



Analeptic Properties of Vitamin D

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Systematic Review

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ABSTRACT

This article is an examination of the Analeptic Properties of Vitamin D. The scientific development and subsequent need to develop new strategies to tackle problems related to joints, dermatitis, cancer, respiratory disorders, dysfunctional immune system and COVID-19, continues to influence researchers all over the globe today. This article examines the research done and published by researchers and scientists. Consideration of current trends and data in scientific queries and demonstrates further aspects of Analeptic Properties of Vitamin D. Additionally, this article explores options for using Vitamin D to treat problems related to joints such as Rheumatoid Arthritis and

Osteoarthritis, its applications in atopic dermatitis and eczema, its potential in treating Inflammatory Bowel Disease (IBS), cancer, immune disorders and common respiratory diseases and additionally its use as a prophylaxis for COVID-19.

Keywords: Vitamin D; joints; dermatitis; COVID-19; IBS.

1. INTRODUCTION

Vitamin D is a fat-soluble vitamin, it occurs in two forms- Ergocalciferol (D2) and Cholecalciferol (D3). The best source of Vitamin D is sunlight, other sources include: fish, red meat, liver, egg yolk and fortified foods like breakfast cereals. A deficiency in Vitamin D can cause joint and muscle pain, anxiety, low energy and more frequent illness. To tackle this, supplements in the form of capsules and powders have been formulated to ensure an adequate supply of Vitamin D is provided at all times. It is the only vitamin that possesses hormonal properties, once it is absorbed via the skin or the digestive system it enters the kidneys and liver where it gets converted to a hormone. As a hormone, it plays a vital role in calcium and phosphorous homeostasis. This property helps strengthen bones and joints and correct related disorders.

Apart from joints, Vitamin D also plays a significant role in tackling Dermatitis, Irritable Bowel Syndrome and CoVID-19, to name a few. The action of Vitamin D is mediated through the VDR receptor, which is known to bind to a number of steroid hormones such as thyroid hormones and sex hormones. VDRs are comprised of 3 domains, an N-terminal DNA binding domain (VDRE), a C-terminal ligand binding domain and a hinge region in between these domains. When Vitamin D binds to the VDR, VDR binds to the VDREs, which leads to the recruitment of coregulatory complexes required of the genomic activity of Vitamin D. These coregulatory complexes can be gene/ cell specific thus allowing cell/tissue specific action of Vitamin D. Additionally, Vitamin D also exerts a number of non-genomic effects on chondrocytes and keratinocytes, via activation of enzymes and ion channels.

A tremendous amount of research has already been carried out with respect to the analeptic properties of Vitamin D. It has been used in the prevention of sepsis and enhancement of patient recovery in the Intensive Care Unit (ICU) (Takeuti F. et. al 2018). Vitamin D analogues have been used to treat hyperproliferative skin

diseases like psoriasis. Patients suffering from diabetes mellitus often benefit from the Vitamin D supplementation, which prevents the development of frank diabetes. Another set of Vitamin D analogues have also shown to prevent cancer progression by retarding cancer metastasis. Vitamin D and its analogues have also shown to suppress cardiac hypertrophy.

Gauging the current scenario globally, with the CoVID-19 pandemic wreaking havoc, people have been confined to their homes. This has drastically reduced the amount of time they spend outdoors thus, decreasing the amount of Vitamin D absorbed. The consumption of Vitamin D supplements has increased recently. Thus, to add to the ever-growing pool of knowledge it becomes important to analyse the positive effects of Vitamin D supplementation on joints, dermatitis, Irritable Bowel Syndrome, respiratory diseases, cancer, diabetes mellitus and last but not the least CoVID-19 which is the need of the hour. This meta-review aims to cover all these topics.

2. METHODS

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

3. RESULTS AND DISCUSSION

3.1 Vitamin D in Joints [1–10]

3.1.1 Vitamin D, bone health and its potential mechanisms

Vitamin D is considered a secosteroid hormone, necessary for positively controlling the bone Mineral Density (BMD). Prolonged vitamin D deficiency leads to rickets in children and osteomalacia in adults. Studies have shown that vitamin D supplementation improves muscular strength, which helps decrease incidence of

fractures. Osteoporosis is considered to be an inflammatory condition. Pro-inflammatory cytokines are associated with increased metabolism of bone. Thus, the immunoregulatory mechanisms of vitamin D control the effects of cytokines on bone health. Hence, vitamin D may influence fracture risk through different mechanisms. Research has shown that inadequate vitamin D intakes over long periods of time may lead to bone-demineralization. Vitamin D deficiency causes decreased calcium absorption and ultimately the release of calcium from the bones in order to maintain circulating calcium concentrations. Continuous bone turnover and resorption weakens the bones and increases fracture risk via secondary hyperparathyroidism and ultimately leads to osteomalacia and osteoporosis. Osteoporosis is clinically defined as a BMD 2.5. There is a direct relationship between BMD and fracture risk, with a decrease in bone strength and density associated with an increased number of fractures. Given the relationship between vitamin D and bone mineralization, optimal vitamin D status is essential for minimization of fracture risk. Bischoff-Ferrari (2005) had conducted a meta-analysis and proved vitamin D in the range of 700-800 IU/d reduced the risk of hip/non-vertebral fractures by 25% while a calcium intake of more than 700 mg/d was required for non-vertebral fracture prevention. A recent analysis reported that 400-800 IU/d of vitamin D in itself was not effective but 400 IU/d combined with calcium reduced the rate of hip fracture by 16%

and reduced overall fractures by 8%. 5 out of 9 studies of vitamin D alone, plus 16 of 22 studies of vitamin D in combination with calcium have reported significant positive effects on BMD. Therefore, based on the evidence reported, vitamin D, supplemented with calcium, can have a beneficial effect on the prevention of falls and thus fractures. Evidence from both epidemiological and observational studies has pointed the immune regulatory effects of vitamin D. Moreover, in relation to bone health, a study has investigated the potential of vitamin D to alter cytokine production in individuals at increased risk of fracture and concluded that 20 IU/day of calcitriol for 6 months decreased both IL-1 and TNF- α concentrations and increased BMD in post-menopausal women with osteoporosis. Hence, it is possible given the immune regulatory effects of vitamin D together with the reported inflammatory aetiology of osteoporosis, that the beneficial effects of vitamin D on fracture risk may be mediated by an effect of vitamin D on cytokine concentration. It is therefore clear that vitamin D is essential for bone health; and insufficient intakes result not only in diseases of rickets and osteomalacia but also in increased bone metabolism and enhanced risk of fracture. Research findings indicate that supplementation with vitamin D in those most at-risk of impaired bone health has a beneficial effect on fracture prevention. Research clearly suggests vitamin D not only improves BMD but also enhances muscle function leading to a decreased number of falls and controls the effect of pro-

Table 1. Vitamin D in Joints

Sr no	Title of Paper	Year Published
1	Vitamin D and Bone health: Potential Mechanisms	2010
2	Vitamin D and Bone	2012
3	Vitamin D and Rheumatoid arthritis	2012
4	Role of Vitamin D in osteoarthritis: Molecular, Cellular and Clinical Perspectives	2015
5	The effect of vitamin D supplementation on knee osteoarthritis, the VIDEO study: a randomised controlled trial	2016
6	Vitamin D attenuates inflammation, fatty infiltration, and cartilage loss in the knee of hyperlipidemic microswine	2016
7	Vitamin D and its effects on Articular Cartilage and osteoarthritis	2017
8	Vitamin D in the prevention and treatment of Osteoarthritis: from Clinical intervention to cellular evidence	2019
9	Effect of 1,25 dihydroxy Vitamin D3 supplementation on pain relief in early rheumatoid arthritis	2019
10	Effect of Vitamin D supplementation on pain and physical function in patients with knee osteoarthritis(OA); an OA trial bank protocol for a systematic review and individual patient data (IPD) meta-analysis	2020

inflammatory cytokines on bone metabolism. The level of supplementation required for an optimal effect on fracture prevention, is still debatable. The majority of trials and meta-analyses indicate that a dose of vitamin D of 800 IU/d combined with a sufficient intake of calcium is optimal. Further studies are required to confirm the optimal dose of vitamin D required to reduce fracture risk in older people and also to explore the effects of vitamin D on pro-inflammatory cytokines and bone health.

3.1.2 Direct and Indirect effects of Vitamin D on bone

All cells that form the skeleton, namely-chondrocytes, osteoblasts, and osteoclasts—contain both the vitamin D receptor and the enzyme CYP27B1 required for producing 1,25 dihydroxyvitamin D. Direct effects of 25 hydroxyvitamin D and 1,25 dihydroxyvitamin D on the bone cells have been demonstrated. However, the major skeletal consequences of vitamin D deficiency or mutations in the vitamin D receptor and CYP27B1, namely rickets and osteomalacia, may be corrected by increasing the intestinal absorption of calcium and phosphate, thus indicating the importance of indirect effects. While, these dietary manipulations do not reverse defects in osteoblast or osteoclast function that lead to osteopenic bone. This review mainly discusses the relative importance of the direct versus the indirect actions of vitamin D on bone. Vitamin D, and particularly 1,25(OH)₂D, is of crucial importance to bone. However, the rickets resulting from vitamin D deficiency or VDR mutations can be corrected by supplying adequate amounts of calcium and phosphate, or in the case of the VDR knockout by expressing the VDR solely in the intestine. This would suggest that vitamin D metabolites are unimportant for bone, or that substantial redundancy has been built into the system. The latter explanation is more appropriate. VDR-ablated mice develop secondary hyperparathyroidism, hypocalcemia, and rickets after weaning; similar changes are also seen when CYP27B1 is knocked out. However, when VDR or CYP27B1 knockout mice are fed a rescue diet containing high levels of calcium, phosphorus, and lactose, serum ionized calcium and PTH levels are normalized, and rickets and osteomalacia are prevented. This suggests that a major effect of 1,25(OH)₂D₃ is the provision of calcium and phosphate to bone from the

intestine, rather than a direct action on bone. However, a more extensive analysis of the effect of the rescue diet on the skeleton of VDR knockout, CYP27B1 knockout, and CYP27B1/VDR double knockout mice demonstrated that even when hypocalcemia and secondary hyperparathyroidism are prevented by the rescue diet, not all changes in osteoblast number, mineral apposition rate, and bone volume are rescued. Additionally, trabecular bone was markedly osteopenic and signified decreased osteoblast number/activity. Other studies have selectively deleted VDR or CYP27B1 in chondrocytes. However, while neither mouse model showed a marked alteration in growth plate development, both showed a decrease in vascular invasion at the chondroosseous junction with decreased osteoclasts and increased poorly mineralized bone in the primary spongiosa. The chondrocyte-specific VDR null mouse had an increase in serum phosphate and 1,25(OH)₂D levels, with decreased FGF23 associated with increased expression of CYP27B1 and the sodium phosphate transporter Npt2a in the kidney. These results indicate that vitamin D signaling in the chondrocyte was clearly affecting endochondral bone formation on the one hand and systemic calcium/phosphate homeostasis on the other. We can conclude that both direct and indirect effects of vitamin D on bone are required, and a deficiency in one can be at least partially compensated by the other. Understanding the relative contributions of direct and indirect actions of vitamin D on bone is very complex. Dietary calcium and phosphate can to some extent compensate for deficient vitamin D signaling, and vitamin D can compensate to some extent for deficiencies in calcium and phosphate. But all are involved. Defining the optimal level of vitamin D to maintain bone health remains debatable. However, achieving a level of 25OHD around 30 ng/mL is safe and effective. Additional research will be necessary to determine whether this is the optimal level or not.

3.1.3 Vitamin D and its effects on autoimmune disease and rheumatoid arthritis

Vitamin D deficiency has been implicated in the pathogenesis of many autoimmune diseases. Reduced vitamin D intake has been associated with increased susceptibility to the development of rheumatoid arthritis (RA) and vitamin D deficiency has been found to be associated with disease activity in patients who have RA. The

main objective was to evaluate vitamin D status in patients with RA and to assess the relationship between vitamin D levels and disease activity. In a cohort of 44 patients with RA, 25-hydroxyvitamin D₃ [25(OH)D₃] levels, parathyroid hormone levels, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured. Disease activity was also evaluated by calculating the 28-joint Disease Activity Score (DAS28). A control group (*n* = 44), matched for age and sex, was also evaluated. All patients had a full clinical and laboratory evaluation. The DAS28 score was calculated for all patients. In addition, the HAQ disability index and the VAS pain score were calculated. Statistical analysis was performed using the statistical package SPSS19. Student's *t*-test was used to compare the patient group with the control group. Regression analysis was performed to analyze the relationship between indices of disease activity and 25(OH)D₃ levels. In the cohort of 44 patients with RA 25(OH)D₃ levels were found to be low compared with the control group, 25(OH)D₃ being 15.26 ± 1.07 ng/ml and 25.8 ± 1.6 ng/ml in the patient and control group respectively (Student's *t* test, *p* < 0.001). Parathyroid hormone levels were 71.08 ± 7.02 pg/ml (mean ± SEM) (normal values 10.0–65.0 pg/ml), CRP 7.6 ± 1.57 mg/litre (mean ± SEM) (normal values < 3 mg/litre) and ESR was 38.0 ± 4.6 mm/h (mean ± SEM) in the group of patients with RA. The levels of 25(OH)D₃ were found to be negatively correlated to the DAS28, the correlation coefficient being -0.084. Levels of 25(OH)D₃ were also found to be negatively correlated to CRP and ESR, the correlation coefficient being -0.115 and -0.18, respectively. It appears that vitamin D deficiency is highly prevalent in patients with RA, and that vitamin D deficiency may be linked to disease severity in RA. As vitamin D deficiency has been linked to diffuse musculoskeletal pain, these results have therapeutic implications. Vitamin D supplementation may be needed both for the prevention of osteoporosis as well as for pain relief in patients with RA.

3.1.4 Molecular, cellular and chemical perspectives of the role of vitamin D in osteoarthritis

Vitamin D has been found to play essential roles in a number of diseases including osteoarthritis. Many cell types within osteoarthritic joints appear to experience negative effects at increased sensitivity to vitamin D. These findings contrast

some clinical research which has identified vitamin D deficiency to have a very high prevalence among osteoarthritis patients. Due to the conflicting effects of vitamin D in knee OA, further research is required to fully conclude its role in the disease. The primary functions of vitamin D are calcium homeostasis and regulation of bone metabolism. With such a potent effect on bone, vitamin D has been investigated as to its role in OA. Here we review the current understanding of vitamin D and the roles it plays in OA. 24% of advanced stage elderly OA patients in a United Kingdom study were found to have deficient vitamin D levels according to the National Diet and Nutrition Survey definition of less than 40 nmol/L. In a 2010 study in Ireland of rheumatology outpatients, 70% were found to be vitamin D deficient and 26% were severely deficient. The study also noted 62% of OA patients suffered from hypovitaminosis D and 13% were severely affected. A systematic review performed by Cao et al. examined the associations between serum 25(OH)D₃ and OA. They found that there exists convincing evidence for an association between 25(OH)D₃ and cartilage loss in knee joints; the authors also observed moderate evidence to support a positive association between low levels of vitamin D and radiographic knee OA. Ding et al. found both vitamin D levels and sunlight exposure to be associated with decreased knee cartilage loss. However, Felson et al. found that there was no association between low vitamin D and structural worsening of affected joints. However, the clinicaltrials.gov website lists a number of trials which are ongoing that aim to shed light on the efficacy of vitamin D supplementation in OA and possible benefits against the disease development and progression. Vitamin D plays a crucial role in bone metabolism. It has a range of effects on various cell types within joints which have been shown to be altered on osteoarthritis. Subchondral bone sclerosis is a hallmark of OA, but so too is bone remodeling which is associated with loss of bone density, increased porosity, and transient bone loss, a paradox explored by Burr and Gallant. It could be suggested that vitamin D, with its conflicting actions on bone growth, may be involved in the changes in bone behaviours at different stages of OA progression. Further studies are required to settle the debate as to the role of vitamin D deficiency in the development and progression of OA.

3.1.5 The effect of vitamin D supplementation on knee osteoarthritis- a randomised controlled trial (VIDEO study)

Knee osteoarthritis (OA) is a problem with increasing prevalence in an ageing population. Epidemiological data suggest that low serum 25-hydroxyvitamin D₃ levels are associated with radiological progression of knee OA. This study is mainly aimed to assess whether vitamin D supplementation can prevent the radiological progression of knee OA. The VIDEO study was a double-blind, randomised, placebo-controlled trial performed at five UK NHS hospitals. Participants were randomly assigned to receive either 800IU of oral cholecalciferol or matched placebo daily. Eligible participants were randomised centrally by the UK Medical Research Council Clinical Trials Unit (MRC CTU) via telephone to receive either oral vitamin D or matching placebo tablets (1:1) by computer-generated randomisation with stratification by recruitment centre. At the baseline visit knee radiographs and blood samples were taken, and the assigned drug dispensed in six month packs. Radiographs and blood sampling were repeated at 12 months and 36 months. Questionnaires (WOMAC) were completed at 6-monthly intervals until the final visit. Blood was drawn to measure serum 25-OH-D₃ at baseline and 12 months to assess baseline vitamin D status and response to supplementation. 198 of participants in the placebo group (84%) and 188 of those in the treatment group (79%) attended the 3-year follow-up visit. Six patients in the placebo group and seven in the vitamin D group received a TKR of the index knee during the follow up period. 380 patients had baseline and at least one follow up JSW reading available and were analysed separately as a sensitivity analysis. A separate analysis of the 242 patients with complete follow-up was also performed. Despite correcting vitamin D deficiency in the majority of participants, vitamin D supplementation at a dose of 800 IU/day made no significant difference in any of the radiological or functional outcomes. Vitamin D supplementation at a dose sufficient to elevate serum vitamin D₃ levels by almost 10 µg/L in one year, when compared with placebo, does not slow the rate of JSN or lead to reduced pain, stiffness of functional loss over a three year period. On the basis of these findings, vitamin D supplementation has no role in the management of knee OA.

3.1.6 Study of how vitamin D attenuates inflammation, fatty infiltration, and cartilage loss in the knee of hyperlipidemic microswine

Vitamin D as an immunomodulator and anti-inflammatory agent may attenuate inflammation in the knee. The aim of this study was to assess the anti-inflammatory effect of vitamin D on inflammation in the knee. This study was conducted with 13 microswine on a high cholesterol diet categorized into three groups of vitamin D-deficient, vitamin D-sufficient, and vitamin D supplementation. After 1 year, microswine were killed, and their knee joint tissues were harvested. Histological and immunofluorescence studies were carried out on the tissue specimens to evaluate the effect of vitamin D status. Histological and immunofluorescence studies of the knee joint tissues showed (1) increased inflammation in the knee joint tissues, (2) fatty infiltration in quadriceps muscle, patellar tendon, and collateral ligaments, and (3) chondrocyte clustering in the vitamin D-deficient and vitamin D-sufficient groups compared with the vitamin D supplementation group. Architectural distortion of the quadriceps muscle, patellar tendon, and collateral ligaments was also seen in the areas of inflammatory foci and fatty infiltration in the vitamin D-deficient group. The results of this study demonstrate the potential beneficial effect of vitamin D in decreasing inflammation and fatty infiltration in knee joints, which may decrease pain and disability. However, the role of vitamin D supplementation in decreasing the progression of cartilage loss or OA needs to be investigated.

3.1.7 Effects of vitamin D on articular cartilage and Osteoarthritis

Vitamin D deficiency has been associated with an increased risk of patients developing OA in some studies, but the results of other studies have been inconsistent. The main purpose of this article is to summarize the role of vitamin D in articular cartilage physiology and OA and review the current literature that investigates the role of vitamin D in regeneration of articular cartilage. The articular cartilage degeneration leads to loss of articular cartilage and ultimately the presentation of pain as a symptom of OA. Recent evidence suggests that the role of vitamin D in the progression of OA is promising. Some authors have found that vitamin D deficiency increases the risk of patients' developing OA.

Zhang et al found that individuals with similar characteristics who were deficient in vitamin D and who were assessed radiographically for OA had an increased risk for OA of the knee. It has been shown that patients with OA have decreased vitamin D serum levels. Bassiouni et al and Veronese et al both found that serum 25(OH)D levels were significantly decreased in the patients with knee OA. Quite interestingly, Konstari et al found in a longitudinal cohort study that low serum 25(OH)D concentration did not predict increased incidence of knee and hip OA when looking at Finnish patients. Malas et al found that vitamin D deficiency significantly decreased femoral cartilage thickness in women between 20 and 45 years of age. In another longitudinal cohort study performed in the United States, men with vitamin D deficiency had a 2-fold increased likelihood of radiographic hip OA compared with men showing normal levels of vitamin D. While these studies seem promising, imaging studies looking at increased vitamin D serum levels as a way to decrease the risk for OA have been inconclusive. Hussain et al showed that increased vitamin D serum concentrations were associated with an increased risk of hip arthroplasty for men with OA. Arden et al showed that there was no significant difference in the rate of joint space narrowing in the medial compartment of knees due to vitamin D supplementation. Studies have shown conflicting results as to whether low vitamin D levels are correlated with OA-related pain in patients. Furthermore, there are conflicting reports as to whether vitamin D supplementation decreases pain in OA. Vitamin D-sufficient patients have a lower risk of developing OA, and vitamin D sufficiency and supplementation decrease articular cartilage degeneration radiographically. Some of the studies have investigated the effect of vitamin D on OA progression and pain management; but, while there is no general consensus on the effects of vitamin D on OA, some results seem promising. Vitamin D supplementation may be considered as a safe method to treat and prevent OA, but future research is required to define the specific pathway and ultimate efficacy.

3.1.8 Vitamin D in preventing and treating Osteoarthritis- From Clinical Interventions to Cellular Evidence

The relationship between vitamin D and OA during OA initiation and progression were considered in this review. Subset analyses

and one randomized controlled pilot trial indicated that vitamin D supplementation may alleviate joint pain in OA patients with low vitamin D status (<50 nmol/L). According to currently available clinical results, evidence is lacking to set a vitamin D level to prevent OA, and increasing vitamin D status above 50 nmol/L does not seem to benefit OA patients. Observational studies in participants with relatively high (≥ 50 nmol/L) vitamin D status suggest that there is no relationship between vitamin D status and initiation of radiological OA. Although the results of cross-sectional studies are conflicting, most prospective observational studies report a null relationship. Few studies have reported the role of vitamin D on OA progression in animal models. The results indicate that vitamin D may initiate or aggravate OA. On the other hand, vitamin D may protect OA joints in vivo if it prevents the action of articular cartilage TGF β , which aggravates the condition of OA joints as seen in other cells. The direct interaction between vitamin D/VDR and TGF β /SMAD3 has been reported in cell lines and renal and hepatic cells, whereas research in chondrocytes is limited. Through a meta-analysis, Zhu et al. reported that the VDR Apal polymorphism is associated with OA of the knee, hip, and lumbar spine in Asians. Associations between VDR polymorphisms and OA need more research. Low vitamin D status, MetS, and OA share obesity as a common risk factor. Some results indicate the possibility that vitamin D/VDR ameliorates OA by disturbing the activation of TGF β pathway or through interaction with SMAD3 or MMP13. However, currently, no studies have been performed to elucidate this mechanism. Whether vitamin D acts on OA joint cartilage locally or through the endocrine system in humans is unclear. Clinical observations provide little evidence of a protective effect of vitamin D on cartilage volume loss or radiologic OA initiation. Most trials did not find an benefit of vitamin D supplementation; however, subset analyses point to the possibility that patients with low 25(OH)D (<50 nmol/L) may show alleviated joint pain with vitamin D supplementation. The reviewed studies suggest that current evidence is lacking on the effect of vitamin D on the prevention of OA, however, serum 25(OH)D above 50 nmol/L, may be adequate for joint health of OA patients as well.

3.1.9 The effect of 1,25 dihydroxy vitamin D3 supplementation on pain-relief in early rheumatoid arthritis

Preliminary data suggest that RA associated diffuse musculoskeletal pain could be linked to vitamin D deficiency. Vitamin D decreases the production of inflammatory mediators and increases the production of Interleukin-4 (IL-4) by Th-2 cells resulting in immunosuppressive action. Several studies have indicated the status of vitamin D deficiency as a potential risk factor in RA. The current standard therapy for RA is disease-modifying antirheumatic drug (DMARD) therapy along with anti-inflammatory therapy using non-steroidal anti-inflammatory drugs (NSAIDs). Lately, many clinicians recommend 1,25 dihydroxy vitamin D3 supplementation along with calcium supplementation in RA, mainly due to its positive role in RA-associated osteoporosis and suppression of autoimmunity. However, preliminary clinical data is inconclusive. This study was designed to assess the effect of 1,25 dihydroxy vitamin D3 supplementation on pain relief in the setting of early RA. A pilot questionnaire survey was conducted to estimate minimum time required for onset of pain relief (T_m). A total of 25 patients with RA who were initiated on 1, 25 dihydroxy vitamin D3 therapy within the past 6 months were surveyed in the clinic. The survey data indicated that most patients had varying amounts of pain relief scores ranging from 20% to 70%. Primary outcome included (i) the minimum time (days) required for onset of pain relief (T_m); (ii) % change in visual analog scale (VAS) score from onset of pain relief to end of 8-weeks. Secondary outcome included change in DAS-28. With regard to disease status, mean DAS score at baseline in subjects with low vitamin D levels was significantly higher at 3.6 ± 0.01 . Assuming DAS-28 >3.2 in case of active disease, 74.28% ($n = 26$) cases were diagnosed having active disease compared to 29.62% ($n = 24$) cases with normal vitamin D levels. Mean disease duration in vitamin D deficient population was significantly lower (4.7 ± 0.9 months). Put together, vitamin D levels were lower in the setting of female gender ($P < 0.001$), higher disease activity ($P < 0.001$) and shorter mean disease duration ($P < 0.001$). The vitamin D levels were inversely correlated with disease activity assessed by DAS-28 ($r = -0.604$; $P < 0.001$). This study depicts that additional pain relief is clinical benefit in early RA could be achieved by supplementing existing

DMARD therapy with 1, 25 dihydroxy vitamin D3 at 60,000 IU/week. However, many studies have been contradictory. In the current study, a higher dose of 60,000 IU/day was associated with higher pain relief. This study data indicated that vitamin D levels were lower in subpopulation with shorter mean disease duration. This indicates that in the setting of a strong inverse correlation between serum vitamin D level and DAS-28 score, vitamin D deficiency can trigger and initiate disease sequelae in RA.

3.1.10 Effect of vitamin D supplementation on pain and physical function in knee osteoarthritis (OA): an OA Trial Bank protocol for a systematic review and IPD meta-analysis

Various observational data suggest that vitamin D deficiency is associated with the onset and progression of knee osteoarthritis (OA). However, randomised controlled trials (RCTs) investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Further research is needed to clarify the effects of vitamin D on patient-reported outcomes and to determine whether there are patient subgroups who may benefit from the supplementation. The aim of this individual patient data (IPD) meta-analysis is to identify patient-level predictors of treatment response to vitamin D supplementation on pain and physical function.

With available data, potential treatment effect modification for the following variables measured at baseline were:

- Radiographic knee OA staged at baseline using either the Kellgren–Lawrence (KL) or Osteoarthritis Research Society International (OARSI) joint space narrowing (JSN) grading system. Mild to moderate disease defined as a KL Score ≤ 3 or an OARSI JSN Score ≤ 2 , and severe disease will be a KL score of 4 or an OARSI score of 3.
- Vitamin D deficiency is defined as serum levels of 25(OH)D less than 30 nmol/L at baseline. Insufficiency is defined as serum 25(OH)D levels from 30 to <50 nmol/L. Serum 25(OH)D levels ≥ 50 nmol/L is considered as vitamin D sufficiency.
- Clinical signs of local inflammation or the presence of effusion-synovitis (yes or no). Clinical signs of local inflammation should be assessed by physical examination—

tumour (swelling), dolor (pain), rubor (redness), calor (heat) and functiolaesa (disturbance of function)—or by additional laboratory testing (eg, serum C reactive protein and erythrocyte sedimentation rate). Effusion-synovitis were measured on either ultrasound or MRI.

- Depressive symptoms were measured using a validated questionnaire, such as the Patient Health Questionnaire-9 and the Geriatric Depression Scale.

Vitamin D supplementation may improve pain and function in patients with knee OA; however, the evidence from observational studies and RCTs are controversial. The purpose of the proposed IPD meta-analysis is to evaluate the treatment response of vitamin D supplementation on pain and physical function for knee OA in specific subsets of patients according to disease severity, vitamin D levels, presence of BMLs, inflammatory signs and depressive symptoms, over both short-term and long-term follow-up. The current proposed IPD meta-analysis attempts to differentiate subgroups by identifying subtypes of patients that respond better to vitamin D supplementation on pain and physical function.

3.2 Vitamin D in Dermatitis [11–18]

3.2.1 Effect of vitamin D Intake in Infantile Eczema

Eczema is a skin inflammatory disease. The American Academy of Dermatology has estimated that about 20% of infants are diagnosed with eczema. Various methods have been assessed for treating this disease including supplementation of vitamin D. This study focuses on the association of maternal intake of vitamin D and eczema in offspring. From the results, it can be implied that risk of occurrence of infantile eczema can be reduced if vitamin D is supplemented in higher dosage.

Although the balanced ORs for the second and third quartiles were borderline significant, there was an inverted J-shaped relationship between maternal vitamin D intake during pregnancy and the risk of eczema in infants. Higher intake of vitamin D was significantly related to lower risk of eczema in the child. This study focused on maternal intake of vitamin D and its association with the occurrence of eczema in the offsprings. This study had certain strengths methodologically as their subjects belonged to

the same background making the population under study homogeneous. Now, from the results obtained it was seen that the risk of eczema had been lowered in infants with high maternal intake of vitamin D during pregnancy. Hence, vitamin D possesses certain preventive properties against eczema. However, further confirmation regarding the study is still needed. In addition to this, samples from other backgrounds should be studied for analyzing if there are other factors that must be monitored.

3.2.2 Facts and Controversies about the Association of Atopic Dermatitis and Vitamin D

Patients diagnosed with atopic dermatitis viz., a common chronic inflammatory dermatitis. This immune dysregulation disorder has various risk factors that are genetically associated, affecting the protective function of skin and immune responses with the external factors. As a result, the skin becomes pruriginous and inflamed, allowing penetration of irritants and allergens and predisposes the patients to infectious microbes. Vitamin D is one out of many etiological factors emphasized to be responsible for atopic diseases. This study discusses the facts and controversial relationship between atopic dermatitis and vitamin D. Vitamin D is known to be involved in both epidermal barrier dysfunction and dysregulated immune response, and these two processes are associated with the atopic disorder (dermatitis). Different studies by Peroni *et al.* and Oren *et al.* evaluated the prevalence and severity of AD in vitamin in patients with vitamin D deficiency. Data results suggested that vitamin D deficiency may be associated with the severity of AD, for example, people with low intake of vitamin D or children born from mothers with vitamin D intake. However, there are also several controversies associated. Some studies showed AD was found to be prevalent in people with increased vitamin D intake irrespective of any atopic history in the family. At the same time, some studies showed that intake of vitamin D in the first year of life is associated with a higher prevalence of atopy and allergic rhinitis. From the above study, it can be stated that vitamin D acts as both a protective as well as risk factor. However, a predominance of papers point to an inverse association between serum levels of vitamin D, nutritional intake or sun exposure, and AD's prevalence and severity. But there are several limitations in the vitamin D studies that affect the results and the patient's actual status.

3.2.3 Therapeutic Role of Vitamin D in Childhood Atopic Dermatitis

Vitamin D is a corticosteroid which helps in maintenance of phosphate and calcium homeostasis. It also exhibits anti-proliferative, anti-inflammatory and immune-modulatory properties. Recent research has been throwing light on its role on skin diseases such as dermatitis, psoriasis etc. Childhood atopic dermatitis (AD) is a chronic inflammatory disease which has prevalence of about 20% of the child population. This review focuses to affirm its role in childhood AD. Vitamin D plays a significant role in calcium and phosphate homeostasis, however, the therapeutic potential of the secosteroidal vitamin has been assessed in various inflammatory skin diseases. It has been proven to display satisfying results in children suffering from AD in various studies. However, there are multiple factors (such as treatment duration, limit of dosage of vitamin D) that are essential to be considered while affirming its role as a therapeutic option for treating childhood AD. Clinical studies and standardization of AD intensity are required to conclude further. With various studies being conducted on the functional role of vitamin D, there has been an array of varied results. Studies by Oren *et al.* and Peroni *et al.* noticed that serum levels of vitamin D were affected by the SCORAD index. However, Back *et al.* show a different side wherein children at a specific age showed symptoms of eczema if they were administered with vitamin D. Hence, it is essential to monitor the intake of vitamin D while giving it as supplements to cure skin inflammatory diseases. Studies on the impact of allergens and heliotherapy was also compared wherein a positive association of vitamin D and SCORAD index was observed. In addition to this, an inverse relation was found between IgE levels and vitamin D serum levels. Hence, with further analysis of specific pathways involving vitamin D, it can be deduced whether to administer supplements of vitamin D (or analogues) to treat childhood AD. Vitamin D appears to play a protective role in AD based on epidemiological and clinical evidence. It is difficult to ascertain how such a complex system will translate into health standards and supplementation advice for the overall population. Additional studies with a proportion, dose adjustment based on specific serum vitamin D levels, significantly longer period, and standardization of AD intensity is necessary.

3.2.4 The Role of Vitamin D and its Clinical Correlation with Atopic Dermatitis

Vitamin D has displayed its beneficial roles in various diseases. In this study, the main focus is to deduce the therapeutic function of vitamin D in skin inflammatory diseases – atopic dermatitis and psoriasis. Given the health benefits of vitamin D, numerous clinical and laboratory studies are being conducted to develop new vitamin D analogues with improved clinical efficacy. However, its role in atopic dermatitis is yet inconclusive as compared to psoriasis which seems to be confirmed.

SlgE: Serum immunoglobulin E, SCORAD: Scoring atopic dermatitis, TIS: Three Item Severity score, AD: Atopic dermatitis, RCT: Randomized controlled trial. Aside from its effectiveness in preventing of rickets and other bone disorders, intriguing findings on the association between vitamin D and other clinical manifestations (skin inflammatory diseases) has been taking shape, with several tests being performed to explore its other potential benefits, though the data remains contradictory and woefully inadequate for any clinical recommendations. More research with respect to mechanistic studies of vitamin D is necessary to understand the predicament.

3.2.5 Review on Efficiency of Vitamin D Supplementation in Atopic Dermatitis

Research has signified the role of vitamin D supplementation in treatment of atopic dermatitis and eczema. This study focuses on the efficiency of vitamin D supplementation. Levels of Vitamin D were found to be lower in AD patients thus implying its potent role in treatment of the skin inflammatory disease, AD. The study was carried out by comparing the healthy control and AD groups. This was done separately for pediatric AD patients and adult AD patients. With not much of a statistical difference, adult AD groups had lower vitamin D levels in the serum whereas the levels of vitamin D in pediatric AD patients was statistically significantly lower. Further, the SCORAD index and EASI score for four randomized trials showed inverse relation between the scores and vitamin D levels. This study focused on case trials which helped assess the relation between 25(OH) D levels in AD patients. Though it was found that lower 25(OH) D levels were observed in AD patients, however, still the relationship is not yet clear, especially for vitamin D supplementation in adult AD patients.

Table 2. Vitamin D in dermatitis

Sr. no.	Title of paper	Year Published
1	Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants	2010
2	Atopic dermatitis and vitamin D: facts and controversies	2013
3	Vitamin D and Atopic Dermatitis in Childhood	2015
4	Vitamin D and Skin Diseases: A Review	2015
5	Vitamin D Status and Efficacy of Vitamin D Supplementation in Atopic Dermatitis: A Systematic Review and Meta-Analysis	2016
6	Vitamin D and the Pathophysiology of Inflammatory Skin Diseases	2018
7	Successful Treatment of Severe Atopic Dermatitis with Calcitriol and Paricalcitol in an 8-Year-Old Girl	2018
8	Lower vitamin D levels in the breast milk is associated with atopic dermatitis in early infancy	2019

Table 3. Quartile points distribution in Eczema in 763 Japanese children (16–24 months old) by quartiles of maternal intake of vitamin D during pregnancy

Variable#; Vitamin D	Cases n	Crude OR (95% CI)	Adjusted OR (95% CI)"
Q1 (3.5)	46	1.00	1.00
Q2 (5.1)	31	0.61 (0.36-1.004)	0.63 (0.37-1.09)
Q3 (6.4)	29	0.56 (0.33-0.93)	0.59 (0.34-1.02)
Q4 (9.1)	36	0.73 (0.44-1.19)	0.67 (0.39-1.13)
p-value for trend		0.18	0.13

Table 4. Studies evaluating the role of vitamin D in atopic dermatitis, psoriasis

Study	Study Design	Results
Samochocki <i>et al</i>	95 AD patients 58 control subjects	After supplementation, both mean objective SCORAD and SCORAD index were significantly lower ($P<0.05$)
Peroni <i>et al.</i>	37 patients	Serum concentration of vitamin D and intensity of the disease expressed by SCORAD index was found to be inversely related.
Amestejani <i>et al.</i>	60 AD patients; randomized, doubleblind, placebo-controlled trial First group: 1600 IU cholecalciferol (vitamin D); second group: placebo	Vitamin D group's SCORAD and TIS index depicted significant improvement in patients with mild, moderate, and severe AD ($P<0.05$) in comparison to placebo-controlled trials
Case study 1 for	Usage of Tacalcitol	Cutaneous irritation in 5.9% cases

Study	Study Design	Results
treating psoriasis Case study 2 for treating psoriasis	Calcipotriene applied twice daily up to 100 g/week	< 0.05% of the effect of vitamin D on Ca-metabolism. Cutaneous irritation observed in 20% cases

Additionally, vitamin D should be carefully administered (specifically to breastfeed AD infants). The relationship between 25(OH) D levels and vitamin D is unclear due to contradictory results in various studies. It is essential to carry out an observational study which includes a large sample-size. Further, for assessing the effect of vitamin D, research should be carried out focusing on specific pathways involving vitamin D.

3.2.6 Role of Vitamin D in Physiopathology of Dermatitis

Vitamin D is a group of fat-soluble secosteroids responsible for its function in different organs. Vitamin D shapes various functions, including keratinocyte proliferation, differentiation, cell death, as well as barrier repairs and immunoregulatory mechanisms. Vitamin D is being explored as a potential treatment for atopic dermatitis which is a chronic inflammatory disease. This review highlights its functional role and focuses on the non-classical component of vitamin D on atopic dermatitis. It has been deduced that not only does vitamin D functions as an anti - tumor, pro-differentiative, anti-apoptotic, and immune-modulator, but also it has quite a pleiotropic impact in the skin. Prospective research is needed to examine the specific pathways influenced by vitamin D in a mechanistic and intensive manner. AD patients demonstrate significant epidermal barrier disruption and trans-epidermal loss of water. This loss of water causes AD skin more susceptible to allergen permeation, bacterial, fungal, and viral invasion. AD showcases a defective immune system, further, AD patients possess abnormalities in multiple immune system components such as barrier function disruption, greatly reduced mobilization of innate immune cells (NK cells, pDCs, neutrophils) to the epidermis, TLR2 defects, and reduced AMP secretion. According to studies, populations in higher geographic latitudes have a higher prevalence of AD because of less exposure to the sun and vitamin D production. Moreover, the intensity of AD was found to be associated with vitamin D levels wherein there has been a mention about decline in vitamin D levels in serum in AD patients. However, there has been a controversial study wherein vitamin D is said to have a positive association with development of AD. Clinical studies assessing the effect of vitamin D on AD have also garnered mixed findings: some findings demonstrated an activation of thymic stromal lymphopoietin with

topical treatment of calcitriol or its reduced calcemic analogue MC903, which resulted in an AD-like syndrome in mice. Researchers have claimed while examining the relationship between vitamin D and AD may be impeded by spatial, periodic, and lifestyle vitamin D variations in AD patients and healthy controls. Mostly, it has been claimed that administration of vitamin D (calcitriol, paricalcitol) helps lower the symptomatic reactions in AD patients. Animal studies on the effect of vitamin D on AD have also yielded contradictory results. However, it is essential to determine the specific pathways involving vitamin D mechanistically for futuristic research to help conclude about the functional role.

3.2.7 Supplementation of Calcitriol and Paricalcitol for treating Severe Child Atopic Dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is a chronic inflammatory disease which can affect a specific range of population. Atopic dermatitis is related to other allergies such as asthma, food allergy etc. It is an implication of defects in the epidermal barrier which are reflected with acute lesions due to filaggrin deficiency or a loss in other protective factors in combination of genetic and environmental factors. In this report, the purpose of this research was to determine the relationship between AD and vitamin D. Furthermore, the researchers wanted to assess the therapeutic potential of vitamin D supplementation (using calcitriol and paricalcitol therapy) to the patient suffering from AD. In conclusion, calcitriol treatment may be considered for patients with chronic or refractory AD, and its analogue paricalcitol may be a relatively safe medication in terms of hypercalcemia and, in particular, hypercalciuria risk. It is crucial to monitor Ca-metabolism parameters in any particular patient case. The effect of Vitamin D supplementation has been carried out in various research papers. Generally, to maintain remission during acute flares, the first-line treatment remains local corticosteroids combined with local calcineurin inhibitors. And, conventional therapies for Atopic Dermatitis include administering emollients topically to restore the epidermal barrier function. However, in this case, the child was finally administered with a paricalcitol dose. From the studies conducted by Javanbahkt et al., Sidbury et al. and Di Filippo et al., supplementation of vitamin D to treat AD was proven beneficial as there was a significant improvement in SCORAD

index. It has also been mentioned that vitamin D was known to normalize the interleukin patterns in the patients, hence, acting as an immunomodulating agent. Vitamin D has a significant impact in reducing the IgE levels. Hence, the treatment of the 8-year old child with paricalcitol to cure severe AD can be considered a safe and secure method essentially in the case of hypercalcemia. However, control studies are needed to demonstrate the efficacy and safety of its therapeutic potential. Further, it is essential to determine the best possible dose of medication and method of vitamin D administration.

3.2.8 Relationship between Occurrence of Infantile Atopic Dermatitis and Deficiency of Vitamin D in Breast Milk

Vitamins A and D possess potential which influences the immune system. Therapeutic roles of vitamin A and D could be of significant roles while treating infantile atopic dermatitis. In this study, the relation between occurrence of infantile AD and levels of vitamins A and D are examined. The SCORAD index was negatively correlated to levels of Vitamin D in the given breast milk samples. Further, one can infer that there is a chance of occurrence of infantile AD if low levels of vitamin D are present while breastfeeding. There was no significant difference obtained when control groups and infants diagnosed with AD were characterized based on age, sex, parental atopy history and mother's exposure time to sun. Further, the study to find the association between 25-(OH) D3 with AD wherein negative relation between the objSCORAD and 25-(OH) D3 levels was found. In multiple regression study it was found that other than mother's sun exposure time, no other factor had any impact on the association between 25-(OH) D3 levels and AD. It can be deduced from the study that low levels of vitamin D in BM could increase the chance of occurrence of AD in infants. Atopic Dermatitis is a chronic inflammatory disease which coexists with multiple allergies. About 20% of the population expresses symptoms of AD at a very young age. Vitamins A and D possess immunomodulatory and anti-inflammatory properties. However, from the study there was no clarity with respect to the effect of vitamin A. On the other hand, when analyzing the role of vitamin D in infantile AD, some correlation was deduced from the study, however, there are controversies wherein vitamin D is linked with eczema in kid under the age of 2 years. This study employed small sample size, thus, it is essential to conduct in larger cohorts.

Further, vitamin D administration for treatment of infantile AD should be carried out once the therapeutic roles are monitored.

3.3 Vitamin D in other aspects [19–28]

3.3.1 Relation between unexplained musculoskeletal pain and vitamin d hypovitaminosis

Vitamin D is responsible for maintenance of calcium metabolism and bone and muscle development. Deficiency of Vitamin D is associated with diseases like secondary hyperparathyroidism. People in old age experience musculoskeletal pain the cause of which is unknown. Unexplained musculoskeletal pain is known to be occurring in lower and upper parts and that had no prior relation to other injuries that can cause pain. Vitamin D hypovitaminosis can be one of the reasons of this unexplained musculoskeletal pain as the vitamin has part in bone metabolism. Several studies on patients of unexplained musculoskeletal were done and level of vitamin D of these patients was found out. Those with severe vitamin D hypovitaminosis had more danger of developing musculoskeletal pain and some also suffered from unexplained musculoskeletal pain. Vitamin D hypovitaminosis can be one of the causes of unexplained musculoskeletal pain. Its deficiency can affect bone and skeletal structures and lead to musculoskeletal pain. Unexplained musculoskeletal pain and vitamin D hypovitaminosis can be associated with each other as hypovitaminosis of vitamin D can lead to musculoskeletal pain and it can be one of the leading causes of it as well. Elderly people commonly suffer from unexplained musculoskeletal pain. Vitamin D hypovitaminosis can produce an impact on bone and skeletal structures of the body and thus can contribute towards development of musculoskeletal pain. Vitamin D supplementation treatments can be used to help patients of unexplained musculoskeletal pain.

3.3.2 Vitamin D3, immune regulatory activity in neck and head cancer

Vitamin D3's active metabolite can produce an impact on cancerous cells by lessening the metastasis of malignant cells and help patients suffering from head and neck squamous cell cancer. Vitamin D supplementation can produce an effect on patients of cancer as vitamin D due

to its immunomodulatory effect can affect progression of a disorder. Mice that consumed low vitamin D3 had high chances of developing malignancy. "A high expression of CD34+ progenitor cells were detected in patients of head and neck cancer along with faulty dendritic cells." Vitamin D can play a beneficial role in reducing the impact of cancer but still various pathways regarding it are under review. Vitamin D can have anti-cancer activity. CD34+ cells isolated from patients were cultured with vitamin D3. It was found that there were increases the number of dendritic cells in patients of head and neck cancer. These cells differentiated from CD34+ cells. Studies regarding effect of active metabolite of vitamin D3 on patients of Head and Neck cancer showed that such patients show an increase in dendritic cells which arise from CD34+ progenitor cells, however strong evidence is needed on this.

3.3.3 Role of supplementation therapies of vitamin d on anthropometric parameters in patients with metabolic syndrome

In today's world, Obesity has become one of the biggest problems. Metabolic syndrome is linked with obesity and with disorders of heart. It involves risk factors like elevated blood pressure, increase blood sugar level, elevated triglyceride level. Vitamin D hypovitaminosis was considered to affect obesity and anthropometric factors in patients of metabolic syndrome. Vitamin D supplements were administered to patients aged 30 to 65 years that suffered from metabolic syndrome. Various anthropometrical factors in the body were determined prior to start of supplementation therapy and were determined after the doses were administered as well to measure the change and effect vitamin D could bring in patients of metabolic syndrome. Vitamin D supplementation therapy can produce an effect on some of the anthropometric parameters of patients with metabolic syndrome. However, evidence regarding this is weak and needs further study. Reduction in waist circumference, one of the anthropometric factor was observed after the studies, however, other factors provided no significant evidence to prove the effect of vitamin D on obesity and anthropometric parameters on those suffering from metabolic syndrome. Vitamin D treatment can play a part in lessening the circumference of waist of patients of metabolic syndrome but evidence regarding other anthropometric factors did not provide strong results.

3.3.4 Effect of vitamin D on some respiratory disorders: A review

Respiratory & Pulmonology related diseases such as chronic obstructive pulmonary disease, tuberculosis and asthma have a connection with Vitamin D" hypovitaminosis and supplementation of this vitamin may help in recovering from the disease. Respiratory ailments can be lined with Vitamin D hypovitaminosis. It is known to produce an effect on causative agent of tuberculosis and hence control it as well. The risk factors of asthma and hypovitaminosis of vitamin D are similar and its deficiency can lead into Chronic obstructive pulmonary disorder, however there are no established trends. More investigation is essential to establish an association between Vitamin D hypovitaminosis and respiratory problems. Its role in regulation of these respiratory disorders is still unclear. More evidence is needed to prove a relation between them. Previous studies and research have established that there is an impact of Vitamin D intake on the health of patients who have respiratory problems. This has lessened the probabilities of catching the respiratory ailments discussed. However, fact based strong research and data is required to establish this relationship and impact.

3.3.5 Effect of vitamin D supplementation on sickle cell disease

Vitamin D is known to produce an effect on bone mineralisation and calcium metabolism of the body. Sickle cell disease is a hereditary ailment that produces altered form of haemoglobin, while it can cause other diseases as well like stroke, bone disorders like osteomyelitis, osteonecrosis, osteoporosis. Patients suffer from several macro-nutrient and micro-nutrient deficiencies due to a rise catabolism and one such deficiency is of vitamin D. Vitamin D is responsible for maintaining calcium level of bones throughout the body and is important for bone mineralisation, deficiency of it can have a worst impact on patients of sickle cell disease and can lead to more musculoskeletal disorders. Vitamin D supplements were administered to patients of sickle cell disease for a fixed period of time and then results were observed. The results showed that, the patients who were administered with vitamin D had lower frequency of pain. However, evidence regarding this need to be collected. Administration of vitamin D to patients of sickle cell disease led to increase in the level of 25

Table 5. Vitamin D in other aspects

Sr. No.	Title of Paper	Year Published
1	Association between Vitamin D Deficiency and Unexplained Musculoskeletal Pain	2008
2	Immune Regulatory Activity of Vitamin D3 in Head and Neck Cancer	2013
3	Effect of Vitamin D Supplementation on Anthropometric Parameters in Patients With Metabolic Syndrome	2014
4	A review of Vitamin D effects on common respiratory diseases: Asthma, chronic obstructive pulmonary disease, and tuberculosis	2016
5	Vitamin D supplementation for sickle cell disease	2017
6	Vitamin D signaling in intestinal innate immunity and homeostasis	2017
7	Action and Function of Vitamin D in Digestive Tract Physiology and Pathology	2017
8	Vitamin D deficiency and hepatitis viruses-associated liver diseases: A literature review	2018
9	Vitamin D in Inflammatory Bowel Disease: Biological, Clinical and Therapeutic Aspects	2019
10	Basic and pleiotropic effects of vitamin D in patients with diabetes mellitus type 1 and 2	2020

hydroxyvitamin D and frequency of pain experienced in the patients was less as well. However, the evidence regarding it is weak. Patients administered with Vitamin D supplement had high level of it in their blood. The difference in the number of side effects observed between vitamin D group and placebo group was not there. Bone ailments can occur in those suffering from sickle cell disease due to shortage of vitamin D. Studies conducted to establish association between them revealed that by supplying vitamin D doses pain in patients can be reduced, however, evidence was inconclusive.

3.3.6 Role of vitamin D signalling in management of intestinal homeostasis and innate immunity

The microbiota of gut is involved in important functions to manage intestinal homeostasis. Enteric flora, food antigens and toxins can produce inflammatory immune response, which can lead to several gastric disorders like Inflammatory Bowel Disease. It is significant to preserve the gut microbiota so that proper immune response can be generated against pathogens. Vitamin D signalling produces an impact on intestinal homeostasis. Vitamin D because of its immunomodulatory activity can control innate immune responses to manage pathogens. Vitamin D signalling produce an effect on environment of intestine and can keep gut healthy. Studies have found that Vitamin D signalling can prevent over growth of bacterial populations and increase the function of

intestinal barrier. However, evidence regarding it was not strong and need further research. Vitamin D signalling mechanism can influence the intestinal microbiota and can prevent several gastric diseases. Several studies have claimed that supplementation treatments of Vitamin D can be effective in Crohn's disease. Vitamin D signalling mechanisms can have a profound effect on gut homeostasis and supplementation therapies of vitamin D can prove beneficial for patients of gastric disorders like Inflammatory Bowel Disease. However, evidence regarding it is still weak. Vitamin D signalling has an immunomodulatory role which helps keep the balance of the gut and prevent disorders. The signalling mechanisms can help increase the function of intestine barrier and overcome poor intestinal barrier. However, sufficient evidence regarding it is missing and further studies can prove that Vitamin D signalling mechanisms can affect gut homeostasis and can be beneficial for gastro disorders as well.

3.3.7 Vitamin D and its role in physiology and pathology of digestive tract

Vitamin D has a role in bone and calcium metabolism, but is now known to produce an effect on numerous other processes of the body like its role in affecting functions of digestive tract is under research. Its role in treatment of various gastrointestinal diseases is being examined. However, evidence regarding it is weak and needs further studies to establish a concrete relation between role of deficiency of vitamin D and gastroenterological disorders. Management

of gastrointestinal cancers can be done by vitamin D receptor. Supplementation treatment of vitamin D can reduce risk associated with gastroenteric diseases. Vitamin D receptor can control the expression of numerous genes and can regulate cell proliferation as well. However, the process by which vitamin D can prevent the cancer cells from proliferating and prevent gastrointestinal cancers is still under research and strong evidence to support the fact that vitamin D supplementation therapies can reduce risk of cancer patients is weak. Vitamin D can play a role in treatment of gastrointestinal diseases as well as cancer of gastrointestinal tract as Vitamin D receptor has shown various forms of interaction with several different aspects of gastrointestinal tract. Vitamin D has a huge potential to be used for personalized medications like P4 medicine. However, several studies still need to be conducted with proper dose of vitamin D being administered to patients and monitoring of the effects have to be done as well to provide a strong evidence regarding it. Vitamin D receptor polymorphism can play a great role in management of gastrointestinal diseases as studies reveal that it can improve the progression and prognosis of gastrointestinal diseases. Hedgehog signalling by Vitamin D equivalents can help in attacking cancer cells and can recover the condition of Inflammatory Bowel Disease as well. Studies revealed that vitamin D hypovitaminosis can cause irritation in the gut as well. However, evidence regarding it was inconclusive and is still under research.

3.3.8 Vitamin D hypovitaminosis and hepatitis virus associated liver disorders: a literature review

Vitamin D can play a role in management of immune response against infectious agents apart from playing a role in calcium metabolism. Vitamin D hypovitaminosis can produce an impact on hepatitis virus associated liver diseases as well. These viruses associated liver disorders have been linked to vitamin D hypovitaminosis as this vitamin can help prevent virus replication and affect the pathogenesis of the disease. Deficiency of Vitamin D is measured by quantification of Vitamin D serum level. Surrogate markers like level of Parathyroid hormone can be used in detection of Vitamin D hypovitaminosis as there is an inverse relation between level of parathyroid hormone and vitamin D level. Deficiency of this vitamin is seen in cases of patients suffering from liver disorders

regardless of the cause of disease. Patients with liver disorders caused by Hepatitis viruses have shown deficiency of vitamin D. It can affect the progression of disease and so Vitamin D supplementation therapies can be a new treatment option for patients with chronic liver diseases that are associated with hepatitis B and C viruses. Vitamin D activation occurs by vitamin D receptor which is expressed on several tissues, making it a powerful controller of several important pathophysiological processes in infectious diseases, other disorders. Studies have shown a relation between level of vitamin D and hepatitis B and C virus liver infections. However, sufficient evidence regarding it is still accumulating.

3.3.9 Role of vitamin D in inflammatory bowel disease

Vitamin D by acting as an immunomodulator can affect gastrointestinal tract and shortage of it can lead to Inflammatory Bowel Disease.” It can regulate the pathogenesis of this disease as it affects the gut microbiota by influencing intestinal permeability and by maintaining intestinal homeostasis. The efficiency of Vitamin D against Inflammatory Bowel Disease still needs to be proved. Patients of this disorder had to undergo several studies relating to level of vitamin D in their body to establish a link between them. It was found that most of the patients of this disease had Vitamin D hypovitaminosis and this shortage could affect the progression of the ailment, however, evidence regarding this was inconclusive. Vitamin D hypovitaminosis can affect Inflammatory Bowel disease. However, studies regarding it need to be conducted, with proper management of dose of Vitamin D to record its efficiency against the ailment and to know its effect as an immunomodulator. Vitamin D hypovitaminosis can affect development of a disease as it has an immunoregulatory action and through this it can maintain environment of intestine and effect the microbiota of gut as well. Inflammatory Bowel Disease can be affected due to shortage of this vitamin and further studies need to be conducted to provide conclusive evidence regarding it.

3.3.10 Effects of vitamin D on patients of type 1 and type 2 Diabetes mellitus

Diabetes mellitus can be controlled by Vitamin D which has a role in regulating calcium metabolism of the body.” Studies have found that proper amount of vitamin D play a role in

maintenance of glucose homeostasis by appropriate secretion of insulin. Level of this vitamin in patients of diabetes is also known to impact other factors like blood pressure, lipid profile of body. Experiments were directed to find the role of vitamin D in maintenance of glucose homeostasis and it was found that the mice with mutant receptor of Vitamin D had insufficient level of glucose in their system and these mice showed increased chances of developing diabetes. Vitamin D in patients of diabetes can play a role in management of blood pressure but this needs further evidence to be proved. Cholesterol levels can be managed by vitamin D in patients of diabetes but evidence regarding it was inconclusive. Conclusion: Vitamin D is indispensable for maintenance of glucose homeostasis and normal insulin secretion. Regarding its role in regulation of blood pressure and cholesterol of patients of diabetes more evidence is needed. Vitamin D is needed for secretion of insulin in patients suffering from diabetes. Vitamin D can regulate the lipid profile as well as blood pressure but further research needs to be done on it. Vitamin D level is essential for maintenance of glucose homeostasis. Its role in blood pressure management is not clear and evidence regarding it has to be established.

3.4 Vitamin D in CoVID-19 [29–41]

3.4.1 Effect of heavy dose of vitamin D supplementation for COVID-19 disease: RCT (Randomized controlled trial)

Vitamin D is determined to reduce viral infection in other coronaviruses and its deficiency can increase the risk of Covid-19. The aim is to determine whether Vitamin D can be utilized as a therapeutic agent in SARS-CoV-2. The implications of the study were to evaluate the number of patients with SARS-CoV-2 negative reports before the 3rd week and to analyze the change in the level of inflammatory markers in both groups. 40 participants were randomized (16 in intervention and 24 in control). On day 7, ten participants in intervention reached 25(OH)D levels >50ng/ml and two participants by day 14. "The 25(OH)D levels at day-14 were 51.7 (48.9 to 59.5) ng/ml and 15.2 (12.7 to 19.5) ng/ml, $p < 0.001$ with a median increase of 42.4 (39 to 48.8) ng/ml and 5.1 (0 to 12.3) ng/ml ($p < 0.01$) in the intervention and control group, respectively.

Participants who achieved SARS-CoV negativity were 10 out of 16 ((62.5%) in intervention group and 5 out of 24(20.8)in the control group. In intervention and control group, the mean duration of SARS-CoV-2negativity was 17.6 ± 6.1 and 17.6 ± 6.4 days ($p = 0.283$) respectively. In intervention group, there was a significant decrease in fibrinogen ($p < 0.01$). In some of the mentioned studies, Vitamin D did affect the multiplication of viruses as it can express various gene in immune systems. As SARS-CoV 2 positivity in a host can present many inflammatory markers (IL-6, TNF-a, IL-1b), which were not accessed in this study. The dose of Vitamin D given to the patients was high compared to normal and this toxicity was not checked. Though a large portion of people achieved SARS-CoV-2 negativity with a high dose of Vitamin D.

3.4.2 The evidence that supports vitamin D supplementation could decrease the risk of Influenza and Covid-19 infections and deaths the risk

Vitamin D is an immunomodulatory hormone, has shown a decrease in the risk of viral infections and death. Viruses infect the host by disturbing the junction integrity but Vitamin D maintains tight junctions, gap junctions, and adherens junctions by E-cadherin. It also induces antimicrobial peptides such as human cathelicidin, LL-37, by 1,25-dihydroxyvitamin D and defensins. They play a crucial role as antimicrobial, antiviral agents. It is proven that Vitamin D reduces the replication rate in Influenza A virus, rotavirus. It also enhances cellular immunity which can reduce the chance of cytokine storm and also increases expression of anti-inflammatory cytokines. It also heightens the expression of genes which results in antioxidation which gives rise to the production of glutathione which spares the use of ascorbic acid- an antimicrobial agent. As age increases Vitamin D levels decrease. Many factors affect the absorption of Vitamin D as age progresses which increases case-fatality rates. Vitamin D should reduce the risk of influenza but further studies may be needed to prove that. In the case of Covid-19, it can prevent it but not reduce the transmission. Vitamin D can reduce the inflammatory cytokine storms which are caused in severe cases of Covid-19.

Table 6. Vitamin D in CoVID-19

Sr.No.	Title of Paper	Year Published
1	Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths	2020
2	COVID-19: is there a role for immunonutrition, particularly in the over 65s?	2020
3	Calcitriol, the active form of vitamin D, is a promising candidate for COVID-19 prophylaxis	2020
4	Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results	2020
5	Vitamin D Status in Hospitalized Patients with SARS-CoV-2 Infection	2020
6	Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study)	2020
7	Vitamin D and Covid-19: an update on evidence and potential therapeutic implications	2020
8	Association Between Vitamin D and Novel SARS-CoV-2 Respiratory Dysfunction - A Scoping Review of Current Evidence and Its Implication for COVID-19 Pandemic	2020
9	Circulating Vitamin D levels status and clinical prognostic indices in COVID-19 patients	2021

3.4.3 Vitamin D status and other clinical characteristics associated with Covid-19 test results

As Vitamin D does reduce the chances of other viral infections, it is not found that whether it helps prevent Covid-19. Vitamin D deficiency is found commonly and is affected by many factors. So, are vitamin D levels and treatment associated with test results of covid? In this cohort study, there is a possibility that Vitamin D levels are associated with Covid -19 testing but further clinical trials may be required to determine the risk. Patients' characteristics are shown in table 1." Combining vitamin D deficiency and treatment after the most recent vitamin D level to assess vitamin D status before COVID-19 testing, 124 (25%) patients were likely deficient, 287 (59%) were likely sufficient, and 48 (10%) and 30 (6%) were in the 2 groups with uncertain deficiency". (Meltzer et al.,2020) Patients testing positive for Covid-19 were 71(15%). Out of 172(35%) Vitamin D deficient patients,32(19%) tested positive for Covid-19.39(12%) patients were not deficient. It is found that Vitamin D levels are associated with Covid testing. If a patient is Vitamin D deficient then there is a possibility that COVID-19 positive result can be obtained, as many factors like age, comorbidities, etc play a major role. Further trials may be necessary for detecting if it helps with COVID-19 transmission.

3.4.4The active form of vitamin calcitriol is a promising candidate for prevention of Covid-19

As Vitamin D is associated with reduced SARS-CoV 2 infection, can there be a possibility of calcitriol being utilized as the main component for prophylaxis of Covid-19. African green monkey kidney cells (Vero E6 cell), human hepatoma cells, and human nasal epithelial cells are utilized in this study. Differentiated hNECs which are 3-4weeks old are subjected to SARS-CoV-2 injection. Two sets of primary screening are done on 96 well plates each. The first using ACE2-targeted inhibitors and 57 compound natural product libraries. The second primary screening is done using FDA-approved drugs and flavonoids library.0.1%DMSO and 100µM remdesivir are included as vehicle and positive controls. Hits are selected by CPE using light microscopy. Validation of hits for pre-infection treatment are citicoline, pravastatin sodium, and tenofovir alafenamide and for post-infection are imatinib mesylate, calcitriol, dexlansoprazole, and prochlorperazine dimethylate was done by dose-dependent inhibition assays (done for both cell lines). These assays are incubated for 4 days at 37°C 1,5%CO₂. Supernatants of the virus are harvested for virus titer and plaque assay was done to measure the individual samples.

Conclusions: In this study, the inhibitory effect of calcitriol is measured. In Vero E6 cell lines, Dose dependent inhibition was observed in pre-treatment and at lower concentrations non-dose dependent inhibition was found. Reductions in SARS-CoV-2 were found in treatment with $>10 \mu\text{M}$ dexlansoprazole and post-infection treatment with $10 \mu\text{M}$ calcitriol prompted in 1.3 \log_{10} reduction. In HuH7 Cells, $10 \mu\text{M}$ imatinib mesylate and $\geq 10 \mu\text{M}$ prochlorperazine dimaleate resulted in a reduction of SARS-CoV-2 titres to non-detectable levels in post-infection treatment. The calcitriol value was not replicated because of CC50 value. In Primary human nasal epithelial cell line (hNEC), Only calcitriol proved effective with reduction of 0.69 \log_{10} in viral titre. The conclusion was to find compounds that can cause significant reduction in SARS-CoV 2. Out of all the other compounds only Calcitriol had inhibitory effect in hNEC, which is the first point of entry in SARS-CoV-2.

3.4.5 Potential therapeutic implications of vitamin D and Covid-19

In late December, 2019 a novel Coronavirus disease i.e., COVID-19 spread in China which resulted in a pandemic. The symptoms of the disease included fever, febrile, dyspnea, dry cough, sore throat, and bilateral lung glassy opacities. In severe cases, it caused acute respiratory distress syndrome (ARDS), which could lead to septic shock. It also causes systemic elevation of pyrogenic cytokines which are responsible for inflammation. Chloroquine (CQ) and its hydroxychloroquine derivative (HCQ) are found to be effective in severe patients. Vitamin D three main immune responses are physical barriers (first point of entry), cellular natural immunity, and adaptive immunity. It shows a high amount of antimicrobial activity Covid causes the body to generate both pro-inflammatory activity and anti-inflammatory cytokines. Vitamin D can reduce the pro-inflammatory T-helper cytokines and promote anti-inflammatory cytokine production by macrophages. Vitamin D levels tend to decrease with age and many factors play an important role for causing that, many of the medications taken by the elderly can cause that too. It is proven that vitamin D can reduce the risk of influenza is also said that vitamin D has beneficial properties against HIV and if baseline levels are not maintained it can increase the progression of disease. It might be prevention for Covid-19 and may decrease the severity of the diseases. As Vitamin D expresses anti-inflammatory properties

and has show favourable effects in other viral infections, it can be likely that it has immunomodulatory effects that result in reduction of Covid-19.

3.4.6 Role for Immunonutrition for individuals of age group above 65

When the novel SARS-CoV 2 emerged in December 2020, it caused large infectious which resulted in a pandemic. There are six different corona viruses and only two (SARS & MERS) of them cause severe diseases. It is a possibility that immunonutrition can have a crucial role in prevention of the disease. Immune system of our body is the initial barrier against infections which is maintained by nutrition. As we age, immune systems are compromised due to many factors, it is called 'immunosenescence'. There can be a chance that nutrition can support innate and acquired immune functions. Vitamin C, Vitamin D and Zinc out of all other nutrients show largest immune functions. Vitamin C is used for immune support since a long time. It maintains epithelial tissue barriers and is an antioxidant. Vitamin C also shows prophylaxis of pneumonia for more than 80% in a prophylactic clinical trial. Vitamin C is also an antioxidant which reverses the oxidative stress. Vitamin D is a strong immunoregulator and it has been observed that it is effective on respiratory viruses and pneumonia. It is also known that vitamin D receptors are expressed by majority of immune cells and its deficiency is associated with high risk of respiratory infection. It also modulates the expression and secretion of chemokines and proinflammatory cytokines. Zinc is an important micronutrient as it can regulate intracellular signalling pathways in adaptive and innate immune cells. It is also a play a crucial role in pathogen-eliminating transduction pathways. In several studies, it is proven that zinc supplementation can prevent pneumonia. Vitamin C, vitamin D, and Zinc have great immunoregulatory benefits against respiratory diseases but further research should be done to be confirmed.

3.4.7 The association of vitamin D and novel SARS-CoV-2 respiratory dysfunction

To evaluate the association between vitamin D deficiency and Covid 19 respiratory dysfunction. An initial search is done from 1946 till date in Ovid Medline for the following terms: Vitamin D (cholecalciferol or ergocalciferol or vitamin D2 or vitamin D3 or vitamin D or 25OHD) and

Coronavirus (SARS-CoV-2 or corona virus or COVID or beta coronavirus or MERS-CoV or SARS-CoV or respiratory infection or acute respiratory distress syndrome or ARDS). As the pandemic happened and the papers published doubled in quantity, a second search was conducted on PubMed with the same terms. Vitamin D showed correlation between deficiency levels and incidence and mortality of Covid-19 but two showed opposite correlations. From all the studies and papers found, it can be concluded that supplementation of vitamin D is preventive but still there are some uncertainties about therapeutic effect. A total of 59,25 papers showed some new studies also explored the role of Vitamin D deficiency in ARDS in Covid-19. It is also found that Vitamin D supplementation has a preventive role. There have been studies showing vitamin D levels can affect incidence of Covid-19. Vitamin D has a crucial role in respiratory infections and preventing cytokine storms by reducing the number of pro-inflammatory agents.

3.4.8 The vitamin d levels status and clinical prognostic indices were compared in covid-19 patients

Coronavirus has been associated with altered immune responses and inflammation which causes cytokine storm in the host. Vitamin D plays a crucial role in immune responses and might be a possibility of reducing the risk of COVID-19 infection. In this study, Vitamin D plasma levels are measured. Patients with different lung involvement during Covid-19 infection. Covid-19 positive 52 patients with different levels of lung involvement are enrolled in the study Vitamin D serum levels, Inflammatory markers, cellular damage and coagulation are evaluated in patients at the time of admission. Lymphocyte phenotypes are evaluated by flow cytometry. CT scans of chest were acquired by image analysis program. Quantification of CT scans was done using pulmonary inflammation index (PII) and is evaluated into two groups based on their lung involvement i.e. TSS level <7 and TSS level >7. The SOFA (Sequential Organ Failure Assessment) is a predicating mortality score based on degree of dysfunction of six organs (Respiratory system, Nervous system, Cardiovascular system, Liver, Coagulation, Kidneys). To analyse this result, two groups were formed-SOFA <2 and SOFA > 2. Lung Immune Prognosis Index (LIPI) score is acquired by combining baseline dNIR and LDH and is also

segregated into two groups -LIPI 0-1 values and LIPI=2. Student's t test is utilized for comparison of quantitative variables and for independent samples Mann-Whitney-Wilcoxon test is used. For Categorical data (SOFA; LIPI and CT score) chi-square test or Fisher's exact test is used. GraphPad software was used to statistically analyse the data. Two Classified groups according to the Vitamin D plasma levels are: Group 1 (under 10 ng/mL) and Group 2 (over 10 ng/mL). The results obtained had difference in cell counts and moderate correlation was demonstrated comparing Vitamin D plasma Levels to TCD8+ cytotoxic lymphocytes and CD4+ Cd8+ ratio in both groups, it was assessed using Spearman's Correlation test. D-Dimer plasma levels were statistically increased in comparison to group 2, which were not found for other inflammatory markers. The categorical data (SOFA; LIPI and TSS values) scored low in group 2 (over 10 ng/mL) and high score was found in Group 1 (under 10 ng/mL). Despite the number, group 1 showed high mortality rate. Vitamin D plays a crucial role immune response as it prevent pathogen entry in the host and it values if are lower than normal the risk of fatality and severeness of the disease. In Covid-19, elevated neutrophil suggest ongoing inflammation and decreased lymphocyte count is an indicator of poor prognosis. The data explained in the study explains the relationship between Vitamin D plasma levels and different serum markers of disease. It does not establish the fact that vitamin D plays a role in fighting Covid-19 but it can be used as a safe recommendation for all patients.

3.4.9 The status of vitamin d in hospitalized patients with sars-cov-2 infection [rct (retrospective case) study]

To estimate levels of serum 25-hydroxyvitamin D (25OHD) in hospitalized patients with SARS-CoV-2 infection and whether vitamin D levels status effect on disease. Control Group of 216 Covid-19 patients were enrolled as a retrospective case. 19 Covid-19 patients were on oral vitamin-D supplements for 3 months at admission were considered a separated group with a control group who also received the same treatment. Then a separate group was assessed solely on the serum levels and the disease severity. Additional data of the patients was collected from the hospital. Hospitalized Covid-19 patients showed low levels of 25OHD levels. The study did not find any relation between Vitamin D concentrations and the severity of the

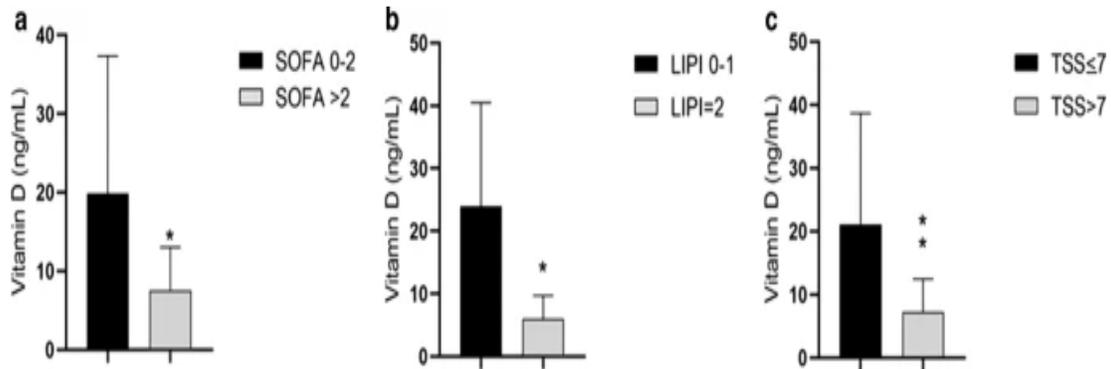


Fig. 1. This histogram represent SOFA (a), LIPI (b) scores and TSS (c) values from patients in group 1

disease. 82.2% and 42.7% were vitamin D deficient in Covid-19 positive patients and control groups respectively. The Covid-19 patients who were Vitamin D deficient had a longer stay in the hospital and had high levels of serum ferritin and troponin levels. The study found no connection between vitamin D deficiency and SARS-CoV-2 disease. Low levels of vitamin D were found in hospitalized Covid-19 patients especially in males. No relation was found that could relate to Vitamin D deficiency to severity of the disease but SAR-CoV-2 infection can cause severe complications and hyperinflammatory state. This state can lead to more severity of the disease leading to mortality. But Vitamin D modulates expression of the T regulatory cells to inhibit the pro-inflammatory cytokines. This can be beneficial in lowering the risk of cytokine storm. Even if there was correlation, it was observed that patients who were on Vitamin D supplements had less risk factors.

4. CONCLUSION

This research review's purpose is to help the reader understand different aspects posed by the research on the Analeptic properties of Vitamin D. This is significant because it gives insights about the role of Vitamin D in joints, dermatitis, other aspects and last but not the least Covid-19. There has been much research and discussion conducted on these opinions of Vitamin D and its role as a supplement in various diseases as seen in the results section. Most of the research found was on the positive role of Vitamin D in alleviating symptoms of arthritis, dermatitis, eczema, Irritable bowel syndrome, cancer, sickle cell disease, liver disease, Diabetes Mellitus and Covid-19. More research and testing is required

to gain a better understanding of the Analeptic properties of Vitamin D.

HUMAN AND ANIMAL RIGHTS

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

AVAILABILITY OF DATA AND MATERIALS

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

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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