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A Study on the Effect of Vitamin D Supplementation on Articular Cartilage Volume in Patients with Primary Knee Osteoarthritis

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Abstract: *Older persons suffer from pain, incapacity, and poor quality of life due to primary knee osteoarthritis (KOA), one of the most common degenerative joint illnesses. Vitamin D may help preserve bone and cartilage health by modulating inflammatory pathways, calcium homeostasis, and chondrocyte metabolism. Vitamin D deficiency worsens osteoarthritis, cartilage deterioration, and clinical symptoms. The efficacy of vitamin D therapy in maintaining articular cartilage volume and lowering disease severity in primary knee osteoarthritis patients is unclear. This research examines how vitamin D supplementation affects articular cartilage volume and clinical disease severity in primary knee osteoarthritis patients. Patients with radiographically verified primary knee osteoarthritis and low blood vitamin D levels will be studied in a prospective, randomized, controlled manner. Standardised vitamin D supplementation and follow-up will be provided. Clinical results will be assessed using validated measures such pain ratings, functional evaluations, and disease severity indices, while MRI will quantify articular cartilage volume. We will also examine serum vitamin D, inflammatory biomarkers, and radiographic data for cartilage preservation and symptom alleviation. The research should provide light on vitamin D supplementation's ability to treat knee osteoarthritis. The results may help design better primary knee osteoarthritis care options to halt cartilage deterioration, reduce disease progression, improve joint function, and improve quality of life.*

Keywords: Knee osteoarthritis, vitamin D, articular cartilage volume, MRI, randomized controlled trial, chondroprotection

I. INTRODUCTION

1.1 Background

Osteoarthritis (OA) is the most common form of arthritis worldwide and a leading cause of chronic disability among older adults. The knee is the most frequently affected joint, with prevalence increasing dramatically with age. The disease is characterized by progressive degradation of articular cartilage, accompanied by changes in subchondral bone, meniscal degeneration, synovial inflammation, and osteophyte formation. Current therapeutic approaches focus on symptom management, with no disease-modifying agents available to prevent structural progression.

Vitamin D deficiency has emerged as a potentially modifiable risk factor in KOA. It is estimated that 20–100% of elderly populations in North America and Europe are vitamin D deficient, typically defined as serum 25-hydroxyvitamin D (25(OH)D) below 50 nmol/L. High prevalence rates have also been reported in Australian communities, particularly in Tasmania and Victoria. The presence of vitamin D receptors (VDRs) in articular chondrocytes and the established role of vitamin D in bone and muscle metabolism provide a biological rationale for investigating its potential disease-modifying effects in OA.

1.2 Rationale and Objectives

Previous observational studies have demonstrated associations between low serum 25(OH)D levels and increased knee cartilage loss, greater knee pain, and higher prevalence of radiographic OA. However, randomized controlled trials

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have produced conflicting results regarding the efficacy of vitamin D supplementation in preserving cartilage volume and improving clinical outcomes.

The primary objective of this investigation is to determine whether vitamin D supplementation reduces the loss of knee articular cartilage volume in patients with symptomatic primary KOA and vitamin D insufficiency. Secondary objectives include evaluating effects on knee pain, other knee structural changes, lower limb muscle strength, and exploration of potential molecular mechanisms.

II. BIOLOGICAL MECHANISMS: VITAMIN D AND CARTILAGE HOMEOSTASIS

2.1 Vitamin D Receptor Signaling in Chondrocytes

Vitamin D receptors are expressed in human articular chondrocytes, enabling direct genomic effects of 1α,25-dihydroxyvitamin D_3 (the active metabolite) on chondrocyte function. Through VDR binding and heterodimerization with the retinoic acid receptor (RXR), vitamin D regulates the expression of matrix metalloproteinases (MMPs) and prostaglandin E_2 (PGE_2) in chondrocytes, influencing cartilage matrix turnover.

2.2 Inhibition of Inflammatory Pathways

Recent mechanistic studies have elucidated multiple pathways through which vitamin D exerts chondroprotective effects:

NF-κB Pathway Suppression: Vitamin D inhibits NF-κB phosphorylation and nuclear translocation through VDR-NF-κB interaction, thereby reducing chondrocyte apoptosis and extracellular matrix degradation. This interaction also regulates the AMPK/mTOR signaling pathway, promoting autophagy and delaying OA progression.

MyD88-TAK1-ERK Axis: In OA rat models, vitamin D treatment (2.34 μg/kg/day for 6 weeks) significantly downregulated inflammatory signaling through the MyD88-TAK1-ERK axis, reducing serum IL-6 levels and suppressing MMP13 expression by 74.72%. Histological analysis demonstrated a 567.76% increase in cartilage area and 39.13% decrease in Osteoarthritis Cartilage Histopathology scores.

Catabolic Enzyme Regulation: Vitamin D modulates the expression of MMPs (particularly MMP-3, -9, and -13) through VDR-mediated pathways, reducing proteoglycan loss and preserving cartilage matrix integrity.

2.3 Effects on Subchondral Bone

Emerging evidence suggests that subchondral bone metabolic dysfunction may initiate or accelerate OA progression. Vitamin D enhances subchondral bone mass (61.81% higher bone volume/total volume ratio in treated animals) and improves bone quality, potentially stabilizing the osteochondral unit.

III. EPIDEMIOLOGICAL EVIDENCE

3.1 Cross-Sectional and Longitudinal Observational Studies

The Tasmanian Older Adult Cohort Study provided foundational evidence linking vitamin D status to knee cartilage health. Cross-sectional analyses demonstrated significant positive associations between serum 25(OH)D levels and knee cartilage volume in older men and women. Longitudinally, higher baseline serum 25(OH)D predicted reduced cartilage volume loss over 2 years, with increases in vitamin D levels conferring additional protective associations.

The Osteoarthritis Initiative (OAI) cohort study, including 783 participants (mean age 62.3 years), found that higher vitamin D intake (both dietary and supplemental) was associated with significantly greater cartilage thickness and volume at multiple knee compartments, including the medial tibia, central lateral femur, central medial femur, and central medial tibiofemoral compartment. These associations remained significant after adjustment for ten potential confounders, with each 250 IU increase in daily intake corresponding to improved MRI parameters.

3.2 Meta-Analyses of Randomized Controlled Trials

A comprehensive meta-analysis of eight RCTs including 3,077 patients evaluated vitamin D supplementation effects in KOA. Results demonstrated statistically significant improvements in tibial cartilage volume, synovial fluid volume, and Visual Analog Scale (VAS) pain scores. However, no significant differences were observed in joint space width, bone marrow lesions, or WOMAC stiffness subscale scores. Notably, subgroup analysis indicated that daily supplementation exceeding 2,000 IU significantly slowed synovial tissue progression.

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A separate systematic review concluded that while vitamin D supplementation improved pain and function outcomes, structural benefits were less consistently demonstrated, suggesting potential dissociation between symptom modification and cartilage preservation.

IV. SYSTEMATIC REVIEW: VITAMIN D SUPPLEMENTATION TRIALS

4.1 The VIDEO Trial

The VItamin D Effects on Osteoarthritis (VIDEO) study, a randomized, placebo-controlled, double-blind trial, enrolled 400 participants with symptomatic KOA and serum 25(OH)D levels between 12.5 and 60 nmol/L. Participants received either 50,000 IU vitamin D_3 or placebo monthly for 2 years, with MRI assessment of cartilage volume as the primary endpoint.

Key findings included:

No significant difference in tibial cartilage volume loss between groups

Significant improvements in WOMAC pain scores in the treatment group

No significant effects on other structural parameters including bone marrow lesions

4.2 Other Major Trials

The VIDEO study results were corroborated by other major trials. A separate US-based RCT found no significant effect of vitamin D supplementation on cartilage volume loss over 2 years, despite achieving significant increases in serum 25(OH)D levels. However, the meta-analysis suggests potential benefits with higher-dose regimens (>2,000 IU daily), raising questions about optimal dosing strategies.

4.3 Explanations for Discordant Results

Several factors may explain the discrepancy between observational and RCT findings:

Timing of Intervention: Supplementation may be ineffective once significant cartilage damage has occurred; earlier intervention may be necessary for chondroprotection

Dosing Considerations: Monthly 50,000 IU dosing may not provide optimal biological exposure compared to daily regimens

Outcome Sensitivity: Cartilage volume loss may be too insensitive to detect subtle treatment effects over 2 years

Patient Selection: Inclusion criteria based on vitamin D deficiency alone may not identify patients most likely to benefit

Disease Duration: Advanced disease may be less responsive to metabolic interventions

V. PROPOSED RESEARCH PROTOCOL

5.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group clinical trial conducted across two sites (Tasmania and Victoria, Australia) with 24 months of follow-up.

5.2 Participants

Inclusion Criteria:

Age 50–79 years

Symptomatic knee OA for ≥6 months (ACR criteria)

Knee pain ≥20 mm on 100-mm VAS

Serum 25(OH)D 12.5–60 nmol/L

ACR functional class I–III

Willing to comply with study requirements

Exclusion Criteria:

Severe radiographic OA (grade 3 per Altman's atlas)

Severe knee pain (>80 mm on VAS)

Contraindications to MRI

Inflammatory arthritis, lupus, or cancer

Severe cardiac or renal impairment

Hypersensitivity to vitamin D

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Vitamin D supplementation within previous 30 days
Anticipated knee or hip surgery within 2 years

5.3 Intervention

Participants will be randomized 1:1 to receive either:
Intervention: 50,000 IU vitamin D_3 (cholecalciferol) compounded capsule, one capsule monthly for 24 months
Control: Identical inert placebo capsule, one capsule monthly for 24 months
All participants will receive standard care recommendations, including dietary advice and activity modification.

5.4 Randomization and Blinding

Computer-generated random numbers will be used for allocation (1:1 ratio). Allocation concealment will be maintained through centralized automated allocation and use of identical placebo capsules. Investigators, research assistants, and outcome assessors will be blinded to treatment assignment.

5.5 Outcome Measures

Primary Outcomes (24 months):
Change in tibial cartilage volume (medial and lateral compartments) measured by MRI
Change in WOMAC knee pain score
Secondary Outcomes:
Other MRI parameters: cartilage defects, tibial plateau bone area, bone marrow lesions, meniscal tear and extrusion
Lower limb muscle strength at 3, 6, 12, and 24 months
WOMAC function and stiffness subscales
VAS pain scores
Quality of life measures (SF-36)
Physical performance (gait speed, chair stand test)
Exploratory Outcomes:
Serum biomarkers of cartilage turnover (COMP, CTX-II, PIIANP)
Serum inflammatory markers (IL-6, TNF-α, hs-CRP)
Core muscle function (transversus abdominis and lumbar multifidus)

5.6 MRI Protocol

MRI assessments will be performed at baseline and 24 months using a 1.5-T or 3.0-T scanner with:
Coronal 3D FLASH with Water Excitation sequence for cartilage volume measurement
Intermediate-weighted fat-suppressed fast spin-echo sequences for cartilage defects and bone marrow lesions
Sagittal T2-weighted sequences for meniscal evaluation
MRI analysis will be performed by trained readers blinded to clinical data and treatment allocation, using validated software for cartilage segmentation and volume calculation.

5.7 Sample Size Calculation

Based on previous studies, a sample size of 160 participants per group (total 320) will provide 90% power to detect a clinically meaningful difference in cartilage volume loss (≥2%) with an anticipated dropout rate of 20%. Thus, 400 participants will be enrolled (200 per site).

5.8 Statistical Analysis

Primary Analysis: Intention-to-treat analysis using linear mixed models to compare changes in cartilage volume between groups, adjusted for baseline values, age, sex, BMI, and site. Sensitivity analyses will include per-protocol analysis and multiple imputation for missing data.
Secondary Analyses: Linear regression for continuous outcomes and logistic regression for categorical outcomes. Pre-specified subgroup analyses will explore effect modification by baseline vitamin D levels, BMI, and disease severity.

5.9 Sub-Studies

Muscle Strength Sub-Study: Assessment of lower limb muscle strength using dynamometry and core muscle function using MRI at 3, 6, 12, and 24 months.
Cardiovascular Sub-Study: Evaluation of vitamin D effects on blood pressure (ambulatory and central) and arterial stiffness (aortic pulse wave velocity) as exploratory outcomes.

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VI. DISCUSSION

6.1 Interpretation of Existing Evidence

The collective evidence from observational studies provides compelling support for an association between vitamin D status and knee cartilage health. The biological plausibility is reinforced by mechanistic studies demonstrating direct chondroprotective effects through multiple molecular pathways. However, the translation of these findings into clinical benefit through supplementation trials has been inconsistent.

Several important considerations emerge from the discordance between observational and trial data. First, the timing of intervention is likely critical: vitamin D may be more effective in preventing cartilage degradation than in reversing established disease. Second, the sensitivity of outcome measures matters; cartilage volume may be too crude to detect biologically meaningful effects that could manifest as preservation of cartilage quality or function. Third, the heterogeneity of KOA as a disease suggests that vitamin D may benefit specific subgroups—perhaps those with more inflammatory phenotypes or specific genetic backgrounds.

6.2 Implications of Proposed Research

This protocol addresses several limitations of previous trials. The inclusion of comprehensive MRI parameters beyond cartilage volume allows investigation of effects on other joint structures. The extended 24-month follow-up period may capture effects that require longer observation. The integration of biomarker, muscle function, and cardiovascular outcomes reflects the emerging understanding of OA as a systemic disease with multiple contributors.

6.3 Limitations

The proposed study has limitations, including:

Participants with established OA may have irreversible structural damage, potentially limiting treatment effects

Vitamin D deficiency alone may not be the appropriate selection criterion for identifying responders

MRI cartilage volume measurement, while validated, may not capture all aspects of cartilage health relevant to clinical outcomes

The 50,000 IU monthly dose, while practical, may not provide optimal biological exposure compared to daily dosing

VII. CONCLUSION

The relationship between vitamin D and knee osteoarthritis progression represents a complex interplay of molecular mechanisms, epidemiological observations, and clinical trial outcomes. While substantial evidence supports the biological plausibility of vitamin D as a chondroprotective agent, clinical translation remains uncertain. This research protocol provides a framework for addressing gaps in current evidence through a rigorous, comprehensive approach incorporating multiple outcome measures and extended follow-up. The results will contribute to the ongoing effort to identify disease-modifying interventions for knee osteoarthritis.

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