's thyroiditis (HT).

Studies show that low levels of vitamin D contribute to the chapter of autoimmune thyroid diseases (AITDs) like Hashimoto's thyroiditis and Graves' disease. Also, the replacement of vitamin D has been effective in the treatment of the AITDs by diminishing levels of thyroid antibodies and suppressing the autoimmune reaction of the body. This paper aims to study the effect of vitamin D on Hashimoto's thyroiditis (HT). It tries to check whether the low vitamin D levels [25(OH)D] are the direct cause of HT disease. An experiment was performed with 88 patients suffering from HT. The concentrations of vitamin D, thyroid autoimmunity markers, and cytokinins produced by Th1, Th2, and Th17 cells were compared with a control group of 71 healthy people. Hashimoto's thyroiditis (HT) was found to be the most prevalent autoimmune disorder and characterized by the destruction of thyroid cells created by leukocytes and antibody-mediated immune processes accompanied by hypothyroidism. In recent years, Vitamin D deficiency has been especially demonstrated in HT patients' evidence has emerged and investigated if vitamin D affects circulating thyroid autoantibodies(Anti-TPO Ab, Anti-Tg Ab) and hormones profile(T4, T3,& TSH). Forty-two women who had HT disease were enrolled and divided into two groups for vitamin D and placebo groups. The former group was directed with 50000 IU vitamin D and the placebo group with placebo pearls, once a week for 3 months, respectively.

The serum levels of [25(OH)D]aka 25-hydroxy vitamin d; calcium ions(Ca^{++}); anti-TPO Ab (aka anti-thyroperoxidase antibody); anti-TgAb (aka anti-thyroglobulin antibody); T4; T3; and TSH levels were measured before and after the study. These serum levels were studied using ELISA (enzyme-linked immunosorbent assay).

Vitamin D plays an important role in keeping calcium and phosphorus balance, as well as bone health like Osteoporosis is a common avator of diseases affecting bone health due to an imbalance between osteoclast and osteoblast functions.it has gained increasing interest because of its important role in other non skeletal diseases too; Such as "Bouchemal et al. have told about the important role vitamin D plays in metabolic syndrome". 'Djeraba et al. have revealed vitamin D deficiency was associated with active Behcet's disease (BD) and after the treatment of vitamin D down-modulates nitric oxide production in BD'. We also previously described that vitamin D deficiency is also a risk factor for neuropsychiatric disorders and autoimmune diseases. Now vitamin D, as it also appears to regulate the immune system, is newly identified as an immunomodulatory hormone. Among some common thyroid diseases, such as Hashimoto's thyroiditis (HT) and Graves' disease (GD), there are often autoimmune factors involved in their development. Current studies have reported that the vitamin D receptor (Vitamin DR) is expressed on immune cells, where it can regulate their proliferation and differentiation, resulting in thyroid damage, and vitamin D has been revealed to be associated with thyroid disease.

Role of Vitamin D in Diabetes - Type 2 (T2DM)

Type 2 diabetes (T2D) has become a universal health care problem. Observational studies have shown a correlation between Vitamin D deficiency, onset and progression of T2DM and future macrovascular events. Moreover, in vivo and in vitro studies have projected possible roles of Vitamin D in glucose metabolism, e.g., insulin secretion via the vitamin D receptor (Vitamin DR) on pancreatic β cells; regulating immune responses and lowering systemic inflammation; and reducing peripheral insulin resistance through Vitamin DR in the muscles and liver. More cases of T2DM have been reported in Vitamin D-deficient individuals. Vitamin D deficiency impairs the normal function of beta cells in synthesis and secretion of insulin.

The diabetic foot ulcer (DFU) is a severe condition associated in patients with diabetes mellitus (DM). Patients with DFU have a higher mortality in contrast with diabetic patients unaccompanied by the foot ulcer. The mortality rate of DFU is about twice that of nonulcerated DM patients. Some researchers have reported effects of Vitamin D on T-cell-arm immunity, pancreatic insulin release, cell growth and healing. Low concentrations of Vitamin D may be related to the progression of diabetic foot infections. In vitro studies reported that Vitamin D could restore the production of antimicrobial peptides in the cells from DFU and improve wound-healing. In rats, the topical application of Vitamin D increased the wound healing in a dose-dependent approach. Another study reported calcitriol use to promote endothelial and keratinocyte cell movement in a DFU model.

Diabetic neuropathy (DN) is a long-term complication of diabetes mellitus (DM) that is linked with reduction in the quality of life of the victims. DN symptoms include foot and hand muscle weakness, balance disturbance, and neuropathic pain like alterations in touch, pain, or heat sensations; burning; pins and needles; tingling; or numbness.

DN involves both small and larger nerve fibres. The small nerve fibres include C-fibers associated with electric shock or burning symptoms. Pathological changes in these fibers go undetected in EMG. Involvement of the large nerve fibers impairs balance but can be determined by performing EMG. Pathophysiology of DN is complex, but Vitamin D deficiency can be an independent predictor of DN progression. Vitamin D deficiency is linked to IGT and T2DM in humans and was confirmed in animal models. Insulin secretion is inhibited by Vitamin D deficiency. The effector pathway is a vitamin D-dependent calcium-binding protein known as calbindin-D28k. It protects beta cells from cytokine-mediated cell death.

Possible Mechanisms of Vitamin D and Calcium on T2DM

Vitamin D influences β-cell function, insulin sensitivity, and systemic inflammation which are characteristic of T2DM pathways. 1,25-dihydroxyvitamin D3 could invigorate insulin secretion because of Vitamin DRE, in the insulin gene promoter of pancreatic β-cell. Vitamin DRE initiates the transcription of insulin genes and others involved in cellular growth, cytoskeletal organization and intracellular junctions of β-cell. 1-α-hydroxylase in β cells produces 1,25-dihydroxyvitamin D3, which creates a paracrine effect. A study on Vitamin D–deficient rats showed 48% decrease in insulin secretion as compared with rats supplemented with Vitamin D before the procedure. Human studies showed an increase of insulin secretion during oral glucose tolerance tests in diabetic patients and in patients at high risk of developing diabetes after administration of Vitamin D.

Serum calcium plays a role in the glucose-stimulated insulin secretion and in insulin action. A non-genomic effect of Vitamin D is the elevation in cytosolic calcium level modulated by the activation of signalling pathways mediated by protein kinase A (PKA) and protein kinase C (PKC). An in vitro study showed that in calbindin- D28k transfected pancreatic β-cells, calbindin inhibited the free radical formation induced by cytokines and protected β-cells against degeneration.

Vitamin D, exclusively affects the insulin response to glucose stimulation, but does not influence basal insulinemia. The direct effect of Vitamin D may be mediated by binding of its active form, 1,25-OHD, to the β-cells vitamin D receptor. Activation of Vitamin D may occur within the þ-cell by the 1-a-hydroxylase enzyme expressed in β-cells. The indirect effects include extracellular calcium and calcium flux through the β-cells. Insulin secretion is a calcium-dependent process; therefore, alterations in calcium flux can have adverse effects on β-cells secretion.

Insulin Resistance

Vitamin D stimulates the expression of insulin receptors and enhances insulin responsiveness for glucose transport, or indirectly via its role in regulating extracellular calcium and ensuring normal calcium influx through cell membranes and adequate intracellular cytosolic calcium [Ca2+]i pool. Changes in [Ca2+]i in primary insulin target tissues may contribute to peripheral insulin resistance via impaired insulin signal transduction, leading to decreased glucose transporter-4 activity. As a compensatory mechanism, insulin secretion increases and contributes to a progressive failure of the β-cells. Observational studies have shown a converse correlation between Vitamin D or calcium status and insulin resistance. 1,25-dihydroxyvitamin D3 may target insulin-responsive tissues, such as liver, skeletal muscle and adipose tissues. Vitamin D may directly influence insulin sensitivity by stimulating expression of insulin receptors (IRs) on target tissues.

In Vitamin DR knockout mice, the absence of the Vitamin DR is associated with atrophy fibres, poor musculoskeletal performance in behavioural tests, and marked changes in gait. Indirectly, Vitamin D could decrease insulin resistance in skeletal muscle through the modulation of cellular calcium concentration.

Inflammation

T2DM is related to systemic inflammation. Systemic inflammation has been linked to insulin resistance, but elevated cytokines may also play a role in β-cells dysfunction by triggering þ-cell apoptosis. Vitamin D improves insulin sensitivity and promotes β-cells survival by modulating the generation and effects of cytokines. In

In particular, it protects β cells from apoptosis and cytokine-induced insulin resistance by modulating the expression and activation of cytokines and inhibiting activation of NF-κB. Moreover, Vitamin D also inhibits DC differentiation and immune activation by a reduction of MHC class II complex expression in cells surface, and inhibits the production of cytokine pro-inflammatory, such as IL6, IL1, IL12 and TNFα.

Association of Vitamin D status and T2DM

The role of Vitamin D in T2DM is suggested by a seasonal variation in glycemic control reported in patients with T2DM being worse in the winter, which may, be due to prevalent hypovitaminosis D. In cross-sectional studies, inverse associations between serum 25-OHD and measurements of glycemia or presence of T2DM have been reported, but the relationship is not consistent. Vitamin D supplementation at an early stage in the development of diabetes may benefit in delaying progression to clinical T2DM.

In prospective studies, low calcium intake is found to be inversely related with T2DM. In nondiabetic patients with hypertension, supplementation with calcium *vs.* placebo, improved insulin sensitivity, as measured by euglycemic hyperinsulinemic clamp. Combined supplementation of Vitamin D3 and calcium as calcium citrate malate had no consequence on glycemia or insulin resistance. However, participants with impaired fasting glucose at baseline, had a significantly lower rise in fasting glycemia and insulin resistance with those on placebo. In relation to T2DM, it is difficult to draw a definitive conclusion about an optimal level because available studies were done in a large range of 25-OH D levels. However, serum 25-OH D concentrations above 20 ng/ ml are desirable, but those above 40 ng/ml may be better. Calcium insufficiency is difficult to biochemically document. Combined insufficiency in Vitamin D and calcium intake may be even more prevalent. Therefore, given the potential link between Vitamin D, calcium, and diabetes it is plausible that the rising incidence of T2DM may be due to suboptimal Vitamin D and calcium status. Furthermore, certain factors like aging, physical inactivity, dark skin, and obesity are also strong risk factors for T2DM.

Various Randomised Controlled Trials investigated the effects of Vitamin D administration on T2DM-related parameters. For example, some trials found that Vitamin D supplementation had no effect on glycemic parameters, whereas the concomitant supplementation of Vitamin D and calcium improved fasting plasma glucose levels. In contrast, combination of vitamin D and calcium supplementation did not reduce risk of incident T2DM and had no effect on fasting glycemia and insulin resistance. All these studies give contrasting data about the effect of vitamin D and calcium supplementation on T2DM development. A better designed placebo-controlled trial evaluated the impact of vitamin D supplementation, with or without calcium, improved β-cell function and insulin sensitivity in patients with high risk of T2DM. Patients received 2000 IU of cholecalciferol daily or matching placebo and 800 mg of calcium carbonate daily for 16 weeks. The researchers demonstrated an enhanced β- cell function after supplementation with cholecalciferol; no differences were found in insulin sensitivity in any group. Therefore, the supplementation with calcium alone did not have any significant effect. The major weakness of this study was the short term of the supplementation with cholecalciferol and calcium. A double-blind RCT showed no changes in insulin sensitivity, inflammatory markers and insulin secretion after Vitamin D supplementation in patients affected by T2DM.

Role of Vitamin D in Type 1 Diabetes. (T1DM)

T1DM is an autoimmune disease that destroys pancreatic β cells, causing insulin insufficiency. The patients must take insulin injections for survival. Genetic inclination and environmental contributions underlie the development of T1DM. Vitamin D plays a defensive role by regulating sections of the immune system and modulating calcium homeostasis.

A seasonal pattern of disease has been described for T1DM. Supplementation of Cod liver oil during early years of life reduced the risk of childhood-onset type 1 diabetes, but in some cases, Vitamin D dosage in neonatal and early life provided no protection against T1DM in nonobese diabetic (NOD) mice or in BioBreeding (BB) rats, but the prevalence of diabetes is doubled in NOD mice rendered Vitamin D-deficient in early life. The identification of Vitamin DRs on antigen-presenting cells and activated T lymphocytes, suggested 1,25-dihydroxyvitamin D3 to be a potential immunomodulator. Immune cells contain the enzyme 1α-hydroxylase. It is identical to the renal enzyme, but its regulation is different. The renal enzyme is under the control of calcaemic and bone signals (parathyroid hormone and 1,25-dihydroxyvitamin D3), the macrophage enzyme is regulated by immune signals, with IFN-γ and Toll-like receptors. Beta cell damage by cytokines and other inflammatory agents is important in pathogenesis of T1DM. Beta cell function inhibition, induced by IL-1β or IFN-γ in vitro , is arrested by 1,25-dihydroxyvitamin D3 (MC903 and KH1060 - D3 analogues). Mauricio observed no effect of 1,25-dihydroxyvitamin D3 on IL-1β-induced beta cell dysfunction. The discrepancy may be due to the difference in incubation time. To summarise, 1,25-dihydroxyvitamin D3 protects beta cells from cytokine-induced beta cell dysfunction but fails to protect them from direct cytokine-induced cell death.

Functional form of Vitamin D shields β cells against proinflammatory cytokines and chronic inflammation involved in cellular stress and apoptosis. T1DM onset is characterized by chronic infiltration in the islets of Langerhans. 1,25-dihydroxyvitamin D3, can hinder lymphocyte and macrophage activation, abolish CD4+ expression by inhibiting interleukin 2 and interferon γ, and reduce expression of major histocompatibility complex class II molecules.

In nonobese diabetic (NOD) mice, extreme Vitamin D deficiency heightened the risk of developing T1DM. Administering high-dose 1,25-dihydroxyvitamin D3 in early life suppressed insulitis and reduced incidence of T1DM in NOD mice. Some studies showed more critical diabetes in vitamin D–deficient NOD mice.

A study of rats with inflammation-operated diabetes incited via streptozotocin also showed Vitamin D's potential role in T1DM. However, elevated doses of Vitamin D could cause calcemic concomitant effects, like hypercalcemia, hypercalciuria, and kidney stones. To overcome these limits, researchers developed synthetic analogues that had less effect on calcium homeostasis but had the same effect on regulating the immune system. The administration of Vitamin D analogues in NOD mice-MC1288 or BXL-219-prevented T1DM from progression by inhibiting inflammation even after the initiation of insulitis. T1DM patients were reported to have lower levels of 25(OH)D than healthy control groups. In a large observational study, children were evaluated with the increased risk of the development of T1DM. Children with multiple islet autoantibodies (pre-T1DM state) and children newly diagnosed with T1DM have lower 25(OH)D concentration than children with negative autoantibodies. However, some studies argued that Vitamin D deficiency is a consequence of metabolic derangements in T1DM. Recent studies interlinked polymorphisms of Vitamin D metabolism–related genes (DHCR7/NADSYN1 and CYP27B1) with low 25(OH)D level and associated them with a higher risk of developing islet autoimmunity and later diabetes.

Two clinical trials investigated the safety and tolerability of the dual administration of Vitamin D and glutamic acid decarboxylase–based vaccine Diamyd alone or in combination with etanercept, a tumor necrosis factor inhibitor, in T1DM patients. Another trial evaluated the efficacy of Vitamin D merged with saxagliptin and insulin against that of insulin alone and adults with latent autoimmune diabetes.

Vitamin D and Diabetic Nephropathy

Considerable data exist on the role of Vitamin D in diabetic nephropathy. Patients with chronic kidney disease (Chronic Kidney Disease) are deficient in 25(OH)D and 1,25(OH)2D, which is associated with a high cardiovascular mortality. These risks can be partially treated with Vitamin D analogues. Although in patients with Chronic Kidney Disease, high levels of Vitamin D may also be associated with vascular calcification. Experimental studies have shown Vitamin DR, and Vitamin DR-mediated Vitamin D actions are renoprotective in diabetic nephropathy. Vitamin

D/Vitamin DR signalling in podocytes have a protective function in the kidney from diabetic injury. In a small double-blind, randomized placebo-controlled trial of paricalcitol (a Vitamin D analogue) in patients with proteinuria despite adequate Renin Angiotensin Aldosterone System blockade, the urinary albumin excretion rate was significantly further lowered compared to placebo. Furthermore, combination therapy with an AT1 blocker and a Vitamin D analogue markedly ameliorated diabetic nephropathy in an experimental model of diabetic nephropathy. In a placebo-controlled, double-blind RCT, paracalcitriol added to Renin Angiotensin Aldosterone System inhibition significantly lowered blood pressure and residual albuminuria in patients with diabetic nephropathy, further highlighting the role of vitamin D as a potent Renin Angiotensin Aldosterone System inhibitor. A review suggested that despite a higher risk for nephropathy in Vitamin D-deficient patients with diabetes, Vitamin D supplementation did not support causality in this association.

Vitamin D regulates innate immunity through microbial recognition peptides, Toll-like receptors (TLRs). TLRs are membrane-bound receptors that discern structurally conserved molecules obtained from microbes and activate immune responses. Macrophages synthesize antimicrobial peptides such as cathelicidin, that is facilitated in the presence of 25(OH)D, might be an important negative feedback mechanism to deactivate innate and inflammatory responses of activated macrophages. Synthetic Vitamin DRA, paricalcitol, hampers renal inflammation by promoting Vitamin DR mediated sequestration of NF-κB signalling. The potent antiproliferative, prodifferentiative, and immunomodulating activities seem to be modulated via Vitamin DR–dependent genomic effects.

<u>Vitamin D deficiency in Chronic Kidney Disease Patients</u>

Declined renal functions are directly correlated with decreased levels of 1,25(OH)2D, leading to a Vitamin D–deficient state. Heightened removal of 25(OH)D via nonrenal pathways may have a role in causing a low 25(OH)D level. Apparent nutritional Vitamin D deficiency could be an indication of inflammation in patients with Chronic Kidney Disease. In this context, Vitamin DRA administration may lead to depletion in the inflammatory state. Endothelial cells can also induce 1- hydroxylase activity in response to inflammatory cytokines and may serve to deplete the stores of 25(OH)D.

De Boer reported an increase in the prevalence of albuminuria with decreasing concentration of 25(OH)D. In a survey, 25(OH)D deficiency and eGFR both were independently related to insulin resistance, cardiovascular risk factors, hypertension, diabetes, obesity, and high serum triglyceride levels. Urinary MCP-1 and renal macrophage infiltration have a contrary relation with 1,25(OH)2D. Increased 25(OH)D were correlated with lower inflammation. Patients with acute renal inflammation elevated urinary and kidney MCP-1, macrophage infiltration, and macrophage and renal epithelial 1- hydroxylase (CYP27B1) expression but significantly lower levels of 1,25(OH)2D in comparison with patients with chronic ischemic disease despite similar stages of renal damage. Thus, decreased Vitamin D metabolites and activated paracrine/autocrine Vitamin D system are important associates of inflammation in patients with Chronic Kidney Disease. 25(OH)D is associated with endothelial function and conversely with arterial calcifications in patients with Chronic Kidney Disease. 25(OH)D deficiency in patients with Chronic Kidney Disease is associated with adverse risk factors (albuminuria, insulin resistance, inflammation, hypertension, dyslipidemia, and endothelial dysfunction) for advancement of kidney disease. 25(OH)D plasma concentration was an unrelated inverse predictor of disease progression and death in patients with stages 2 through 5 Chronic Kidney Disease after multivariate adjustment. Agarwal reported reduction in proteinuria detected semi-quantitatively by dipstick using an automated analysis in patients who had stages 3 and 4 Chronic Kidney Disease with secondary hyperparathyroidism and participated in three randomized, controlled trials of oral paricalcitol. In that analysis, reduction in dipstick proteinuria occurred in the face of the frequent use of agents that block the Renin Angiotensin Aldosterone System. Lowering of albuminuria or proteinuria in these trials occurred without changes in BP, raising the notion that improvement in kidney disease conferred by the use of drugs may occur via non hemodynamic pathways. Randomised Controlled Trials with paricalcitol are being used to study whether paricalcitol will have antiproteinuric or cardioprotective effects in patients with Chronic Kidney Disease.

Vitamin D, Nerves and Diabetic Neuropathy

Multiple neurodegenerative diseases including multiple sclerosis and Parkinson's disease, cognitive decline in the elderly, have been linked with declining Vitamin D status. Some data suggests that treatment with high doses of vitamin D3 slows down the progression of multiple sclerosis. Nerve growth factor (NGF) is essential for the development of nociceptors that have a role in inflammatory hyperalgesia in adults. NGF is responsible for the development and maintenance of neurons in the CNS. In addition, following a neuronal injury, NGF has the ability to promote myelination of Schwann cells, stimulate axonal sprouting, and guide axonal growth. 1,25-dihydroxyvitamin D3 has been shown to cross the blood–brain barrier in experimental models and may specifically increase NGF in glial cells and fibroblasts. In experimental studies, Vitamin D has been linked to the regulation of neurotrophins (NGF) and neuronal Ca homeostasis, which play a neuroprotective role in the peripheral nerve. Sciatic nerve NGF was preserved in animals exposed to a Vitamin D analogue (CB1093) whilst another Vitamin D analogue (MC903) has been shown to increase NGF synthesis. NGF is known to get depleted in experimental diabetes.

Stimulation of neurotrophin production by 1,25-dihydroxyvitamin D3 is correlated with a neuroprotective effect and other than NGF, glial cell line-derived neurotrophic factor (GDNF) is also upregulated by 1,25-dihydroxyvitamin D3. Promoted healing of diabetic ulcers was seen with the application of NGF. Vitamin D deficiency and insufficiency is related with various pain syndromes and low levels of Vitamin D is correlated with the presence of peripheral neuropathy in primary Sjögren's syndrome which can lead to a small fibre neuropathy. In a study, Vitamin D deficiency was identified as a risk factor for DPN, assessed using the neuropathy symptom score and other clinical and electrophysiological measures of DPN. The group with peripheral neuropathy had a longer duration of diabetes as well as low density lipoprotein-cholesterol (LDL). Vitamin D and cholesterol share a common metabolic pathway through 7-dehydrocholesterol. Reduced serum 25(OH)D was associated with DPN. Large nerve fibre deficits have also been associated with Vitamin D status in diabetes mellitus. A double-blind RCT using QR-333 (Vitamin D analogue) showed positive effects on numbness, jolting pain, and irritation in subjects with painful DPN. Overexpression of Renin Angiotensin Aldosterone System leads to the development of hypertension and increased cardiovascular risk. Wild-type mice injected with 1,25-dihydroxyvitamin D3 demonstrated suppression of renin mRNA expression. Vitamin D is a potent negative regulator of the Renin Angiotensin Aldosterone System system, which may play an important role in the development of neuropathy in diabetes. Renin Angiotensin Aldosterone System inhibition is a proven therapy, which delays diabetic peripheral neuropathy.

Vitamin D and Diabetic Retinopathy (DR)

25(OH)D concentrations are associated with optic chiasm volume. Vitamin D deficiency and age-related macular degeneration (AMD) are also correlated. In a mouse model of ischemic retinopathy, 1,25(OH)2D was shown to inhibit neovascularization in retinal tissue. It demonstrated an inverse correlation between worsening diabetic retinopathy and lower 1,25-dihydroxyvitamin D3. Vitamin D deficiency was associated with early retinal nerve fibre layer (RNFL) thinning, but no relationship was found between 25(OH)D levels and retinopathy severity. DR has been reported to be significantly higher in persons with T1DM as compared to persons with T2DM. So far there has been no known effective interventions that can be utilised to prevent/treat DR, other than to optimize glucose control and blood pressure. Base Level for the appearance of DR is at 6.5% HbA1c, slightly above the upper limit of normal. Residual hyperglycemia shows an increased risk of DR.

A contrary relationship exists between presence and severity of DR, and Vitamin D concentrations. Vitamin D being the lowest in severe DR and the highest in diabetic patients without DR. Vitamin D deficiency was associated with increased prevalence of DR in T1DM patients; a study showed the prevalence of severe and mild DR were higher in poorly controlled patients with hypovitaminosis D vs. Vitamin D sufficient patients. DR treatment is often associated with the administration of dietary supplements, but only few studies specifically supplement Vitamin D in patients with DR, have been published. The study mainly focused on biochemical, immunological and inflammatory markers of vascular damage in patients with DR showing marginal effects of the Vitamin D supplementation on these parameters.

Vitamin D is related to reactive hyperemia index (RHI), a marker of microvascular function, in healthy subjects. Oral Vitamin D supplementation allowed for improved vascular functions. Furthermore, diabetic patients with Vitamin D deficiency had reduced endothelium-dependent microvascular function which was assessed by iontophoresis of acetylcholine, when compared to patients with diabetes and non-deficient Vitamin D levels. It promoted vascular regeneration through activation of Vitamin DR, which regulated the expression of various genes involved in fundamental processes or potential relevance to cardiovascular function. Vitamin D promoted NO production in EC. In the presence of oxygen, eNOS catalyses the oxidation of L-arginine to form L-citrulline and NO. NO gas diffuses across the cell membrane where it leads to the relaxation and dilation of the vessels. NO has a key role in the pathogenesis of DR and its modulation by Vitamin D may have protective effects in DR. Vitamin D mitigates oxidative stress by enhancing the antioxidant defence systems, preserving mitochondrial function, restoring eNOS function, and reducing the activation of monoamine oxidases (MAO). Vitamin D treatment has shown increased cell viability, reduced reactive oxygen species production and caspase-3/7 activities in high-glucose-treated retinal pigmented epithelial cells suggesting that Vitamin D can protect the retina from high- glucose-induced oxidative damage and inflammation.

Pre-treatment of mesothelial cells with Vitamin D inhibits high glucose and LPS-induced TGF-β production. Diabetic rats receiving Vitamin D showed lower levels of TGF-β in the retina, when compared to non-Vitamin D treated diabetic controls. Vitamin D has been shown to reduce albuminuria in diabetic patients in a prospective and in a randomized double-blind controlled study. TGF-β has an essential role in retinal microvascular homeostasis. When increased in the retina, it shows excess extracellular matrix, tortuosity, and aneurysms. It could be a possible biomarker for DR.

Discussion:

Vitamin D in Covid-19

As vitamin D deficiency becomes a major cause of covid 19 and public health problems worldwide due to the decrease of sun exposure and cutaneous synthesis. Vitamin D plays a major role in bone strengthening and the innate immune system also plays a major role in zinc metabolism which becomes a major reason for decreasing the symptoms of COVID-19 in the human body. We acknowledge that vitamin D is already shown as a protective layer against acute respiratory infections. This particular hypothesis focuses on finding the increased risk of testing positive covid-19 with deficient vitamin D status and this study fails to accurately reflect any particular effect of vitamin D on outcomes. A person on vitamin D treatment has low chances to come under the contact of viral infections but not a guaranteed outcome. Test low cost of vitamin D support argument for population-level supplements but a wide group of low-level vitamin D deficiency becomes a major issue for this particular treatment. It is still a question that vitamin D treatment decreases the covid 19 incidents just to reduce the transmission of COVID-19 or just strength over the immune system although vitamin D also helps to increase the metabolism of zinc which decreases the replication of coronavirus. AS vitamin d is evaluated there is no association between the deficiency of vitamin d and clinical inflammatory markers but the scientist observed that the high C- reactive protein is inversely related to 25(OH)D and can work as inflammatory markers for cytokine storms. CPR level increases of s suppresses, risk and increases production of inflammatory cytokine in such as IL-6. The pathology of COVID-19 tells about the interaction between virus and human immune body response it states that the release of cytokines .May help vitamin d to find macrophages and release chemokines which prevents them from cardiovascular diseases as well as inflammatory diseases but in the end, we are not highly confirmed about that vitamin d treatment of cold 19 his he complete outcome against Kuwait 19 and work as a supplement for the prevention of patients

This study has many limitations, some of them are clinical parameters infrequent timings patient's medical issues and some small limitations as well. E Laird, J Rhodes also conducted a literature search study to conclude that optimizing vitamin D status certainly has benefits in COVID-19. The results have a few limitations as well because the study was conducted in central located India which is the area of hi victim indeed deficiency. Some other limitations are also there like the time elapsed between the patients admitted to the hospital. So this study is considered to be a hypothesis but has solid evidence that vitamin deficiency mark Lee increases the chances of having COVID 19 infection.

In this report, we found 10 patients with confirmed COVID -19 infection. We found that the elderly and females tend to have lower vitamin D levels. This shows that hydroxyvitamin D (25(OH)D) concentration decreases with age. Vitamin D is also a beneficial effect on the immune system because vitamin D increases innate immunity. Which is anti-viral, antifungal and antimicrobial. This study was 90% has vitamin D insufficiency and only 1 patient had vitamin D insufficiency. So, doctors should continue to treat people with vitamin D deficiency especially in managing COVID-19 patients A study in Chicago university showed that the rate of covid 19 is inversely proportional to the rate of vitamin d deficiency in the human body in this study they compared the results of positive PCR with negative PCR patients and a correlation study found especially in Europe that, there were found 40% more vitamin D deficient and 13% were more severely deficient.

According to another report, COVID-19 mortality is high in adults who were admitted to respiratory intensive care unit it is about 50%, and then that rate was about 5%.CRP levels are used to determine cytokine storm and the severity of covid- 19 cases different relations and studies were agreement that 84.6% were ICU patients whereas 51.71 were non- icu have vitamin D insufficiency. As per this report, 372 patients were admitted out of which 202 were enrolled for the study and 48 were excluded after application of exclusion criteria and hence 154 patients were left from these 154 patients 91 in Group A (asymptomatic) and 63 in Group B (severely ill). So the mean concentration of Group A for 25(OH)D was 31.86% and for Group B was96.82%. So there was the more severe condition of Group B where there were more vitamin D deficient patients. The difference was found to be statistically significant. Diabetes followed by hypertension was most common in both the groups and the fatality rate of Group A based on vitamin D deficiency was 21% whereas the fatality rate of Group B based on vitamin D deficiency was 3.1%. The research from Indonesia revealed that the majority of vitamin D weakness was 23.0%. Vitamin D has been confirmed to increase the expression of antioxidant–related genes, modulate adaptive immunity, improve cellular immunity, and have immuno- modulator properties. The effect of Vitamin D against the COVID -19 is to suppress the cytokine response and decrease the risk for ARDS. This information is from a meta-analysis of regular oral vitamin D2 / D3. The research aims to explain that the majority of COVID-19 patients have a low vitamin D level, which may decrease immunity. The data exists from the COVID -19 confirmed real- time PCR, Clinical symptoms, cyclonical signs, and laboratory examination.

As per the result of patients, no difference was found on the basis of gender in the case of vitamin D levels. The major difference was that patients with deficient vitamin D status were found to have an increased risk of testing positive for COVID -19 Due to hypertension, obesity and diabetes can be responsive to vitamin D treatment. In this result, there were 10 participants with COVID-19 consisting of 5 males and 5 females detected from a real-time PCR test for COVID -19. The average age is about 49.6 years old. In this study, about 60% of patients had symptoms of fatigue, 50% with fever, 40 % with dry cough, 10% with headache, and other symptoms. But in this study, about 90% had vitamin D deficiency status.

As COVID-19 moves to deadliest diseases have different severity levels in the same age group of people. The people were multiple organ dysfunction syndromes and other serious diseases are serious forward patients and admitted to ICU only 10 to 15% of cases have serious disease had the same level of age months ago, a mechanism was underlined for the pulmonary injury of COVID-19 which includes several cytokines that play an important role in pathogenic diseases. Vitamin D is usually known for bone strength and calcium- phosphorus metabolism also plays an essential role in any immune system. So they tested vitamin deficiency which states that patients in ICU have increased chances of brutality and have a very critical condition. So according to the whole discussion we can conclude that Vitamin D plays a beneficial role to prevent COVID-19 patients but still not successful in severe cases and even plays a vital role to boost the immune system of the human body.

Vitamin D in Thyroid

In addition to the well-characterized genomic effects of hormones, some cardiac responses appear to be mediated by the non-genomic mechanisms. Hypothyroidism is taken into account as a disease that will alter blood pressure (BP) and has been seen as a cause of secondary hypertension.

Methods of hypothyroid-related hypertension - *Increase in peripheral vascular resistance*: T3 & Hypothyroidism deficiency are related to peripheral vasoconstriction and increase in arterial stiffness.

Renal dysfunction and hemodynamic changes: Thyroid hormonal inadequacy has been associated with deterioration of renal function which is attributed to the cardiovascular consequences of T3 deficiency. Hypothyroidism ends up resulting in a reduced kidney to body weight ratio.

Hormonal changes: within the hypothyroid state, the density of alpha-adreno-receptors is increased but the density of beta-adreno-receptors is reduced.

Obesity: this is often another possible mechanism by which hypothyroid individuals express an increase in BP. Hypothyroid individuals are found to be significantly more overweight and obese than normal healthy volunteers.

The thyroid phenotype Vitamin DR of knockout mice was studied in comparison to wild-type(WT) controls. The mice were fed a normal diet or a calcium-rich diet to circumvent effects induced by hypocalcemia. Thyrocyte function was not changed but C cell activity was increased in the absence of the Vitamin DR, confirming that 1,25(OH) 2 D 3 negatively regulating the calcitonin via the Vitamin DR. A similar observation was made by others in rats with severe vitamin D deficiency, but serum T4 levels remain uninterrupted. Overview of 1,25-dihydroxyvitamin D3 homeostasis maintained by PTH, FGF23, and calcitonin. Low calcium level triggers the PTH release which further stimulates CYP27B1. High calcium levels stimulate calcitonin release, also inducing CYP27B1. FGF23 represents the negative regulator/controller of CYP27B1. PTH, FGF23, and calcitonin are regulated by 1,25-dihydroxyvitamin D3 through the Vitamin DR. Thyroid morphology was unbruised in Vitamin DR knockout mice. Also, the expression of different parameters of thyrocyte function was comparable(immunohistochemistry). C cell physiology was, however, altered in the absence of the Vitamin DR, resulting in increased thyroid calcitonin expression (immunohistochemistry), side by side increased in serum calcitonin levels, but only in the normocalcemic mice. To study the possible effect of vitamin D status on basal calcitonin levels, serum calcitonin concentrations were compared in humans between vitamin D-deficient and -sufficient patients (serum 25-OH vitamin D 3 ^ 10and 6 40 ng/ml, respectively), but no difference was exhibited. The molecular mechanism by which vitamin D showcase its action seems to be mediated by its binding to Vitamin DR, an intracellular receptor related to the steroid or thyroid nuclear receptor family, expressed by human immune cells, like macrophages, dendritic cells, and T and B lymphocytes. Vitamin D main targets are the dendritic cells (DCs).

Some studies evaluated the association between functional polymorphism within the Vitamin DR gene or vitamin D binding proteins and AITD risk. However, the results are still ambiguous and inconclusive. Vitamin D has the power to trigger both innate and adaptive immune responses and to modify the immune system during a tolerogenic sense, avoiding the autoimmune response. The molecular basis of the hypothesized antitumoral effect of vitamin D relies on the actions of 1,25-dihydroxyvitamin D3 through binding to the Vitamin DR, a nuclear hormone receptor that's present, although variably, in benign and infectious thyroid tissue. Vitamin D supplementation is recommended for the cure of hypovitaminosis D conditions. 25(OH)D is regarded as the best indicator for monitoring vitamin D levels. This is the main circulating form of vitamin D, with a half-life of 2–3 weeks. The vitamin D active form comes from the 1-α-hydroxylase protein. This protein, encoded by the CYP27B1 gene and expressed mainly within the kidney. The active sort of vitamin D binds the nuclear vitamin D receptor (Vitamin DR) and heterodimerizes with retinoic acid.

Several polymorphic variants of the genes involved in the metabolism, transport, and activity of vitamin D are described within the last few years. The simplest characteristics are the four single-nucleotide polymorphic (SNP) variants of the Vitamin DR gene (ApaI, BsmI, FokI, and TaqI) that are related to several pathological situations, including autoimmune disorders or cancers. Thyroid hormones are key for the control of metabolism and for maintaining the specific function of several tissue and cell types. Biosynthesis of TH occurs within the thyroid and it's stimulated by the thyrotropin (TSH) secreted by the pituitary. Many studies indicate that vitamin D plays an important role in the modulation of the immune system. Vitamin D may enhance the innate system and regulate the adaptive system, promoting immune tolerance and acting to decrease the likelihood of developing autoimmune disorder'. As the majority of autoimmune disorders, AITDs are that the consequence of a posh interaction between genetic susceptibility factors, existential factors (sex, parity, etc.), and various environmental triggers (i.e. cigarette smoking, stress, iodine, selenium, etc.) The role of both vitamin D and Vitamin DR in the pathogenesis of AITD has largely been investigated within the last few years. Vitamin D receptor is expressed in lymphocytes, macrophages also as in antigen-presenting cells.

A weak connection between low vitamin D levels and AITDs was identified during a study conducted by a population from India. Against this, 'Kivity et al. observed that anti-thyroid antibodies were more frequently elevated in patients with vitamin D deficiency. The Vitamin DR is that the specific vitamin D receptor and its activity are often compromised by certain polymorphisms and in the results, it was observed that there was no significant difference in age, weight, BMI, daily levothyroxine dose, and serum level of Vitamin D, calorie and macronutrients, except for vitamin D intake, the duration of exposure to sunlight and the mean levels of TSH, T3, T4, 25(OH) D, anti-TPO Ab, and anti-Tg Ab were in both groups before supplementation. But it was seen After supplementation, that the serum levels of 25(OH) D and calcium increased significantly, and the levels of TSH and anti-Tg Ab decreased significantly in the vitamin D group compared to baseline levels recorded. However, in the placebo group, the serum level of T4 decreased significantly compared to the baseline level. It was also found out that the levels of anti-TPO Ab and anti-Tg Ab decreased by 15.3 and 28.2 % in the vitamin D-supplemented group, respectively. Hence, Vitamin D did not affect the serum levels of T3 & TSH and has no significant changes.

Therefore, the study showed that vitamin D association deficiency in the serum levels anti-Tg Ab ($p = 0.009$) and TSH ($p = 0.027$) was significantly less compared to the initially recorded levels. In this study, vitamin D administration decreased the concentration of TSH compared to initial baseline levels but no significant difference was observed between vitamin D-supplemented and placebo groups. However, no significant differences were observed between vitamin-supplemented and placebo groups and it was an inference from this study that vitamin D supplementation can be helpful for alleviation of the disease activity in HT patients. Although there exists some inconsistency in the results of the studies. The most commonly cited explanation is the decrease in the immunomodulatory role of 1,25(OH)2D, in patients with deficiency, contributing to the development of AID.AITD gives back a consequence, rather than a cause, of the disease. AID may lead to VitD deficiency by causing incapacitation and lower sunlight exposure, malabsorption, and the use of corticosteroids. Kozai et al. found noticeable decreases in 1,25(OH)2D and CYP27B1 expression in rats with T3-induced hyperthyroidism. In HT, the increase in fat mass caused by hypothyroidism could contribute to the deficiency. Botello et al.studied 88 patients with long-term HT and found out a positive connection between 25(OH)D levels, fT4, and (contrary to expectations) Th17 and TNFα. The authors hypothesized that a decrease in levels of fT4 is a predictor of a deficiency of 25(OH)D and that the long evolution of the disease and treatment of hypothyroidism.

GD, aka diffuse toxic goiter, is one of the most common causes of hyperthyroidism, and its pathogenesis is complex and unclear. Two groups have demonstrated that vitamin D inhibits the pathogenesis of GD through the following immunomodulatory mechanisms:

(1) vitamin D inhibits the differentiation and maturation of DCs, lessens the secretion of the pro-inflammatory cytokines IL-2, IL-23, and IL-12 by DCs, and blocks hyperthyroidism caused due to autoimmune responses;

(2) vitamin D can directly act on Th1 and Th2 cells and inhibit the occurrence of autoimmune responses by inhibitingTh1 cells, and by upregulating the activity of Th2 cells and the level of cytokines they secrete; and

(3) vitamin D hinders B cell proliferation, plasma cell differentiation, immunoglobulin secretion, and memory B cell production, and is associated with the onset of GD.

Hyperthyroidism may be a common explanation for isolated systolic hypertension. In hyperthyroidism, T3 dilates resistance arterioles, reducing systemic vascular resistance, and increases flow and pulse pressure. Hypertension appears to be more common in hyperthyroid patients. Treatment narrows the heartbeat pressure, decreases pulse, and reduces cardiac output. This review depicts and showcases the methods of hypertension-related with common endocrine conditions that are not classically considered etiologies involved in the workup of a patient with suspected secondary hypertension. The causality of the disorder and therefore the reversibility of elevated vital signs aren't as clear-cut and concrete as during a patient with classical endocrine hypertension. But because these disorders are much more common, they ought to be routinely sought and a practicing endocrinologist must remember the underlying mechanisms for hypertension to be able to manage these patients more scientifically.

The result showed that vitamin D, calcium, phosphorus, and parathormone levels were similar in patients and the control group. Only the TSH level was more in the patients than in the control group. The interleukins produced by cytokinins also did not show much difference. Low levels of free T4 and lower concentrations of TNF-α indicated lower vitamin D levels in the patients. There was no such correlation in the control group. The main conclusion in this research was that low levels of vitamin D are not associated with HT. However, low levels of thyroxine were shown to be a risk factor for the deficiency of vitamin D.

The experiment was done on a relatively small population in both the control and patient groups. It verified that vitamin D deficiency is not the direct cause for HT but the exact role of vitamin D is yet to be determined. The levels of vitamin D were proportional to the levels of cytokinins. Additional research should be done to identify their correlation with the autoimmunity of HT. Researchers proposed that skeletal health should be maintained at a vitamin D level of 30–40 ng/mL, but higher vitamin D levels do not show better effects. Vitamin D levels higher than 40 ng/mL tend to lose their actual beneficial effects on bone. If supplementing vitamin D is considered to be useful for AITD patients, it should also be thought about: how to supplement vitamin D, and monitor vitamin D level and thyroid function, and at what level vitamin D can enhance the condition of patients with AITD. These things also need to be explored.

Role of Vitamin D in Diabetes and it's pathogenesis.

The active form of vitamin D, 1,25-dihydroxyvitamin D3, and its analogues have been shown to have major involvement in the pathogenesis of T1 and T2 DM. Beta cell function has been shown to be improved by 1,25-dihydroxyvitamin D3 in vitro and in vivo, and the avoidance of Vitamin D deficiency is essential for normal beta cell function. In NOD mice, 1,25-dihydroxyvitamin D3 protects against insulitis, diabetes and disease recurrence post islet transplantation, mainly through immunomodulatory effects. The use of 1,25-dihydroxyvitamin D3 for the prevention or cure of diabetes is limited due to its hypercalcemia and bone remodelling effects, its protective effects are observed in response to supra-physiological doses. Future applications diabetic cures are conceivable because the calcaemic and immunomodulatory effects of 1,25-dihydroxyvitamin D3 can be dissociated by structural analogues of the molecule. Analogues will be used as beta-cell-protective and -stimulating agents as adjuncts for the treatment of T2DM. It could play a role in preventative strategies for T1DM in humans, due to their profile as beta cell-protector and immuno-active drugs.

A meta-analysis evaluated the effects of Vitamin D supplementation on beta cell function as measured by fasting insulin. In contrast with placebo, oral Vitamin D supplementation yielded better effects on HOMA-IR in T2DM patients. Longer durations of supplementation were associated with greater reductions in glycemic control. Firstly, significant reductions in FBG and HOMA-IR were observed in patients with Vitamin D deficiency but not in patients with Vitamin D insufficiency or sufficiency. Even though 25(OH)D increased significantly in all subgroups, the highest improvement came in Vitamin D deficient patients. Second, Vitamin D supplementation produced different effects among various ethnicities. Vitamin D-binding protein polymorphism was associated with increased susceptibility to T2D. In addition, populations with darker skin colour and cultural preferences toward less exposure to the sun, were at a higher risk of Vitamin D deficiency. Third, better glycemic parameters appeared in non-obese patients. This was somewhat opposite to previous studies that suggested, that BMI was negatively associated with serum 25(OH)D concentration; however, the obese population, even with an adequate vitamin D status, does not benefit because of nutrients trapped in fat mass. Finally, optimal baseline glycemic control was associated with preferred effects of Vitamin D supplementation on serum 25(OH)D levels, FBG and HbA1c.

A meta-analysis provided an extensive evaluation of the relation between Vitamin D and DFU. It reported a significantly lower Vitamin D levels in patients with DFU as compared with the DM group. Severe Vitamin D deficiency was definitely associated with a heightened risk of DFU. Lower 25(OH)D played a consequential role in the pathogenesis of foot ulcer. Hyperglycemia disturbed the regular process of cytokine production, which impaired wound healing. An exclusive high dose of oral Vitamin D could considerably improve the brachial artery flow-mediated vasodilatation. Vitamin D stimulated phagocytosis and that assisted in destroying intestinal bacteria. Vitamin D also inhibited the secretion of the T helper type 1 cytokines IFN-γ and IL-2 and restored the production of Th2 cytokines, which promoted wound healing. However, the mechanism is still under study.

The present study juxtaposed neuropathic pain and balance before and after Vitamin D replacement therapy in patients with DN. Results showed a remarkable improvement in the total DN4 scores that indicates the presence of neuropathic pain and Berg Balance Test scores that regulates balance after Vitamin D substitution therapy. Various considerations were undertaken regarding the dose, administration route, and duration of the therapy. Application of a single large dose was more efficient as compared to a single Vitamin D3 dose. A topical agent containing Vitamin D (QR-333) reduced neuropathic pain. Another study reported a substantial reduction in pain scores of patients with T2DM and neuropathic pain symptoms who concluded a 3-month course of Vitamin D3 tablets.

In the present study, improvements in the burning and electric shock sub-scores of the DN4 suggested an advancement in the small fibres, the consequential changes in the Berg Balance Test scores suggested a boost in the large fibres. The latter observation is persistent with the results of previous electrophysiology studies. Time needed to document the changes in Berg Balance Test scores is >8 weeks, which matches to axonal regeneration time. As a result of this study Vitamin D treatment decreased total DN4 scores, electric shock scores and burning scores. Only painful cold sensation, pins and needles and brushing in DN4 subgroup scores did not show alleviation post treatment. One possible explanation for this was given by Bouhassira, comorbidities such as peripheral vascular disease or heart disease might be the cause for painful cold sensations.

Vitamin D deficiency is detrimental to beta cell function, leads to glucose intolerance in animal models and humans, and predisposes to type 2 diabetes and its deficiency in early life predisposes NOD mice and humans to the later development of autoimmune diabetes. Administration of 1,25-dihydroxyvitamin D3, has immunomodulatory effects that lead to diabetes prevention in animal models of type 1 diabetes. There appears to be a relationship between insufficient Vitamin D and calcium status and T2DM. Although the evidence does suggest that Vitamin D and calcium deficiency influences postprandial glycemia and insulin response supplementation may be beneficial in optimizing these processes, the understanding of the mechanisms that promote þ-cell function or ameliorate insulin resistance and systemic inflammation is incomplete. Future research should focus on studies within prospective observational cohorts to clarify and quantify the association between calcium intake and 25-OH D concentration. Additionally, there is a need for Randomised Controlled

Trials to examine the effects of Vitamin D and calcium supplementation with intermediary endpoints (glucose tolerance, insulin secretion, insulin sensitivity) and ultimately with incident T2DM.

An increasing amount of literature also suggests a possible pathogenetic role of Vitamin D in the long-term complications of painful DPN. The association between Vitamin D status and cardiometabolic outcomes is uncertain, especially as intervention trials have shown no clinically significant effect of vitamin D supplementation. Large dosage, short-term vitamin D supplementation was most likely to yield preferred changes in vitamin D deficient, non-obese groups, Additional well-designed studies are required to clarify the impacts of BMI and baseline HbA1c. Extreme Vitamin D deficiency has also been notably associated with an elevated risk of DFU. Vitamin D replacement therapy also showed a reduced neuropathic pain and improved balance in patients with DN. Vitamin D deficiency may be involved in the development and progression of DR

There are no sources in the current document. Therefore, Vitamin D integrated therapy can be useful in patients with DR and severe Vitamin D deficiency. Prevention and treatment attempts of DR mainly consist of drugs that target the pathways of glucose toxicity or discrete molecular abnormalities caused by diabetes. Vitamin D can also provide protection to vascular cells enhancing vascular repair, reversing endothelial dysfunction, decreasing inflammation, and/or oxidative stress. Vitamin D protects retinal microvessels against diabetes and exerts beneficial effects on endothelial dysfunction. In fact, Vitamin D deficiency is extremely common, particularly in patients at increased cardiovascular risk, so its supplementation is both safe and low-cost. Therefore, in conclusion Vitamin D therapy represents a promising therapeutic intervention in the treatment of diabetic complications.

Conclusion:

This research review's purpose is to help the reader understand different aspects posed by the research on the effects of Vitamin D in intractable diseases. This is significant because it gives insights about the options available for treatment of diseases like the current ongoing Covid-19 pandemic, Diabetes and the different forms of its pathogenesis as well as Thyroid using Vitamin D. There has been much research and discussion conducted on these opinions of effects of Vitamin D in treatment and management of these diseases. Most of the research found was on the ways Vitamin D could be used for treating and managing these severe diseases. More research and testing is required to gain a better understanding of the effects of Vitamin D in treating intractable diseases.

Acknowledgement:

We would like to thank our supervisor/guide Bharat Kwatra, from Invenzion Labs Inc. whose expertise was invaluable in formulating the research questions, methodology and drawing conclusions. His insightful feedback and guidance pushed us to sharpen our thinking and brought our work to a higher level.

Ethics Approval and Consent to Participate.

Not applicable.

Human and Animal Rights

No Animals/Humans were used for studies that are the basis of this research.

Consent for Publication

Not applicable.

Availability of Data and Materials

The author confirms that the data supporting the findings of this research are available within the article.

Funding Acknowledgement and Conflict of Interest

The authors whose names are listed immediately above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References:

1. Wang, J. *et al.* Meta-analysis of the association between vitamin D and autoimmune thyroid disease. *Nutrients* vol. 7 (2015).
2. Jacob, J., Chopra, S. & Cherian, D. The thyroid hormone, parathyroid hormone and vitamin D associated hypertension. *Indian J. Endocrinol. Metab.* **15**, (2011).
3. Yisak, H. *et al.* Effects of vitamin d on covid-19 infection and prognosis: A systematic review. *Risk Management and Healthcare Policy* vol. 14 (2021).
4. Yılmaz, K. & Şen, V. Is vitamin D deficiency a risk factor for COVID-19 in children? *Pediatr. Pulmonol.* **55**, (2020).
5. Griffin, G. *et al.* Vitamin D and COVID-19: evidence and recommendations for supplementation. *R. Soc. Open Sci.* **7**, (2020).
6. Ali, N. Role of vitamin D in preventing of COVID-19 infection, progression and severity. *Journal of Infection and Public Health* vol. 13 (2020).
7. Ilie, P. C., Stefanescu, S. & Smith, L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. *Aging Clin. Exp. Res.* **32**, (2020).
8. Anderson, D. C. & Grimes, D. S. Endocrinology, Vitamin D and the UK's Covid-19 Disaster. *J. Endocr. Soc.* **5**, (2021).
9. Munshi, R. *et al.* Vitamin D insufficiency as a potential culprit in critical COVID-19 patients. *Journal of*

Medical Virology vol. 93 (2021).
10. Meltzer, D. O. *et al.* Association of vitamin D status and other clinical characteristics with COVID-19 test results. *JAMA Netw. Open* **3**, (2020).
11. Pinzon, R. T., Angela & Pradana, A. W. Vitamin D deficiency among patients with COVID-19: case series and recent literature review. *Trop. Med. Health* **48**, (2020).
12. Pittas, A. G., Lau, J., Hu, F. B. & Dawson-Hughes, B. Review: The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. *Journal of Clinical Endocrinology and Metabolism* vol. 92 (2007).
13. Clinckspoor, I. *et al.* The Vitamin D Receptor in Thyroid Development and Function. *Eur. Thyroid J.* **1**, (2012).
14. Li, X., Liu, Y., Zheng, Y., Wang, P. & Zhang, Y. The effect of vitamin D supplementation on glycemic control in type 2 diabetes patients: A systematic review and meta-analysis. *Nutrients* vol. 10 (2018).
15. Sari, A., Altun, Z. A., Karaman, C. A., Kaya, B. B. & Durmus, B. Does vitamin D affect diabetic neuropathic pain and balance? *J. Pain Res.* **13**, (2020).
16. Muscogiuri, G. *et al.* Vitamin D and thyroid disease: To D or not to D? *European Journal of Clinical Nutrition* vol. 69 (2015).
17. Simsek, Y. *et al.* Effects of Vitamin D treatment on thyroid autoimmunity. *J. Res. Med. Sci.* **21**, (2016).
18. Botelho, I. M. B. *et al.* Vitamin D in hashimoto's thyroiditis and its relationship with thyroid function and inflammatory status. *Endocr. J.* **65**, (2018).
19. Chahardoli, R. *et al.* Can Supplementation with Vitamin D Modify Thyroid Autoantibodies (Anti-TPO Ab, Anti-Tg Ab) and Thyroid Profile (T3, T4, TSH) in Hashimoto's Thyroiditis? A Double Blind, Randomized Clinical Trial. *Horm. Metab. Res.* **51**, (2019).
20. Vieira, I. H., Rodrigues, D. & Paiva, I. Vitamin d and autoimmune thyroid disease— cause, consequence, or a vicious cycle? *Nutrients* vol. 12 (2020).
21. Zhao, R. *et al.* Immunomodulatory Function of Vitamin D and Its Role in Autoimmune Thyroid Disease. *Frontiers in Immunology* vol. 12 (2021).
22. Jain, A. *et al.* Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. *Sci. Rep.* **10**, (2020).
23. Kwatra, B. Candidate genes of OCD interacts with human retrovirus to form new link in inflammatory hypothesis. *Int. J. Sci. \& Appl. Res.* **7**, 1–2 (2020).
24. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF BROMELAIN. *WORLD J. Pharm. Pharm. Sci.* **8**, 488–500 (2019).
25. Kwatra, B. HACKING THE BLOOD-BRAIN BARRIER. *Eur. J. Biol. Med. Sci. Res.* **5**, 10–13 (2017).
26. Kwatra, B., Yadav, P., Balasubramaniam, S., Garg, S. & Koyande, T. REVIEWING MAJOR MICROBES AS A SINGLE CELL PROTEIN.
27. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF GRAPE SEED EXTRACT. *World J. Pharm. Res.* **9**, 2519–2540 (2020).
28. Kwatra, B. Allicin-An After Digestion Antimicrobial Agent. *ACTA Sci. Microbiol.* **2**, 48–51 (2019).
29. Kwatra, B. & Agarwal, R. Misfolded Proteins in Parkinson's and Alzheimer Disease: A Review. (2020).
30. Kwatra, B. A Review on Potential Properties and Therapeutic Applications of Vitamin D. *Int. J. Sci. Res.* **9**, 682–691 (2020).
31. Kwatra, B., Solanki, A., Pal, M., Jasdanwala, S. S. & Pathak, T. Reviewing Effects of Rosehip, Curcumin, Piperine and Chondroitin Sulfate on Collagen.
32. Kwatra, B. CALCIUM AND IRON ABSORPTION: INVITRO STUDIES. *Int. J. Med. Biomed. Stud.* **3**, 59–61 (2019).
33. Kwatra, B. & Modi, R. Therapeutic Potentials and Applications of Folic Acid and Beta Carotene. *Int. J. Sci. Res. Sci. Technol.* **7**, 271–282 (2020).
34. Kwatra, B. LOCATOR THEORY FOR ELE-MENTS IN PERIODIC TABLE 'LEPT'. *Glob. J. Pure Appl. Chem. Res.* **5**, 9–10 (2017).
35. Kwatra, B. UTERINE CANCER: SEX DOMINANT CHARACTER. *Int. J. Adv. Res.* **8**, 663–667 (2020).
36. Kwatra, B. *et al.* An Overview of Analeptic Applications of Omega-3 Fatty Acids.
37. Kwatra, B. A review on Potential properties and therapeutic Applications of Carrots and Their Seed Extracts.
38. Bharat Kwatra, M. M. Mosquito Menace. *Int. J. Sci. Res.* **8**, 1314–1315 (2019).
39. Kwatra, B. COLLAGEN SUPPLEMENTATION: THERAPY FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS AND OSTEOARTHRITIS: A REVIEW. *WORLD J. Pharm. Pharm. Sci.* **10**, 589–604 (2020).
40. Bharat Kwatra, C. A. Mathematical and Statistical Approach to Define Past Present Future Events. *International Journal of Science and Research (IJSR)* vol. 8 260–263 (2019).
41. Kwatra, B. Procuring Natural Dye for Solar Cell Using Leaf Waste. *Int. J. Sci. Res.* **7**, 46–47 (2019).
42. Kwatra, B. MECHANISMS OF PATTERN FORMATION OF FBP17 IN MAST CELLS. *Int. J. Adv. Res.* **7**, 413–414 (2019).
43. Kwatra, B., Khatun, A., Bhowmik, R. & Rehman, S. In silico-modelling of phytochemicals in septic arthritis. *Pharma Innov* **10**, 14–21 (2021).
44. Kwatra, B. & Mudgil, M. LIGHT ASSISTED TIO2-BASED NANOCOMPOSITE SYSTEMS: A NOVEL TREATMENT FOR CANCER. *Int. J. Med. Biomed. Stud.* **4**, 28–32 (2020).
45. Bharat Kwatra, C. A. Studying the movements of the resonant elastic pendulum. *Indian J. Appl. Res.* **10**, 1–2 (2020).
46. Kwatra, B. & Mudgil, M. PROTONATED CRAB SHELL WASTE AS FUNGAL INHIBITOR. *Int. J.*

Med. Biomed. Stud. **3**, 111–116 (2019).
47. Kwatra, B. HYDROQUINONE: A novel growth inhibitor and apoptosis inducer in U-251 MG CELLS. *Int. J. Med. Biomed. Stud.* **3**, 15–16 (2019).
48. Bharat Kwatra, C. A. THE UNEXPLAINED SIMILARITY BETWEEN THE ATOMIC AND GRAVITATIONAL MODELS. *Int. J. Adv. Res.* **8**, 1099–1107 (2020).
49. Kwatra, B. Studies on People Employed in High Risk Workplace: Between Genetic Polymorphism for Tumor Necrosis Factor (TNF-A) and Blood Pressure. *J. Pharm. Pharm. Sci* **8**, 488–500 (2019).
50. Bharat Kwatra, M. M. Untangling the Mathematical Relation Between Natural Selection and Adaptive Radiation Using Macromolecules and Microevolutionary Forces. *Int. J. Res. Sci. Technol.* **7**, 313–339 (2020).
51. Kwatra, B., Hussain, M. S., Bhowmik, R. & Manoharan, S. Reviewing Therapeutic and Immuno-Pathological Applications of Vitamins and Carotenoids. *Int. J. Sci. Res. Sci. Technol.* **7**, 287–313 (2020).
52. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF LYCOPENE. *Int. J. Med. Biomed. Sci.* **4**, 33–44 (2020).
53. Kwatra, B., Zafar, J., Choudhary, M., Akhtar, N. & Golani, T. ANALEPTIC APPLICATIONS OF PEPTIDES.
54. Kwatra, B. EXPRESSION AND CHARACTERIZATION IN PICHIA PASTORIS BY CLONING OF DELTA 4 DESATURASE FROM ISOCHRYSIS GALBANA. *Indian J. Appl. Res.* **9**, 1–2 (2019).
55. Kwatra, B. *et al.* Analeptic Properties of Vitamin D.
56. Kwatra, B., Ega, G., Mishra, G. & Jain, A. THERAPEUTIC APPLICATIONS OF VITAMINS AND PIGMENTS IN RESPIRATORY DISORDERS. (2020).
57. Kwatra, B. & Arora, C. Investigation of Conductance Quantization with Magnetic Field Control and Application of Biosensor. *Int. J. Innov. Res. Technol.* **6**, 271–272 (2020).
58. Kwatra, B. REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF BRANCHED CHAIN AMINO. *WORLD J. Pharm. Pharm. Sci.* **9**, 561–588 (2020).
59. Kwatra, B. Maprovit 3, 6, 9: Perfect Companion of your Immune System to Fight Corona Virus Hit. *Int. J. Sci. Res.* **9**, 241 (2020).
60. Kwatra, B. & Arora, C. The Studying Of Movements Resonant the Pendulum Elastic. *Indian J. Appl. Res* **10**, 1–2 (2020).
61. Kwatra, B. & Mudgil, M. Finding Closely Related Organisms to Homo sapiens Insulin; Using Computational Biology.
62. Kwatra, B. Tinospora Crispa As A Future Cure For Obesity/Cholesterol. *Int. J. Sci. Technol. Res.* **6**, 340–341 (2017).
63. Kwatra, B. Bioactive-Compounds: alternative to control Candida spp. *Int. J. Sci. Res. Rev.* **8**, 221–223 (2019).
64. Kwatra, B. Effects of Mineral Separation by Time and Enteric Coating Mechanism for Calcium and Iron Absorption in Mammalia. *Int. J. Sci. Res.* **8**, 1265–1270 (2019).
65. Kwatra, B. A REVIEW ON POTENTIAL PROPERTIES AND THERAPEUTIC APPLICATIONS OF BROMELAIN. *www.wjpps.com* **8**, 488–500 (2019).
66. Kwatra, B. Holothuroidea (Sea Cucumber): Key to Anti-Aging. *Int. J. Sci. Res.* **8**, 884–884 (2019).
67. Mudgil, M. & Kwatra, B. Mosquito Menace Aim: Observing the life cycle of Aedes aegypti mosquito and understanding its behavior towards different natural oils for encouraging natural methods of repellence. *Int. J. Sci. Res* **8**, 1314–1315 (2019).
68. Kwatra, B. *et al.* Clinical Applications and Properties of Calcium Citrate Malate.
69. Kwatra, B. COLLAGEN SUPPLEMENTATION: THERAPY FOR SKIN DISORDERS: A REVIEW. *World J. Pharm. Res.* **9**, 2504–2518 (2020).
70. Bharat, K., Ratna, R., Ratul, B. & Sounok, S. DRUG REPURPOSING: IN SILICO MODELING OF COVID-19. *Res. J. Pharm. Biol.* **7**, 19–40 (2021).
71. Kwatra, B., Mir, A. M., Salagundi, R. & Khair, S. Therapeutic and Clinical applications of Ginseng, Curcumin and Allicin. *Int. J. Creat. Res.* **8**, 3113–3124 (2020).
72. Dai, J., Jiang, C., Chen, H. & Chai, Y. Vitamin D and diabetic foot ulcer: a systematic review and meta-analysis. *Nutrition and Diabetes* vol. 9 (2019).
73. Alam, U., Arul-Devah, V., Javed, S. & Malik, R. A. Vitamin D and Diabetic Complications: True or False Prophet? *Diabetes Therapy* vol. 7 (2016).
74. Agarwal, R. Vitamin D, proteinuria, diabetic nephropathy, and progression of CKD. *Clinical Journal of the American Society of Nephrology* vol. 4 (2009).
75. Tecilazich, F., Formenti, A. M. & Giustina, A. Role of vitamin D in diabetic retinopathy: Pathophysiological and clinical aspects. *Reviews in Endocrine and Metabolic Disorders* (2020) doi:10.1007/s11154-020-09575-4.