BOSTON MEDICAL CENTER

CADILA PHARMACEUTICALS LIMITED

The Care Continues...

VITAMIN D

Masterclass for Medical Professionals

MODULE 1

Please scan this QR Code
to visit the website

For **Faster** Correction of **Vitamin D Deficiency**

INDIAN PATENT No: 431119 INDIAN PATENT

World's 1st Aqueous based Vitamin D_3

℞ CALCIROL AQ

Cholecalciferol IP 600,000 IU / 2ML Injection

First and Fast AQueous D3

FASTER & SUSTAINED RISE IN VIT D LEVEL*

LESS PAINFUL THAN OIL FORMULATION*

BETTER COMPLIANCE*

DOSAGE

LOADING (600,000) DOSE[1]
CALCIROL AQ injection (6 L IU/2 ml)
Loading Dose at the time of visit

After **2 Months**

MAINTENANCE DOSE
60,000 IU Oral Formulation
Monthly OR **Every 15 days**

Refs: 1. Harinarayan CV et al. J Clin Sci Res 2015;4:273-80 *Changani M et al. Int J Res Med Sci. 2023 Oct;11(10):3714-3721

Table of Content

Role of Vitamin D beyond Bones - How To Optimize Supplementation Strategies & Ideal Levels Of Vitamin D for Maximum Benefits

Physiological Basis for Using Vitamin D to Improve Health

Authors: *Sunil J. Wimalawansa*

Reference: *Wimalawansa SJ Biomedicines. 2023 May 26; 11(6):1542. doi: 0.3390/biomedicines11061542.*

Overview

Vitamin D, a secosteroid hormone synthesized in the skin upon UVB exposure or acquired through diet, plays a pivotal role far beyond calcium metabolism and bone health. This review elucidates the physiological mechanisms underpinning vitamin D's systemic effects, particularly focusing on its non-skeletal actions, receptor-mediated pathways, and translational relevance in various clinical settings including cardiovascular, immune, and cancer biology.

Physiological Basis of Action:

- Vitamin D Receptor (VDR) is present in over 35 target tissues, including immune cells, pancreatic β- cells, muscle, brain, and endothelium.
- Physiologic level of vitamin D above **50 ng/mL** is proven to aid in infection prevention, sepsis, cancer, and to lower the risk of premature death.
- The active form, 1, 25-dihydroxyvitamin D_3[1, 25$(OH)_2D_3$], functions as a transcriptional regulator, modulating gene expression in both endocrine and paracrine manners.
- Its effects are mediated through genomic actions (via VDR–RXR binding to DNA) and non-genomic pathways, including calcium influx and intracellular signaling cascades (e.g., MAPK, PI3K).

Effects on Key Functional Systems:

1. **Calcium and Phosphate Homeostasis**
   - Promotes intestinal calcium absorption by inducing calbindin and calcium channel proteins.
   - Reduces renal calcium excretion and supports bone remodeling.

2. **Immune System Modulation**
   - Enhances innate immunity by upregulating antimicrobial peptides (e.g., cathelicidin).
   - Suppresses chronic inflammation via downregulation of pro-inflammatory cytokines (e.g., IL-6, TNF-α)
   - Plays a role in autoimmunity prevention, including T1DM, MS, and rheumatoid arthritis.

3. Cancer Prevention and Control

- Inhibits cell proliferation and promotes differentiation in epithelial tissues.
- Exhibits anti-tumor effects through VDR-mediated apoptosis and anti-angiogenesis.

4. Cardiovascular System

- Regulates renin–angiotensin system (RAS), endothelial nitric oxide production, and vascular smooth muscle tone.
- Deficiency associated with hypertension, atherosclerosis, and cardiac hypertrophy.

Clinical Relevance and Guidelines Gap:

- Conflicting guidelines (IoM, NICE, SCAN) and outdated RDAs have fostered confusion and underdosing.
- Misuse of intermittent high doses, synthetic analogs in non-indicated conditions, and fear-mongering around toxicity hinder optimal vitamin D implementation.
- This review clarifies physiology, dosing strategies, and proper clinical contexts for each vitamin D form.

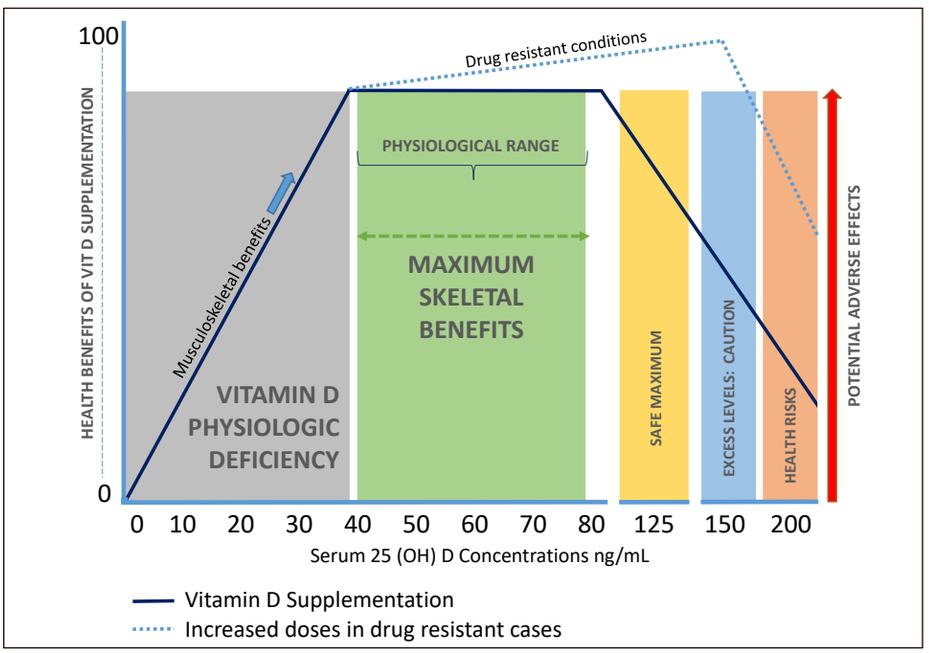
Forms of Vitamin D & Therapeutic Use:

Compound	Functionality	Recommended Use
D3 (Cholecalciferol)	Standard supplement to raise serum 25(OH)D levels	Routine supplementation & deficiency
Calcifediol (25(OH)D)	Rapid elevation of serum levels and immune boost	Emergencies (e.g. ICU, infection), liver issues
Calcitriol ($1,25(OH)_2D$)	Regulates calcium not effective for infections	Use in renal failure, hypo-parathyroidism
Synthetic Analogues	High cost; narrow therapeu-tic window	Select endocrine disorders such as hepatic or renal failure, hypoparathyroidism.

Mechanisms of Action:

- **Genomic Actions:** Calcitriol–VDR complexes translocate to the nucleus, up- or down-regulating genes involved in anti-inflammation, antioxidant defence, cell proliferation and differentiation.
- **Non-Genomic Actions:** Membrane-bound VDRs and PDIA3 mediate rapid calcium influx and second-messenger signaling. Influences mitochondrial dynamics, ion channels, and apoptosis to fine-tune cellular responses.
- **Intracrine/Paracrine Signaling:** Peripheral cells (immune, endocrine, epithelial) synthesize calcitriol locally, enabling tissue-specific regulation.

Serum Vitamin D Levels and Health Outcomes:



This graph illustrates the relationship between serum [25(OH) D] concentrations and the corresponding health outcomes of vitamin D supplementation. It highlights a steep benefit curve in the deficient range (0–30 ng/mL), a plateau of maximal skeletal and systemic benefits within the physiological range (30–80 ng/mL), and increasing risks associated with excess levels (>125 ng/mL). The greatest overall benefit is observed at ≥ 50 ng/mL. The visual also emphasizes the importance of maintaining optimal serum levels to maximize therapeutic outcomes while avoiding toxicity.

Consequences of Vitamin D Deficiency:

- Immune Dysregulation: Prone to cytokine storms and ARDS, notably during COVID-19.
- Autoimmunity: Higher incidence of Kawasaki-like and multisystem inflammatory syndromes in children.
- Impaired Vaccination: Reduced neutralizing antibody titres and memory cell formation post-immunization.
- Increased Morbidity & Mortality: Exacerbates chronic disease complications and infection-related deaths.

Public Health Implications:

- **Target Serum Levels:**
  - General population: ≥ 40 ng/mL
  - High-risk groups (e.g., elderly, ICU patients): ≥ 50 ng/mL
- Implementation Strategy: Combine safe sun exposure with daily cholecalciferol supplementation.

- Within 4 hours of administering an appropriate dose of oral calcifediol, serum 25(OH) D concentrations can rise **above 50 ng/mL**—levels considered sufficient to enhance immune function within a single day.
- Guideline Revision: Current RDAs and fortification policies should be increased 3 to 4 fold to reach effective serum thresholds.
- Cost-effectiveness analyses favour cholecalciferol over calcifediol, calcitriol, and analogues, with the lowest cost per 10 ng/mL increment in serum 25(OH) D.

Vitamin D Dose Recommendations:

- To achieve therapeutic levels—particularly for non-skeletal benefits—serum concentrations should be maintained at >50 ng/mL, preferably 50–90 ng/mL.
- A **weekly dose of 50,000 IU** is generally effective for non-obese adults.
- Individuals with obesity, comorbidities, or malabsorption may require 2–4 times higher doses due to altered vitamin D metabolism or absorption inefficiencies.
- When feasible, serum 25(OH) D monitoring should guide personalized dosing (body weight based).

Vitamin D Maintenance Recommendations:

- For a healthy 70 kg non-obese adult, a weekly dose of 50,000 IU is recommended to maintain serum 25(OH) D levels above 50 ng/mL.
- However, obese individuals or those with malabsorption disorders require significantly higher doses to reach therapeutic concentrations. With optimal dosing, it may take weeks to months to achieve sufficient levels in deficient individuals.
- In emergencies, such as acute infections, a loading dose of 100,000–400,000 IU based on body weight can raise serum levels rapidly.
- Administering these doses in divided intervals enhances absorption and supports efficient hepatic conversion.
- Alternatively, oral calcifediol (0.5–1 mg or \~0.014 mg/kg) can increase serum 25(OH) D within 24 hours, making it a preferred option in emergencies due to its rapid onset of action and immune-enhancing properties.

Conclusions:

Vitamin D functions as a pleiotropic hormone with extensive physiological roles mediated through genomic and non-genomic pathways. While its importance in skeletal health is well-established, growing evidence supports its involvement in immune regulation, cardiovascular function, cancer prevention, and endocrine health. Bridging mechanistic insights with clinical outcomes remains a critical frontier for leveraging vitamin D as a holistic health modulator.

Vitamin D and Cardiovascular Disease: Current Evidence and Future Perspectives

Authors: *Nicola Cosentino, Jeness Campodonico, Valentina Milazzo, Monica De Metrio, Marta Brambilla, Marina Camera and Giancarlo Marenzi*

Reference: *Cosentino N et al. Nutrients. 2021 Oct 14; 13(10):3603. doi: 10.3390/nu13103603*

Overview

Vitamin D deficiency remains a global health concern, affecting nearly half the population. While classically associated with calcium-phosphate homeostasis and bone health, emerging evidence suggests a potential role in cardiovascular disease (CVD) pathogenesis. The presence of vitamin D receptors (VDRs) in vascular endothelium, cardiomyocytes, and smooth muscle cells provides a biological basis for these associations. This brief reviews the mechanistic links, clinical findings, and evidence from trials regarding vitamin D in coronary artery disease (CAD), heart failure (HF), and atrial fibrillation (AF).

Vitamin D in Cardiovascular Health:

Vitamin D exerts its cardiovascular effects through multiple interrelated mechanisms:

- Modulation of RAAS: Down regulation of renin and aldosterone, reducing blood pressure and cardiac hypertrophy.
- Anti-inflammatory action: Suppresses NF-κB and TNF-α, while enhancing IL-10, mitigating endothelial inflammation.
- Endothelial protection: Improves vascular tone, inhibits vascular smooth muscle proliferation, and prevents atherosclerotic changes.
- ACE-2 induction: Counteracts angiotensin II, promotes anti-fibrotic, anti-inflammatory and anti-hypertensive effects.

Vitamin D and Coronary Artery Disease:

Several studies link low serum vitamin D with higher risk and severity of coronary events, such as myocardial infarction and CAD-related mortality. Given this data, it is not surprising that hospitalised patients with AMI consistently had a high rate of vitamin D insufficiency.

Major studies on the clinical relevance of vitamin D levels in patients with CAD

Author, year	Study Type	Population (n)	Major Findings
Raslan, 2019	Case-control/ Prospective	CCS (n=84)	Every 10 ng/mL ↑ Vit. D led to ↓ prevalence of stable angina
Xu, 2020	Case-control/ Prospective	Postmenopausal women (n=93)	Vit. D Deficiency ↑ CAD risk
Brøndum Jacobsen, 2012	Population-based/ Retrospective	General population (n=10,170)	Low Vit. D ↑ risk of CAD (72%), AMI (99%), fatal CAD/AMI (122%)
Ng, 2013	Cohort/ Prospective	NSTEMI/STEMI (n=1,259)	Vit. D deficiency led to ↑ MACE over 1.6 years
Correia, 2013	Retrospective	ACS (n=20,670)	Vit. D deficiency leads to ↑ in-hospital & mortality
De Metrio, 2015	Cohort/ Prospective	NSTEMI/STEMI (n=814)	↑ incidence of mortality, ventilation, HF re-hospitalization in deficient patients

CCS-chronic coronary syndrome; MACE-major adverse cardiac events; NSTEMI-non ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction

Vitamin D and Heart Failure:

Heart failure patients often exhibit profound vitamin D deficiency. Evidence from observational studies and interventional trials suggests potential improvement in cardiac function and remodeling with high-dose supplementation, though results on mortality are inconsistent.

Major studies on the clinical relevance of vitamin D levels in patients with heart failure

Author, year	Study Type	Population (n)	Major Findings
Zitterman, 2003	Case-control/ Prospective	NYHA II (n=53)	Significant reduction of vitamin D levels in HF patients
Anderson, 2010	Cohort / Prospective	General population (n=41,504)	97% of HF patients had vitamin D <30 ng/mL; HR 1.31 for HF development
Kim, 2008	Retrospective	NHANES 2001–2004 (n=8,351)	89% of HF patients with CAD had vitamin D <30 ng/mL

Author, year	Study Type	Population (n)	Major Findings
Gotsman, 2012	Case-control Retrospective	Age ≥45 yrs (n=49,834)	Vit. D deficiency led to HR 1.52 for 1.6-yr mortality; Vit. D therapy led to HR 0.68
Gruson, 2015	Cohort / Prospective	LVEF ≤35% (n=1,709)	Vit. D predicted CV death & heart transplant at 4.1 yrs
Witte, 2016	RCT / Prospective	LVEF ≤45%, NYHA II–III, Vit. D <20 ng/mL (n=229)	High-dose Vit. D (4000 IU daily) led to ↑ LVEF & reverse remodeling

NYHA-New York Heart Association; NHANES-National Health and Nutrition Examination Survey; LV-left ventricular; LVEF-Left ventricular ejection fraction

LURIC study: It is noted in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, vitamin D levels were inversely associated with NT-proBNP and NYHA class, and positively associated with left ventricular ejection fraction.

VINDICATE study: As shown in the Vitamin D Treating Patients with Chronic Heart Failure (VINDICATE) study, high-dose vitamin D supplementation for 1 year significantly improved left ventricular function in chronic heart failure patients with vitamin D deficiency.

Vitamin D and Atrial Fibrillation:

Atrial fibrillation is the one of the most common arrhythmia. There is growing observational evidence linking lower vitamin D levels to a higher risk of atrial fibrillation. However, clinical trials testing supplementation are limited.

Meta-analyses show a **12% increased AF risk in the general population** and **56% increased risk post-CABG** per 10 ng/mL decrease in vitamin D.

Major studies on the clinical relevance of vitamin D levels in atrial fibrillation

Author, year	Study Type	Population (n)	Endpoint Considered	Major Findings
Chen, 2014	Case-control/ Retrospec-tive	General (n=322)	Incidence of AF	Vitamin D deficiency doubled AF risk
Gode, 2016	Case-control/ Prospective	CABG (n=90)	New-onset post-op AF	Lower vitamin D levels in AF vs. non-AF patients

Author, year	Study Type	Population (n)	Endpoint Considered	Major Findings
Cerit, 2018	Retrospec-tive	On-pump CABG (n=128)	New-onset post-op AF	AF patients had lower Vit. D levels than controls
Ozcan, 2015	Case-control/ Prospective	Hypertensive (n=227)	New-onset AF	Vitamin D deficiency in-creased AF risk by 1.7×

AF-Atrial fibrillation; CABG-coronary artery disease graft; post-op-post-operative

Vitamin D and Interaction with Antiplatelet Drugs:

Vitamin D regulates drug metabolism by modulating intestinal and hepatic enzymes, particularly enhancing CYP3A4 expression, which is crucial for activating several drugs, including prodrugs like prasugrel. Deficiency in vitamin D may impair drug efficacy and has been linked to increased platelet reactivity in patients on antiplatelet therapy.

Studies show that vitamin D treatment reduces ADP- and collagen-induced platelet aggregation. In CAD patients on high-intensity statins, higher vitamin D levels further lowered platelet reactivity—supporting its role in the cardiovascular benefits of statins.

Additionally, seasonal and individual variations in vitamin D may influence drug clearance, suggesting that supplementation could help optimize pharmacokinetics and therapeutic outcomes.

Future Perspectives:

While low vitamin D levels are consistently associated with increased cardiovascular disease (CVD) risk, causality remains unproven. Mendelian randomization studies and many interventional trials have failed to show a direct effect—likely due to issues in study design, patient selection, and inconsistent definitions or dosing of supplementation.

Future research should focus on high-risk CVD patients with confirmed severe vitamin D deficiency, use more reliable biomarkers of vitamin D status, and address previous trial limitations to clarify whether vitamin D supplementation can meaningfully prevent or manage CVD.

Conclusions:

To conclude, growing interest in vitamin D's role in cardiovascular health stems from its rising deficiency and potential effects on CVD. While low vitamin D levels are linked to higher cardiovascular risk, it remains unclear whether this reflects causation or mere association. The benefits of supplementation in high-risk, vitamin D-deficient patients are still uncertain and require further research.

Effect of Vitamin D Supplementation on Type 2 Diabetes Biomarkers: An Umbrella of Interventional Meta-Analyses

Authors: *Vali Musazadeh, Zeynab Kavyani, Naghmeh Mirhosseini, Parvin Dehghan and Mahdi Vajdi*

Reference: *Musazadeh et al. Diabetol Metab Syndr 15, 76 (2023) doi: 10.1186/s13098-023-01010-3.*

Overview

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired glucose metabolism. Despite lifestyle interventions and pharmacological treatments, glycemic control remains suboptimal for many patients. Vitamin D, traditionally known for its role in bone health, has emerged as a potential modulator of glucose metabolism due to its anti-inflammatory, antioxidant, and immunomodulatory properties.

Previous randomized controlled trials (RCTs) and meta-analyses have explored the impact of vitamin D supplementation on glycemic biomarkers such as fasting blood sugar (FBS), hemoglobin A1c (HbA1c), insulin levels, and homeostatic model assessment for insulin resistance (HOMA-IR). However, findings have been inconsistent. This umbrella meta-analysis aimed to synthesize evidence from 37 interventional meta-analyses to note the effects of vitamin D supplementation on T2DM biomarkers.

Why Optimal Vitamin D Matters in T2DM:

- Vitamin D deficiency impairs insulin secretion and promotes insulin resistance.
- Suboptimal levels are linked to increased risk of T2DM complications, including cardiovascular and renal dysfunction.
- Achieving serum 25(OH) D levels in the optimal range (typically >30 ng/mL) is associated with improved glucose uptake and reduced systemic inflammation.

Methodology:

Literature Search & Selection

- Databases searched: Scopus, PubMed, Web of Science, Embase, and Google Scholar (up to March 2022).
- Inclusion criteria: Meta-analyses of RCTs evaluating vitamin D supplementation effects on T2DM biomarkers (FBS, HbA1c, insulin, HOMA-IR).
- Exclusion criteria: Observational studies, quasi-experimental designs, case reports, letters, and studies lacking full text or sufficient data.

Data Extraction & Quality Assessment

- Extracted data: Author, year, location, sample size, dosage, duration, effect sizes (SMD and WMD), and confidence intervals.
- Quality tool: AMSTAR2 checklist

Key Biomarkers Assessed

1. Fasting Blood Sugar (FBS)
2. Hemoglobin A1c (HbA1c)
3. Serum Insulin
4. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

Results:

» **Summary of Pooled Results -** Vitamin D supplementation significantly improved all four biomarkers

Biomarker	Weighted Mean Difference (WMD)	Standardized Mean Difference (SMD)	p-value (WMD)	Heterogeneity (I^2)
FBS	-3.08 mg/dL	-0.26	<0.001	92%
HbA1c	-0.05%	-0.16	0.016	50%
Insulin	-2.62 µIU/mL	-0.33	<0.001	82%
HOMA-IR	-0.67	-0.31	<0.001	96%

These findings suggest a consistent beneficial effect of vitamin D supplementation on glycemic biomarkers, despite inter-study heterogeneity, underscoring its potential as an adjunctive strategy in glycemic management.

» **Clinical Insights by Subgroup:**

1. **Effect by Duration**

   Vitamin D supplementation for ≤ 15 weeks showed greater reductions in FBS, insulin, and HOMA-IR.

2. **Effect by Health Condition**

   More significant improvements were seen in patients with:

   - Gestational Diabetes Mellitus (GDM)
   - Chronic Kidney Disease (CKD)

- Cardiovascular Disease (CVD)
- Non-Alcoholic Fatty Liver (NAFLD)

Discussion:

The present umbrella meta-analysis synthesized data from 37 meta-analyses encompassing over 36,000 adults, demonstrated that vitamin D supplementation significantly improved glycemic biomarkers—including fasting blood sugar, serum insulin, HbA1c, and HOMA-IR—particularly when administered at doses ≤ 4000 IU/day and for durations ≤ 15 weeks.

These effects align with epidemiologic findings suggesting that vitamin D deficiency is associated with impaired insulin secretion, resistance, and diminished glucose clearance. Mechanistically, vitamin D may enhance glycemic control by upregulating vitamin D receptor (VDR) expression in pancreatic β-cells, thereby promoting insulin secretion, improving insulin sensitivity, suppressing inflammatory cytokines, and regulating calcium flux vital for insulin signaling.

However, this analysis is not without limitations. Substantial heterogeneity was detected across studies, though it was addressed through detailed subgroup analyses to strengthen the robustness of the conclusions.

Conclusion:

Vitamin D supplementation demonstrates statistically significant improvements in FBS, HbA1c, insulin levels, and HOMA-IR. It should be considered as a safe adjunct in managing T2DM, particularly in deficient or high-risk individuals. Further targeted trials are needed to optimize dosage and treatment duration across subgroups.

Key points:

- **Consistent Glycemic Improvements:** Vitamin D supplementation significantly improved key biomarkers—**FBS, HbA1c, insulin levels, and HOMA-IR**—in individuals with or at risk of type 2 diabetes.
- **Optimal Dosing and Duration Identified:** The most beneficial effects were observed with ≤ **4000 IU/day** of vitamin D over **≤ 15 weeks**, suggesting a dose-dependent and time-sensitive therapeutic window.
- **Enhanced Outcomes in High-Risk Populations:** High risk groups with **GDM, CKD, CVD, and NAFLD** experienced more pronounced improvements, highlighting the potential role of vitamin D in managing T2DM with comorbidities.
- **Mechanistic Support:** Benefits are likely mediated through increased **insulin sensitivity,** improved **β-cell function,** and **anti-inflammatory effects**, making vitamin D a promising adjunct in T2DM management strategies.

Vitamin D and Preeclampsia: A Systematic Review and Meta-Analysis

Authors: *Abdulla AlSubai, Muhammad Hadi Baqai, Hifza Agha, Neha Shankarlal, Syed Sarmad Javaid, Eshika Kumari Jesrani, Shalni Golani, Abdullah Akram, Faiza Qureshi, Shaheer Ahmed and Simran Saran*

Reference: *AlSubai A et al. SAGE Open Med. 2023 Nov 22; doi: 11:20503121231212093.*

Overview

Preeclampsia (PE) complicates 2–8% of pregnancies worldwide and remains a leading cause of maternal and perinatal morbidity and mortality. Characterized by new-onset hypertension after 20 weeks' gestation and often accompanied by proteinuria and end-organ dysfunction, PE not only threatens immediate maternal health but also predisposes mothers and offspring to long-term cardiovascular and metabolic disorders.

Vitamin D status, commonly assessed via serum 25-hydroxyvitamin D [25(OH) D] concentration, has emerged as a potential modifiable factor in PE pathogenesis. A global review found 25(OH) D deficiency rates of 46–87% among pregnant women, depending on region. Observational studies linking low maternal 25(OH) D to increased PE risk have yielded inconsistent findings, and randomized trials of vitamin D supplementation show varied effects on PE incidence. This systematic review and meta-analysis by aims to clarify two questions:

- Is maternal 25(OH) D deficiency associated with heightened PE risk?
- Does antenatal 25(OH) D supplementation reduce PE incidence?

By pooling data from both observational studies and randomized controlled trials (RCTs), the authors aimed to quantify these relationships and assess vitamin D's potential as a preventive intervention against PE.

Methods:

A comprehensive search was conducted across MEDLINE, TRIP, and Cochrane Central up to July 2021. Inclusion criteria encompassed randomized controlled trials (RCTs) and observational studies evaluating the association between 25(OH) D deficiency or supplementation and PE incidence.

34 studies (10 RCTs, 24 observational) met inclusion criteria. Data extraction and quality assessments followed PRISMA guidelines. Meta-analyses used a random-effects model and Mantel-Haenszel odds ratio to estimate pooled odds ratios (OR) and 95% confidence intervals (CI).

Results:

Association between 25(OH) D Deficiency and Preeclampsia

A total of 24 observational studies with 25,996 participants evaluated PE risk at three thresholds of 25(OH) D deficiency:

Vitamin D Level	PE Risk (Pooled OR)	95% CI	p-value	Heterogeneity (I^2)
<25 nmol/L	4.30	2.57 – 7.18	<0.00001	59%
25–50 nmol/L	1.71	1.27 – 2.32	0.0005	66%
50–75 nmol/L	1.61	1.21 – 2.16	0.001	35%

Impact of 25(OH) D Supplementation on Preeclampsia Risk

10 RCTs with 3,451 participants assessed the effects of supplementation. Pooled results indicated significant risk reduction.

Vitamin D Supplementation v/s Placebo	PE Risk (Pooled OR)	95% CI	p-value	Heterogeneity (I^2)
	0.50	0.40–0.63	<0.00001	16%

Clinical Implications:

- **Screening for Deficiency:** Given the strong observational link, early pregnancy measurement of serum 25(OH) D—particularly in high-risk groups (obesity, limited sun exposure)—can identify women who may benefit most from supplementation.
- **Target Concentrations:** Achieving 25(OH) D levels ≥ 50 nmol/L is critical; levels < 25 nmol/L convey the highest PE risk. Clinicians should consider dose adjustments based on baseline status and response monitoring.
- **Optimal Supplementation Regimens:** While standard guidelines recommend 600 IU/day in pregnancy, RCTs achieving significant PE reductions typically used 2,000–4,000 IU/day or 50,000 IU biweekly. Individualized regimens, tailored to baseline deficiency and maternal characteristics, may optimize efficacy.
- **Safety Profile:** High-dose supplementation up to 4 000 IU/day and bolus dosing were well tolerated without hypercalcemia, supporting broader adoption in antenatal care under monitoring.

- **Integration into Prenatal Guidelines:** Incorporating vitamin D status assessment and individualized supplementation into routine prenatal protocols could reduce PE incidence and associated healthcare burdens.

Discussion:

The current meta-analysis reaffirms that maternal vitamin D deficiency significantly increases the risk of preeclampsia, particularly at levels below 25 nmol/L, with over a fourfold increase in risk. Supplementation, especially when started early in pregnancy, effectively reduces this risk by approximately 50%.

Mechanistically, vitamin D supports vascular stability and modulates inflammatory pathways, and its deficiency is linked to oxidative stress, NF-κB activation, and endothelial dysfunction—hallmarks of PE. Weekly doses of 50,000 IU, have shown maximum efficacy without adverse effects like hypercalcemia. Additionally, evidence from RCTs suggests that routine vitamin D screening and appropriate supplementation may lower the incidence of PE and improve overall pregnancy outcomes.

Notably, supplementation initiated in early pregnancy was most effective. This supports the hypothesis that vitamin D status during placental development is critical in modulating PE risk.

WHO and Endocrine Society guidelines recommend 600 IU/day for pregnant women, although evidence supports optimal doses (e.g., 50,000 IU/week) to maintain beneficial serum levels.

Additionally, a stratified RCT by Rostami et al. highlighted the utility of routine vitamin D screening in prenatal care. Women in the screened group had significantly fewer adverse outcomes, including reduced PE incidence (8% vs. 17%).

The study also highlighted that screening led to the reduction in the prevalence of secondary outcomes such as GDM by 50% and preterm delivery up to 40% in women with 25(OH)D <20 ng/ml.

Conclusion:

The findings of the current meta-analysis suggest that 25(OH) D deficiency is associated with increased risk of PE. The results also confirmed that 25(OH) D supplementation was associated with reduced risk of PE. However, more comprehensive RCTs are still required to identify the most effective dosage of 25(OH) D supplementation for women of different ethnicities.

Key points:

- **Vitamin D Deficiency Increases PE Risk:** Women with 25(OH) D levels < 25 nmol/L had a more than 4 times increased risk of developing preeclampsia. Even moderate deficiency (<75 nmol/L) was associated with elevated risk.
- **Supplementation Reduces Preeclampsia Incidence:** Meta-analysis of 10 RCTs showed that vitamin D supplementation reduced PE risk by 50%, with low heterogeneity, indicating consistent results across trials.
- **Biological Mechanism is Plausible:** Vitamin D supports endothelial function, reduces oxidative stress, and modulates immune response—all pathways relevant to preeclampsia development.
- **Clinical Recommendations Support Early and Adequate Dosing:** Doses of 50,000 IU weekly appear safe and effective. Routine screening and supplementation, especially in early pregnancy, may improve maternal outcomes and reduce PE rates.

CALCIROL FOR ALL

MAKING INDIA D STRONG
SINCE 1969

For Weekly & Maintenance Therapy

℞ CALCIROL Sachet

60,000 I.U. Vit. D3 Granules

The Most **Dependable Vitamin D3**

℞ CALCIROL Sachet

Orange Flavour

60,000 I.U. Vit. D_3 Granules

Delicious **Orange** Flavour

℞ CALCIROL Softgels

60,000 IU Vitamin D_3

The WOW Vit. D_3

℞ CALCIROL NANO

Cholecalciferol Oral Solution 60,000 IU/ 5ml

The **TRUE NANO** for Better Health

For Faster & Assured Correction of Vitamin D3 Deficiency

℞ CALCIROL AQ

Cholecalciferol IP 600,000 IU / 2ML Injection

First and Fast AQueous D3

For Daily Supplement therapy

In Women Health

℞ CALCIROL XT™

Methylcobalamin 1500mcg + L-Methylfolate Calcium 1mg + Pyridoxal 5 Phosphate 20mg + Calcium Carbonate 1250mg + Vitamin D_3 2000 IU Tablet

XTRA Health Benefits, Beyond Calcification

Join & share to spread awareness and
Fight against Vitamin-D3 Deficiency

An Unique Initiative
बनेगा इंडिया D STRONG

Scan the QR code to join this initiative

DISCLAIMER

This publication is distributed in India by Globe Pharma Publications Pvt. Ltd. through Cadila Pharmaceuticals Limited under exclusive license from Boston Medical Center to serve and cater scientific and educational information to medical professionals. This publication contains a collection of selected articles on Vitamin D curated by Globe Pharma Publications Pvt. Ltd.

Boston Medical Center does not endorse the quality or value of the advertised/sponsored products described therein. Please refer to full prescribing information before issuing a prescription for any product mentioned in the current module. No part of this publication may be reproduced or transmitted in any form without written permission from Boston Medical Center. Cadila Pharmaceuticals Limited has no influence on the content of this publication; expert comments expressed (if any) in this publication are solely the views of the author or respective experts/clinicians. Cadila Pharmaceuticals Limited is neutral to the views expressed in this publication. Cadila Pharmaceuticals Limited disclaims any responsibility in any way, nor be liable for any injury and/or damage to any persons in view of any errors, omissions or inaccuracies in this publication, whether arising from negligence or otherwise.

GLOBE PHARMA PUBLICATIONS PVT. LTD.
INTERNATIONAL MEDICAL PUBLISHING COMPANY
An ISO 9001:2008 Certified Company

BOSTON MEDICAL CENTER

A scientific initiative by Cadila Pharmaceuticals Ltd.

CADILA PHARMACEUTICALS LIMITED

The Care Continues...