Review Article

The Effect of Vitamin D Supplementation in Various Diseases – A Systematic Review

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ABSTRACT

Introduction: Numerous roles for vitamin D in sustaining human health include regulating gene expression, immune system, inflammation, cell division, proliferation, apoptosis, and angiogenesis. It is a fat-soluble vitamin that is mostly produced in the body by UVB exposure to the skin or when consumed orally through food and/or supplements.

Methodology: Using relevant keywords an extensive literature review was carried out in PubMed and Google Scholar which yielded 928 pieces of literature published between January 2020 and December 2021. Following the removal of duplicates, 516 studies were thoroughly screened according to PRISMA guidelines, and 29 studies were included in this systematic review. All the studies were extensively scrutinised for bias and the risk of bias assessment was carried out.

Result and Conclusion: From the 29 trials which range from a pilot study to placebo-controlled double-blinded randomized controlled trials included in our systematic review 48.3% of the trials emphasize the positive outcomes of vitamin D supplementation on their respective diseases, 34.5% of the trials had no association and 17.2% of the trials had mixed outcomes. All the trials included in this review have been conducted on a mixed population which includes the pediatric, geriatric, and general populations. The large majority of the evaluated trials—including the well-known ones—supported the potential benefits of vitamin D.

Keywords: Vitamin D, 1,25-dihydroxyvitamin D3, Pulmonary diseases, Neurologic and Psychiatric diseases, Renal diseases, Cardiovascular diseases.

INTRODUCTION

Numerous roles for vitamin D in sustaining human health include regulating gene expression, immune system, inflammation, cell division, proliferation, apoptosis, and angiogenesis. McCollum reasoned that the action in treating rickets was attributable to a new and unknown vitamin that he dubbed "vitamin D." Vitamin D was recognized as a necessary nutrient as a result of McCollum and Mellanby's research. It is a fat-soluble vitamin that is mostly produced in the body by UVB exposure to the skin or when consumed orally through food and/or supplements.[1-5]

Role of Vitamin D in Pulmonary Diseases

Due to the plausible associations between Vitamin D deficiency and a number of lung diseases, such as acute lung damage, pneumonia, asthma, and COPD, Vitamin D deficient individuals are more vulnerable to pulmonary disorders with a high mortality and morbidity rate.[6]

Through a variety of pathways, including lung growth, immune response control, and airway smooth muscle remodelling, vitamin D may contribute to the development of asthma. Additionally, disintegrin metalloprotease-33 (ADAM-33) expression, which is important for lung growth and function, can be lowered by vitamin D.[7]

The mechanism by which vitamin D deficiency causes more severe asthma and COPD exacerbations is thought to be an impaired innate immune response to the pathogen followed by an overactive adaptive immune response with increased production of inflammatory cytokines and increased bronchial inflammation.[8]

Role of Vitamin D in Neurologic and Psychiatric Diseases

Vitamin D and its metabolites have a variety of roles in both the health and disease of the neurological system.[9] Vitamin D has been demonstrated to have a variety of nervous system effects, including neurotrophism, neurotransmission, neuroprotection, and neuroplasticity.[10]

It was discovered that 1,25-dihydroxyvitamin D3 promoted the synthesis of nerve growth factor (NGF). 1,25-dihydroxyvitamin D3 has also been demonstrated to increase the synthesis of glial cell line-derived neurotrophic factor (GDNF) and neurotrophin 3 (NT-3) while decreasing the levels of neurotrophin 4 (NT-4).[11]

Axonal guidance, dendritic spine morphogenesis, actin-filament and microtubule reorganization, and integrin-mediated adhesion are just a few of the crucial neural development processes in that vitamin D and the VDR system are involved.[12]

Role of Vitamin D in Cardiovascular Diseases

Vitamin D is linked to a higher risk of developing metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM), and systemic hypertension.[13]

Vitamin D deficiency has been linked to a variety of vascular diseases, including peripheral artery disease (PAD), myocardial infarction (MI), coronary heart disease (CHD), and ischemic stroke. Additionally, the discovery of a nuclear vitamin D receptor (VDR) on cardiomyocytes and vascular endothelial cells has suggested a direct role for vitamin D in the onset and progression of CVD, opening the door for an increasing number of research exploring this potential connection.

Vitamin D has been shown to have a number of cardiovascular effects in experimental models, including anti-hypertrophic properties, a reduction in the proliferation of cardiomyocytes, an increase in the proliferation of vascular smooth muscle cells, the expression of vascular endothelial growth factor, and a reduction in the release of natriuretic peptide.[14]

It has been demonstrated that vitamin D supplementation dramatically reduced the level of hs-CRP and the percentage of glycated haemoglobin, which in turn decreased the risk of cardiovascular disease in type-2 diabetic vitamin D deficient patients.[15]

Role of Vitamin D in Renal Diseases

The ability of 1,25(OH)2D3 to simultaneously suppress 1-hydroxylase and stimulate 24-hydroxylase, as well as its capacity to encourage megalin expression in the proximal tubule, are two of the kidney's most important endocrine functions.

Due to vitamin D3's simultaneous effects on serum Parathyroid Hormone (PTH) and intestinal calcium and phosphate absorption, which have an impact on the filter load of both ions, its involvement in the renal management of calcium and phosphate is still debated. The PTH-dependent calcium transport in the distal tubule, which is the primary regulator of calcium excretion into the urine and the location with the greatest VDR level, is accelerated by 1,25(OH)2D3, which also boosts renal calcium reabsorption and calbindin expression.

Treatment with 1,25(OH)2D3 was discovered to have a renoprotective effect in a rat model of renal disease. Treatment with 1,25(OH)2D3 inhibits the course of albuminuria and the development of glomerulosclerosis through PTH-independent antiproliferative effects. The effects of 1,25(OH)2D3 on podocyte loss and hypertrophy may also lessen the severity of albuminuria and glomerulosclerosis.[16]

MATERIALS AND METHODS

Study design

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. This was only a systematic review. PubMed and Google Scholar were used to conduct a comprehensive literature search. The search encompassed all papers published between January 2020 and December 2021. The study design according to PRISMA guidelines is given in Fig. 1.

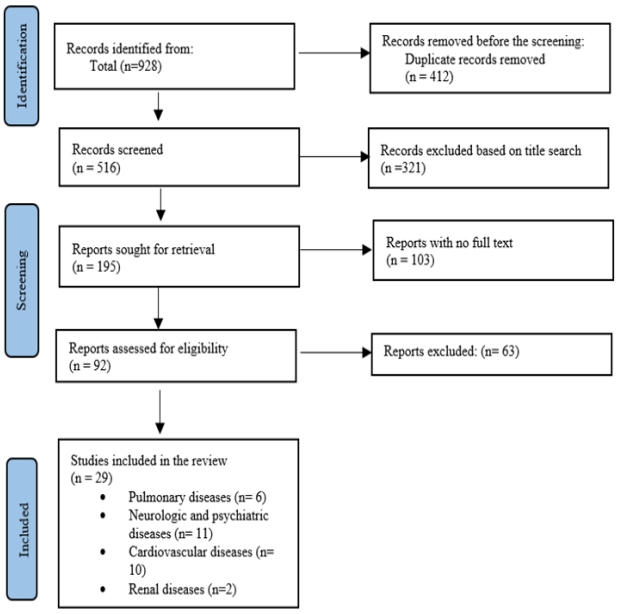

Figure 1: PRISMA chart

Search strategy

A search strategy was initially performed using the Medical Subject Headings (MeSH) and keywords “vitamin D”, “cholecalciferol”, “ergocalciferol”, and “Vitamin D supplements". Based on articles identified during the initial search, the search terms “asthma”, “cardiac disease”, “pediatrics”, “depression”, and “kidney" were added in subsequent searches.

Additional references found in the main research or review papers were checked for eligibility. Filters were used to select research in the English language and studies that only involved human beings and exclude the following publication types: reviews, systematic reviews, meta-analyses, case reports, case series, editorials, and correspondence.

Data Extraction and Synthesis

The articles were examined, the data were extracted separately by two authors (S.S and S.S.M), and any discrepancies were settled by discussion. Extracted data included:

- The title
- The first author's name, year, and country of study
- Dose of vitamin D supplementation
- Population characteristics
- The result

The studies' methodology and content were analyzed qualitatively, and the key conclusions were summarized in accordance with the goal of the research. From the included articles, we retrieved data, which we then organized into tables.

In the results section, the study's findings are presented. The included studies reported associations using various estimates and statistical analyses, making it difficult to translate the present data into a single effect measure. We were unable to use meta-analytic approaches because of the extreme heterogeneity among the studies.

Recovery of data

Our initial search returned 928 literature, out of which 412 studies were excluded due to duplicate searches. Of the 516 studies that were screened, 29 studies were included. Two authors assessed all eligible trials independently, and potentially relevant trials were selected according to PRISMA guidelines.

Any disagreement was reviewed and resolved by two other authors. (A.T, P.P). Finally, data from 29 studies were included in the systematic review.

Evaluation of selected studies and risk of bias assessment of included literature

A risk of bias assessment was carried out for all the included studies using the Review Manager 5.4.

Table 1: Effect of Vitamin D supplementation on Pulmonary Diseases

S. NO	Title	Name of the first author, year, and country of study	Population characteristics and dose of vitamin D supplementation	Result
1	Effect of Monthly High-Dose Vitamin D Supplementation on Acute Respiratory Infections in Older Adults: A Randomized Controlled Trial.[17]	Camargo, 2020, New Zealand	5110 adults aged 50-84 years. Monthly 100 000-IU (daily dose equivalent of ~3300 IU/day) capsule of vitamin D3	Monthly high-dose vitamin D supplementation did not prevent acute respiratory infections in the population of older New Zealand adults.
2	Vitamin D supplementation among Bangladeshi children under five years of age hospitalized for severe pneumonia.[18]	Chowdry, 2021, Bangladesh	Children aged >2-59 months with severe pneumonia 20,000IU: <6 months, 50,000 IU: 6-12 months, 100,000 IU:13-59 months	A mega dose of vitamin D followed by a maintenance dose showed no statistical difference between the two intervention groups., There was a trend of reduction of time to recover from pneumonia and overall duration of hospital stay in under-five children with a sufficient serum vitamin D level on hospital admission.
3	Effect of Vitamin D3 Supplementation on Severe Asthma Exacerbations in Children with Asthma and Low Vitamin D Levels.[19]	Forno, 2020, The United States	Children aged 6 to 16 years old with asthma who are on low-dose inhaled corticosteroids and have serum 25-hydroxy vitamin D levels below 30 ng/mL. vitamin D3, 4000 IU/day	Vitamin D3 supplementation did not drastically improve the time to a severe asthma exacerbation in children with persistent asthma and low vitamin D levels.
4	Influence of Vitamin D Supplementation by Simulated Sunlight or Oral D3 on Respiratory Infection during Military Training.[20]	Harrison, 2021, The United Kingdom	In study 1, 1644 military recruits. In study 2, 250 men received placebo-simulated sunlight and oral vitamin D 1000 IU/day for 4 weeks and then 400 IU/day for 8 weeks	Vitamin D supplementation reduced Upper Respiratory Tract Infections during military training.
5	Clinical Efficacy of Vitamin D3 Adjuvant Therapy in Allergic Rhinitis: A Randomized Controlled Trial.[21]	Liu, 2020, China	60 patients with mild seasonal pollen allergic rhinitis were randomized into placebo and treatment arms. 1.5x106 IU of vitamin D3 nasal spray once every week for four weeks.	Nasal vitamin D3 combined with Desloratadine Citrate Disodium could improve the clinical symptoms of Allergic Rhinitis. Vitamin D3 adjunct therapy significantly inhibits inflammation in patients with AR.
6	Effects of Maternal Vitamin D Supplementation During Pregnancy and Lactation on Infant Acute Respiratory Infections: Follow-up of a Randomized Trial in Bangladesh.[22]	Morris, 2021, Bangladesh	1174 mother-infant pairs were included aged more than 18 years of age between 17 and 24 weeks of gestation. A "low-dose" of 4200 IU per week, a "mid-dose" of 16 800 IU per week, and a high dose" of 28 000 IU per week.	This study found that the intervention did not lower the risk of microbiologically proven ARI in infants up to 6 months of age.

RESULTS

`All the studies were scrutinized and reviewed systematically and the results from all the studies are given below

Effect of Vitamin D Supplementation on Pulmonary Diseases

Evidence from studies on the association between vitamin D supplementation and pulmonary diseases is summarized in Table 1. Serum levels of vitamin D are correlated with lung health and vitamin D deficiency has been shown to elevate the risk of pulmonary diseases and infections. Of the 6 studies included in this systematic review, only 2 randomized controlled trials inferred that vitamin D supplementation has improved the patient's condition in pulmonary infections and inflammatory conditions.[17-22] A prospective cohort, randomized controlled trial conducted in the United Kingdom showed that vitamin D supplementation reduced Upper Respiratory Tract Infections during military training.[19] A randomized controlled trial conducted in China suggested nasal vitamin D3 combined with Desloratadine Citrate Disodium could improve the clinical symptoms of Allergic Rhinitis.[21] Vitamin D3 adjunct therapy significantly inhibits inflammation in patients with AR. This study concluded that vitamin D3 supplementation could be an effective adjuvant therapy in Allergic Rhinitis patients. But a trial conducted in Bangladesh had mixed outcomes with trends in a reduction in the duration of recovery time and hospital stay in patients with pneumonia but had no statistical difference between the intervention and placebo arms.[18] However, the results from the other three trials suggested that the true contribution of vitamin D supplementation in improving the clinical status of patients with pulmonary diseases was found to be negligible.[17, 19, 22] In conclusion, from the evidence collected for our systematic review, we infer that vitamin D supplementation indeed showcased a positive correlation between serum levels of vitamin D and the betterment of patients with pulmonary diseases.

Effect of Vitamin D Supplementation on Neurologic and Psychiatric Diseases

Evidence from the trials on the association between vitamin D supplementation and CNS diseases is summarized in Table 2. Vitamin D helps in the regulation of neurotrophin, neural differentiation, and maturation. Of the 11 trials included in this systematic review, 5 trials had a positive association, 2 had mixed outcomes whereas the other 4 had a negligible association.[23-33] A double-blinded randomized controlled trial conducted in New Jersey found that the 2,000 IU/d dose of vitamin D showed positive effects on visual and working memory and learning, and the 4,000 IU/d vitamin D dose was associated with slower reaction time.[23] A placebo-controlled randomized clinical trial conducted in Norway inferred that the intervention group showed raised vitamin D levels and normal psychophysiological responses to the experimental stress procedure. The control group demonstrated a classic nadir in vitamin D status post-intervention and did not show normal psychophysiological responses to stress conditions.[25] A randomized double-blinded placebo-controlled clinical trial performed in Iran suggested that co-supplementation of vitamin D and magnesium for a duration of 8 weeks could improve the behavioral function and mental health of children with ADHD.[26] Another randomized controlled trial conducted in Iran inferred that vitamin D and omega-3 fatty acids improved depression, anxiety, and sleep quality in women of reproductive age with pre-diabetes and hypovitaminosis D.[30] A double-blinded randomized controlled trial conducted in India reported that there was an improvement in the level of consciousness after 7 days in the vitamin D-treated group compared with the placebo. The GCS score was increased by 3.86 units in the vitamin D-treated group.[31] The other 2 trials had mixed outcomes regarding the supplementation of vitamin D.[27, 33] A two-armed parallel group, double-blinded, randomized controlled trial conducted in Germany indicated that compared to a placebo, immediate vitamin D3 supplementation in depressed child and adolescent psychiatric patients with vitamin D deficiency resulted in a significant reduction in parental reports of depressive symptoms but not in self-reported symptoms.[27] Another trial conducted in China suggested that there was a considerable improvement in anxiety symptoms for the patients in the vitamin D group when compared to the control group, while the vitamin D supplementation had no significant impact on depressive symptoms after the 6-month intervention in the overall cohort.[33] The other 4 trials included yielded no association between vitamin D supplementation and mental health, incidence, and recurrence of depression. It was also found that vitamin D had no role in improving post-stroke outcomes. It did not benefit infants in terms of developmental milestones or socio-emotional skill acquisition.[24, 28, 29, 30] Therefore, from this evidence, we infer that vitamin D supplementation had a positive effect on patients with depression and anxiety. It might also help improve the psychophysiological responses to stress.

Effect of Vitamin D Supplementation on Cardiovascular Diseases

Evidence from the trials on the correlation between vitamin D supplementation and cardiovascular diseases is summarized in Table 3. The link between vitamin D and the cardiovascular system is becoming clearer as new research emerges. Vitamin D has antihypertrophic properties, inhibition of cardiomyocyte proliferation, vascular smooth muscle cell proliferation, expression of vascular endothelial growth factor, and inhibition of RAAS system and natriuretic peptide secretion. Of the 10 trials included in this systematic review, 7 trials had a significant association, one trial had mixed outcomes while 2 trials had a negligible association.[34-43]

Table 2: Effect of Vitamin D supplementation on Neurologic and Psychiatric Diseases

S.NO	Title	Name of the first author, year, and country of study	Population characteristics and dose of vitamin d supplementation	Result
1.	Three Doses of Vitamin D and Cognitive Outcomes in Older Women: A Double-Blind Randomized Controlled Trial.[23]	Castle 2020, New Jersey	55 participants, Healthy, postmenopausal women (50–70 years old; body mass index [BMI] 25–40 kg/m^2) 600, 2,000, or 4,000 IU/d	In this trial, the 2,000 IU/d dose of vitamin D showed positive effects on visual and working memory and learning, and the 4,000 IU/d vitamin D dose was associated with slower reaction time.
2.	Effect of Vitamin D Supplementation on Outcomes in People With Early Psychosis: The DFEND Randomized Clinical Trial.[24]	Gaughran 2021, UK	149 participants, Adults 18 to 65 years old, within 3 years of the first presentation with a functional psychotic disorder. Monthly augmentation with 120 000 IU of cholecalciferol	In this randomized clinical trial, at six months, there was no correlation between vitamin D administration and either metabolic results or mental health.
3.	Vitamin D Supplementation during Winter: Effects on Stress Resilience in a Randomized Control Trial.[25]	Hansen 2020, Norway	86 participants, Age from 31 to 81 years. 40 g cholecalciferol, or 1600 IU	Increased vitamin D levels and typical psychophysiological reactions to the experimental stress procedure were observed in the intervention group. The control group did not exhibit typical psychophysiological responses and showed a classic nadir in vitamin D status post-intervention (spring).
4.	The effect of vitamin D and magnesium supplementation on the mental health status of attention-deficit hyperactive children.[26]	Hemamy 2021, Iran	66 participants, Children aged between 6 and 12 years old, with a serum level of 25(OH)D <30 ng/dL, a diagnosis of ADHD based on DSM IV, and serum magnesium levels <2.3 mg/Dl 50,000 IU/week	In this trial, Vitamin D (50,000 IU/week) and magnesium (6 mg/kg/day) co-supplementation for a duration of 8 weeks could improve the behavioral function and mental health of children with ADHD.
5.	Effect of vitamin D deficiency on depressive symptoms in child and adolescent psychiatric patients.[27]	Libuda 2020, Germany	280 participants, Patients aged 11.0–18.9 years with vitamin D deficiency [25(OH)D ≤ 30 nmol/l] and at least mild depression [Beck Depression Inventory-II (BDI-II) > 13] 2640 IU/day	This RCT's key conclusion was that, compared to a placebo, immediate vitamin D3 supplementation in depressed child and adolescent psychiatric patients with vitamin D deficiency resulted in a significant reduction in parental reports of depressive symptoms but not in self-reported symptoms.
6.	Effect of vitamin D and/or omega-3 fatty acid supplementation on stroke outcomes: a randomized trial.[28]	M Rist 2021, Boston	197 participants, Men aged ≥50 years and women aged ≥55 years 2000 IU/day	In this trial, it was found that randomized supplementation with vitamin D or n-3 fatty acids before stroke did not result in significant improvements in post-stroke outcomes among middle-aged and older individuals.
7.	Effect of Long-term Vitamin D3 Supplementation vs. Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and Change in Mood Scores.[29]	Okereke 2020, US	18353 participants, Men aged 50 years or older and women aged 55 years or older Vitamin D3 (2000 IU/d of cholecalciferol)	A statistically significant difference was not found in the incidence and recurrence of depression or other depressive symptoms or changes in mood scores over follow-up among trial participants 50 years of age or older. The participants also experienced no clinically relevant depressive symptoms at baseline treated with vitamin D3 compared with a placebo
8.	Effect of omega-3 and vitamin D co-supplementation on psychological distress in reproductive-aged women with pre-diabetes and hypovitaminosis D.[30]	Rajabi Naeeni 2021, Iran	168 participants, women aged 15 to 50 years with pre-diabetes and hypovitaminosis D 50,000 IU of vitamin D every 2 weeks, and 1 g twice daily of omega-3.	In this trial, Vitamin D and omega-3 co-supplementation improved depression, anxiety, and sleep quality in women of reproductive age with pre-diabetes and hypovitaminosis D.

9.	Neuroprotective Role of Oral Vitamin D Supplementation on Consciousness and Inflammatory Biomarkers in Determining Severity Outcome in Acute Traumatic Brain Injury Patients.[31]	Sharma 2020, India	35 participants, Both genders between the ages of 16 and 65 years had sustained moderate to severe traumatic brain insult. GCS score of 4–12 Two tablets of 60,000 IU each	After 7 days, the vitamin D-treated group had a higher level of consciousness. In the vitamin D-treated group, the GCS score increased by 3.86 units, while the control group's score decreased by 0.19 units.
10	Effect of High-Dose vs. Standard-Dose Vitamin D Supplementation on Neurodevelopment of Healthy Term Infants.[32]	Tuovinen 2021, Finland	987 participants, 404 infants to receive 400 IU of oral vitamin D3 supplementation daily and 397 infants to receive 1200 IU of oral vitamin D3 supplementation daily from 2 weeks to 24 months of age.	In this trial, 1200 IU vs. 400 IU of vitamin D supplementation did not provide a benefit for healthy term infants' developmental milestones or social-emotional skill acquisition up to 2 years of age.
11	Vitamin D supplementation improves anxiety but not depression symptoms in patients with vitamin D deficiency.[33]	Zhu 2020, China	158 participants Diagnosis of MDD according to DSM-V; age 18–60 years; Han Chinese ethnicity; and serum 25(OH) D levels ≤75 nmol/L 1,600 IU daily	After 6 months, the overall cohort's depressive symptoms were not significantly affected by VD supplementation. The control group, patients in the VD supplementation group experienced a significant improvement in their anxiety symptoms.

Table 3: Effect of Vitamin D supplementation on Cardiovascular Diseases

S.No	Title	Name of the first author, year, and country of study	Population characteristics and dose of vitamin d supplementation	Result
1.	Effect of daily 2000 IU versus 800 IU vitamin D on blood pressure among adults age 60 years and older: a randomized clinical trial.[34]	Abderhalden, 2020, Zurich	273 participants, adults aged ≥60 yr who underwent elective surgery for unilateral knee replacement due to severe knee osteoarthritis, without a planned bilateral knee replacement within the next 2 yr. 2000 IU vs 800 IU	Daily 2000 IU and 800 IU vitamin D3 reduced mean systolic BP over a small and similar extent. In comparison to the 800 IU vitamin D group, BP variability was dramatically decreased in the 2000 IU vitamin D group.
2.	Vitamin D(3) reduces the risk of cardiovascular and liver diseases by lowering homocysteine levels.[35]	Al bayyari N, 2020, Jordan	120 participants, women aged between 18 and 49 years 1250 mcg of vitamin D3	After the second month of vitamin D3 intervention, the levels of tHcy, CRP, AST, ALT, and eGFR were significantly lower and the levels of 25(OH)D, urea, and creatinine were significantly higher in the treatment group.
3.	Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation: A Randomized Clinical Trial.[36]	Albert, 2021, USA	25,119 participants, women and men aged 50 years or older without prior cardiovascular disease, cancer, or AF EPA-DHA (460 mg/d of EPA and 380 mg/d of DHA) and vitamin D3 (2000 IU/d)	Vitamin D3 supplementation in comparison to a placebo had no discernible effect on the risk of incident AF after a median follow-up of over 5 years in persons aged 50 or older.
4.	Efficacy of single-dose cholecalciferol in the blood pressure of patients with type 2 diabetes, hypertension, and hypovitaminosis D.[37]	De Paula, 2020, Brazil	43 participants, Outpatients with type 2 DM (HbA1c 6.5–10%), hypertension (office systolic BP ≥ 140 mm Hg or diastolic ≥ 90 mm Hg or ongoing antihypertensive treatment), and hypovitaminosis D (25(OH)D serum concentration below 20 ng/mL or 50 nmol/L) 100,000 IU of vitamin D3	A single dose of cholecalciferol improved BP in a short period of supplementation in patients with type 2 DM with hypertension and 25(OH)D < 20 ng/ml, regardless of vitamin D3 normalization.
5.	200.000 IU of vitamin D does not reduce resting Blood Pressure and Inhibit Post-Exercise Hypotension in elderly women: a pilot study.[38]	Goncalves, 2020, Brazil	11 participants, having blood pressure < 160/100 mm Hg, female sex, over 60 years old. 200,000 IU of vitamin D	A megadose of vitamin D enhanced sympathovagal balance promoted partial suppression of systolic PEH and did not lower RBP.

6.	Effects of Vitamin D Supplementation on Cardiovascular and Glycemic Biomarkers.[39]	Miao, 2021, Massachusetts	289 participants, Individuals were aged between 18 and 50 years, with low vitamin D status ([25-OH-D] ≤25 ng/mL), and with prehypertension or untreated stage I hypertension (systolic BP 120–159 mm Hg and diastolic BP <99 mm Hg). 400 IU/ day vs. 4000IU/ day	Among participants randomized to high-dose vitamin D supplementation, there were no significant changes in any biomarkers, other than an increase in plasma triglycerides
7.	Short-term Effects of Alfacalcidol on Hospital Length of Stay in Patients Undergoing Valve Replacement Surgery: A Randomized Clinical Trial.[40]	Naguib 2020, Egypt	86 participants, adult patients (aged 18–65 years) scheduled to undergo elective mechanical VRS 2 mcg/day of alfacalcidol started 48 hours before surgery and continued throughout the hospital stay	Daily treatment of 2 g of the vitamin D3 analogue during the hospital stay was linked to decreased postoperative infection rates, shorter ICU and hospital LOSs, and sustained postoperative LV function.
8.	Effect of vitamin D supplementation versus placebo on essential hypertension in patients with vitamin D deficiency: a double-blind randomized clinical trial.[41]	Sheik 2020, Iran	208 participants, patients aged 18 to 75 years with systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg who were vitamin D deficient or insufficient. Vitamin D <20ng/ml – 50,000U every 2 weeks. Vitamin D 20-30ng/ml – 1000U every week for 2 months	A great reduction in systolic and diastolic blood pressure was observed in the intervention group when compared to the control group.
9.	Effect of vitamin D supplementation during pregnancy on mid-to-late gestational blood pressure in a randomized controlled trial in Bangladesh.[42]	Subramanian 2020, Bangladesh	1298 participants, Healthy pregnant women without hypertension were enrolled at 17–24 weeks gestation, 18 years of age, and above. 4200, 16800, 28000 IU per week	Vitamin D supplementation did not influence SBP and DBP until late gestation at high doses. SBP and DBP were greater by 2 mmHg at week 36 in women receiving the highest dose of vitamin D compared to the placebo.
10	Vitamin D Treatment Attenuates Heart Apoptosis After Coronary Artery Bypass Surgery: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial.[43]	Tashdighi 2020, Iran	70 participants, patients undergoing coronary artery bypass graft (CABG) using CPB with vitamin D deficiency (defined as 25-OH D < 20 ng/mL) and normal kidney function (creatinine < 1.5 mg/dL). 50000 IU of vitamin D3 tablet daily for 3 days before the operation	Oral high-dose vitamin D treatment increased the levels of the anti-inflammatory biomarkers IL-10 and IGF-1 in the perioperative period as well as reduced the rate of heart apoptosis induced during CABG

Table 4: Effect of Vitamin D supplementation on Renal Diseases

S. no	Title	Name of the first author, year, and country of study	Population characteristics and dose of vitamin d supplementation	Result
1.	The effect of cholecalciferol supplementation on allograft function in incident kidney transplant recipients: A randomized controlled study.[44]	Doi 2021, Japan	193 participants, Age between 20 and 80 years, eGFR ≥30 mL/min/1.73 m^2, and 1 month after living kidney transplantation. Participants received one capsule of either cholecalciferol 4000 IU or a matching placebo	This trial showed no evidence of the beneficial effects of an 11-month intervention with cholecalciferol on changes in eGFR and did not provide favorable results in histology, and urinary biomarkers related to kidney damage.
2.	A Randomized, Double-Blind, Placebo-Controlled, Clinical Trial of High-Dose, Short-Term Vitamin D Administration in the Prevention of Acute Kidney Injury after Cardiac Surgery.[45]	Eslami 2021, Iran	129 participants, Patients referred for first-time elective and isolated CABG by using CPB, who had VitD insufficiency (<20 ng/mL) and Cr <1.5 mg/dL. 50,000 units of Vit D tablet 3 times a day, for 3 days before the operation.	VitD was not able to reduce the incidence of postoperative AKI in this clinical trial. VitD treatment was linked to noticeably higher serum levels of the anti-inflammatory IL-10 both before and after surgery.

A randomized, double-blinded, ancillary trial conducted in Zurich showed that daily 2000 IU and 800 IU vitamin D3 reduced mean systolic BP over a small and similar extent. When comparing the 2000 IU vitamin D group to the 800 IU vitamin D group, BP variability was dramatically decreased.[34] A double-blinded, placebo-controlled, randomized controlled clinical trial conducted in Jordan showed that the tHcy, CRP, AST, ALT, and eGFR levels after the 2nd month of vitamin D3 intervention were significantly decreased and the 25(OH)D, urea, and creatinine levels were significantly increased in the treatment group.[35] A 2*2 factorial randomized trial conducted in the USA showed that treatment with EPA-DHA or vitamin D3, compared with a placebo, following a median follow-up of more than 5 years, there was no significant shift in the risk of incident AF.[36] A double-blinded placebo-controlled, randomized controlled trial conducted in Brazil showed that a single dose of cholecalciferol improved BP in a short period of supplementation in patients with type 2 DM with hypertension and 25(OH)D < 20 ng/ml, regardless of vitamin D3 normalization.[37] A prospective, randomized, open-label, controlled, parallel-group clinical study conducted in Egypt inferred that daily administration of 2 µg of vitamin D3 analog alfacalcidol during hospital stay was well tolerated and associated with shorter ICU and hospital LOSs, a lower postoperative infection rate, and preserved normal postoperative LV function.[40] A double-blinded randomized controlled trial conducted in Iran concluded that there was a great reduction in systolic and diastolic blood pressure in the interventional group when compared to the control group.[41] Another double-blinded, placebo-controlled clinical trial conducted in Iran concluded that vitamin D treatment decreased the rate of heart apoptosis that was induced during coronary bypass surgery with CPB and also increased the serum level of IL-10 and IGF-1, as anti-inflammatory biomarkers in the perioperative period.[43] Another randomized, controlled trial conducted in Bangladesh inferred that vitamin D supplementation from mid-pregnancy did not influence SBP or DBP until late gestation, and then only at the highest dose. SBP and DBP were greater by 2 mmHg at week 36 in women receiving the highest dose of vitamin D compared to the placebo.[42] The other 2 trials had a negligible association between vitamin D supplementation and cardiovascular diseases. [38, 39] From the evidence included in our review, it is inferred that vitamin D supplementation indeed is helpful in cardiovascular diseases.

Effect of Vitamin D Supplementation on Renal Diseases

Evidence from the trials on the association between vitamin D supplementation and renal diseases is summarized in Table 4. Given the concurrent effects of vitamin D on serum parathyroid hormone and the absorption of intestinal calcium and phosphate, the involvement of the same in renal management is still a hot topic. Of the 2 trials included in this review one had mixed outcomes while the other showcased no significant association.[44, 45] A randomized, double-blinded, placebo-controlled trial conducted in Iran showed that vitamin D treatment before and after cardiac surgery was associated with considerably higher serum levels of anti-inflammatory IL-10, while the supplementation failed to decrease the frequency of postoperative acute kidney injury.[45] Hence from the evidence included in our review vitamin D supplementation might be helpful in renal diseases.

DISCUSSION AND CONCLUSION

A crucial nutrient and hormone, vitamin D controls the levels of serum calcium and phosphate as well as immune response, cell division, proliferation, and apoptosis. Because of this, vitamin D deficiency has been linked to several harmful health effects, such as cancer, diabetes, hypertension, heart disease, bone disease, and autoimmune and infectious diseases. With encouraging results from numerous studies on the role of vitamin D in the prevention and/or reduction of various chronic diseases, there is growing interest in finding out more about the benefits of sufficient vitamin D in maintaining human health. Additionally, a number of epidemiologic studies have discovered a connection between vitamin D levels and the frequency of a number of infectious diseases. Findings from randomized controlled trials, however, only offer sporadic support for such effects because most studies have not been able to find any appreciable impacts.

Vitamin D can have the potential for a vast kind of diseases. Despite the fact that vitamin D is linked to potential disease pathways, the pathogenesis of these conditions are complex. The relationship between vitamin D levels in the serum and the pathogenesis of various diseases, and how the deficiency of vitamin D influences the progression of diseases are being widely researched.

From the 29 trials which range from a pilot study to placebo-controlled double-blinded randomized controlled trials included in our systematic review 48.3% of the trials emphasize the positive outcomes of vitamin D supplementation on their respective diseases, 34.5% of the trials had no association and 17.2% of the trials had mixed outcomes. All the trials included in this review have been conducted on a mixed population which includes the pediatric, geriatric, and general populations. The large majority of the evaluated trials—including the well-known ones—supported the potential benefits of vitamin D.

Most of the evidence included in this systematic review regarding the beneficial effect of vitamin D supplementation on non-skeletal conditions involving pulmonary diseases, neurologic and psychiatric conditions, cardiovascular diseases, and renal diseases, only studies conducted for neurologic and psychiatric conditions, and cardiovascular diseases showcased a significant beneficial effect of vitamin D supplementation in these scenarios.

There was a trend of reduction of time to recover from pneumonia and overall duration of hospital stay in under-five children who had vitamin D supplementation. Vitamin D supplementation reduced Upper Respiratory Tract Infections during military training. Nasal vitamin D3 combined with Desloratadine Citrate Disodium could

improve the clinical symptoms of Allergic Rhinitis. Vitamin D3 adjunct therapy significantly inhibits inflammation in patients with Allergic rhinitis. A large number of trials included in this systematic review showcased the beneficial effects of vitamin D on visual and working memory, learning, depression, anxiety, and sleep quality. Children with ADHD also benefited from the supplementation. Vitamin D decreased BP and had a null association in the case of AF and other CVS conditions. Although vitamin D supplementation for the prevention of acute kidney injury after cardiac surgery was associated with noticeably higher serum levels of the anti-inflammatory IL-10 both before and after surgery, it did not improve histology or urinary biomarkers associated with kidney damage in kidney transplant patients.

The results need to be further investigated to rule out any associations between vitamin D and its beneficial effects on a number of conditions because only trials which were published during a period of two years were analyzed. Further RCTs and long-term cohort studies employing standardized techniques for serial measurement of 25OHD levels are required to evaluate the concept that improving vitamin D status has a positive effect on people with chronic diseases.

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