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Research Paper

Is serum vitamin D level involved in left ventricular remodeling among individuals with impaired renal function? A systematic review with pairwise and dose-response meta-analysis

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Abstract

Introduction: Left ventricular remodeling in individuals with impaired renal function is associated with adverse cardiovascular outcomes. Vitamin D deficiency (VDD) may contribute to remodeling, yet the interaction remains underexplored.

Aim: The aim of this review was to evaluate the relationship between serum vitamin D levels and left ventricular remodeling.

Material and methods: Relevant records indexed in Scopus, PubMed, Web of Science, Europe PMC, and Scilit were identified using predetermined terms. Observational studies reporting the relationship between circulating vitamin D levels and left ventricular remodeling in renal-impaired individuals were considered eligible for the review. Out of 4503 records, 6 studies (n = 3235 participants) met the inclusion criteria. Pairwise, single-arm, and dose-response meta-analyses were performed under a random-effects model.

Results and discussion: The pooled analysis revealed that individuals with VDD had significantly higher left ventricular mass index (LVMI) (SMD = 0.69; 95%CI: 0.21–1.16; P = 0.005). A pooled correlation analysis demonstrated an inverse association between serum vitamin D and LVMI (r = –0.414; 95% CI: –0.48 to –0.34; P < 0.001). Significant heterogeneity was observed in the association analysis (I^2 = 89%; P < 0.001), but not in the correlation analysis (I^2 = 6%; P = 0.30). The correlation between serum vitamin D levels and LVMI exhibited a significant J-shaped pattern, with the optimal maintenance level identified as above 46.26 ng/mL.

Conclusions: Serum vitamin D levels are inversely associated with LVMI in renal-impaired individuals, suggesting that VDD contributes to adverse cardiac remodeling.

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1. INTRODUCTION

Left ventricular remodeling in individuals with impaired renal function is a critical concern, given its association with adverse cardiovascular outcomes. Renal dysfunction triggers a cascade of pathophysiological processes that promote myocardial changes, including hemodynamic overload, chronic inflammation, and activation of the renin-angiotensin-aldosterone system (RAAS).[1] Hemodynamic overload in renal impairment stems from fluid retention due to impaired sodium excretion, leading to increased blood volume and pressure.[2] This heightened workload on the heart results in mechanical stress on the myocardium, initiating hypertrophic and fibrotic remodeling. Additionally, chronic inflammation in renal impairment elevates pro-inflammatory cytokines, which contribute to endothelial dysfunction and myocardial fibrosis.[3] Moreover, elevated parathyroid hormone (PTH) levels in renal impairment induce vascular calcification and disrupt calcium homeostasis, which further accentuate left ventricular hypertrophy and stiffness.[4]

On the other hand, vitamin D plays a pivotal role in both renoprotection and cardiovascular health, influencing several critical pathways that impact left ventricular remodeling. Beyond its well-established function in calcium and phosphate homeostasis, vitamin D exerts potent anti-inflammatory effects by reducing pro-inflammatory cytokines such as interleukin(IL)-6 and tumor necrosis factor-alpha (TNF-α).[2,5] In fact, in our previous meta-analysis circulating vitamin D was strongly associated with IL-6 and IL-8 levels.[6] Vitamin D also modulates the RAAS, inhibiting the overproduction of angiotensin II, which is implicated in vasoconstriction, sodium retention, and cardiac hypertrophy.[7] There is evidence that vitamin D modulates oxidative stress through the nuclear factor erythroid 2-related factor 2 pathway.[8] By attenuating the oxidative stress, vitamin D could prevent the oxidative damage to cardiomyocyte, and subsequently inhibit extracellular matrix deposition. Moreover, elevated PTH levels in VDD increase bone resorption and vascular calcification which eventually lead to left ventricular hypertrophy and stiffness.[9]

Despite its importance, the interaction between vitamin D levels and left ventricular remodeling in renal impairment remains underexplored. Most previous meta-analyses have predominantly focused on clinical outcomes, such as cardiovascular events or mortality, without thoroughly examining the underlying pathophysiological mechanisms.[10,11] The findings have the potential to refine clinical decision-making by highlighting the importance of vitamin D in managing cardiovascular risks associated with renal impairment.

2. AIM

The aim of the present meta-analysis is to evaluate the relationships between vitamin D and left ventricular remodeling in high-risk populations, such as those experiencing chronic kidney disease (CKD) or reduced renal function.

3. MATERIAL AND METHODS

3.1. Materials

We used PubMed, Scopus, Scilit, EuropePMC, and Web of Science to identify 4503, which were further screened down to 6 eligible studies (n = 3235 participants). R Studio (version 4.3.0) with 'meta' package was used in the quantitative analysis. The protocol and reporting of this systematic review and meta-analysis adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

3.2. Search strategy

A systematic review was conducted by searching PubMed, Scopus, Scilit, EuropePMC, and Web of Science from their inception to September 3, 2024, using predefined keywords and medical subject heading (MeSH) terms comprising 'left ventricular' and 'vitamin D'. Additionally, the reference lists of relevant studies were manually screened to identify further eligible articles. Rayyan.ai was utilized for managing records and removing duplicates.[12]

3.3. Eligibility criteria

To be included, studies must include individuals with impaired renal function, defined by a reported estimated glomerular filtration rate (eGFR) below a specified threshold (e.g., <60 mL/min/1.73 m^2).[13] We excluded studies with mixed populations unless data are reported separately for individuals with impaired renal function. Serum vitamin D levels, including 25-hydroxyvitamin D [25(OH)D] or 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], should be reported as the exposure. As for the outcomes, studies must report left ventricular mass (LVM), left ventricular mass index (LVMI), left ventricular end-diastolic diameter (LVEDD), left ventricular diastolic dysfunction (LVDD), left ventricular hypertrophy (LVH), intraventricular septum thickness (IVST), or other structural measures of the left ventricle, assessed using echocardiography or magnetic resonance imaging. Observational studies (cohort, case-control, and cross-sectional) were included. Studies were excluded if they did not report data on the primary outcome or were animal or laboratory-based experiments. Editorials, letters, reviews, case reports, case series, or conference abstracts were not included.

3.4. Screening and selection

Two authors (NG and MI) independently screened titles and abstracts and assessed assessed the full texts of potentially relevant studies. Disagreements were resolved through consensus or, when necessary, with input from a third reviewer (DDCHR). For unclear or missing outcome data, corresponding authors were contacted. Additionally, reference lists of included studies and prior reviews were examined to identify additional relevant studies.

3.5. Data extraction and quality appraisal

Two authors (NG and MI) independently extracted data and assessed the quality of the included studies. The extracted data included subjects' characteristics and left ventricular remodeling-related outcomes. Data was extracted into a Google spreadsheet, ensuring all relevant information was systematically captured. The key baseline variables extracted were age, gender, renal function parameters (CKD status and eGFR levels), and vitamin D levels. Mean and standard deviation (SD) were combined using Cochrane's recommended methods (https://www.statstodo.com/CombineMeansSDs.php). Quality of the studies was appraised using Newcastle-Ottawa Scale, with adjustments made for the cross-sectional studies.[14]

3.6. Data synthesis

Data analysis was performed using R Studio (v. 4.3.0). We synthesized the data using random-effects models with restricted maximum-likelihood estimates to account for heterogeneity among the included studies. For correlation analysis, pooled correlation coefficients (r) were calculated with 95% confidence intervals (CI). Standardized mean differences (SMD) with 95% CI were computed for continuous outcomes comparing vitamin D-deficient (VDD) and non-deficient (non-VDD) groups. A P-value of less than 0.05 was considered statistically significant for all outcomes. Higgins's I^2 test was used to assess heterogeneity. Significant heterogeneity was observed if I^2 was more than 50% and the P-value for heterogeneity (p-Het) was less than 0.1. The dose-response relationship between serum vitamin D levels and LVMI was analyzed using a restricted cubic spline model in a one-stage meta-analysis. The optimal maintenance level was identified as the point where LVMI reached a plateau on the fitted curve.

4. RESULTS

4.1. Results from the screening process

A total of 4503 records were identified through various databases, where 1481 of which were duplicates and removed. Titles and abstracts of the remaining 3022 records were screened for their relevance to the research question of this review, resulting in 109 records being subjected to full-text retrieval. We did not have access to 1 full-text. Following the evaluation of 108 full-text articles, we found that 76 studies did not exclusively recruit patients with impaired renal function. Thirteen studies did not report the serum vitamin D level. Ten other studies did not assign the correct exposure and control groups.[15–24] For example, despite grouping the subjects into normal and impaired renal function, we were uncertain whether the correlation was derived exclusively from the latter group or collectively from the two groups.[22] Two studies did not report sufficient data to draw conclusions on the relationship between serum vitamin D level and left ventricular remodeling.[25,26] One study was reported in a non-English language and was therefore excluded.[27] One study explored the effect of 25(OH)D on LVMI, but the eGFR did not fall within the eligible criteria.[28] Finally, we included six studies in the review.[9,29–33] The screening and selection process for this review is presented in Figure S1.

4.2. Characteristics of the included studies

A total of six studies conducted in the United States, Egypt, South Korea, Romania, and Brazil were included in the review, with their characteristics are presented in Table S1. The sample sizes varied from 40 to 1431 with mean ages ranging from 13.2 ± 3.6 to 61.9 ± 4.98 years. These studies reported eGFR values between 31.8 ± 14.3 mL/min/1.73 m^2 and 47.1 ± 17.3 mL/min/1.73 m^2. Three studies measured only 25(OH)D, while others also include 1,25$(OH)_2$D levels. In general, the included studies reported a significant association of VDD in poorer left ventricular geometry,[9,29–32] except for 1 study.[33]

4.3. Quality of the included studies

Six studies included in the analysis were evaluated for quality using NOS, where the results are presented in Table S2. The NOS scores ranged from 5 to 7. Four out of 6 included studies, received a perfect score of 7, signifying 'good' quality.[29–31] Two studies attained a score of 6, classifying the reporting quality as 'fair,' mainly due to methodological shortcomings in addressing biases.[9,33] One study earned a score of 5, categorizing it as 'poor' quality, indicating significant gaps in comparability and incomplete outcome assessments.[32]

4.4. Effect serum vitamin D level on cardiac left ventricular

Hypovitaminosis D was reported in three studies to be associated with reduced LVMI.[29–31] In 2 other studies, the serum level of vitamin D was inversely correlated with LVMI.[30,32] The association of hypovitaminosis D with LVMI was not observed in 1 study, and another study suggested that hypovitaminosis D was not associated with the change in IVST.[33] It is worth noting that 2 studies reported that the effect on LVMI was more pronounced for 1,25$(OH)_2$D as compared to 25(OH)D.[30,31] Intact PTH was found to be a significant modifying factor in the relationship between serum vitamin D and LVMI.[29,31] Moreover, though the effect of moderator was not reported therein, 1 study also found a strong correlation between PTH and LVMI.[32] In addition, a study also highlighted a significant contribution of eGFR in modifying the vitamin D level and LVMI association.[29] Nonetheless, a study suggested that the associations of serum vitamin D with LVMI, LVDD, and LVH were independent from other variables including PTH and eGFR.[30] Findings from this study cannot negate the modifying effect of PTH or eGFR because the multivariate analysis was performed along with 11 other variables, thus might have diluted the effect.[30]

Two studies reported sufficient data to synthesize the pooled estimate of the association between VDD and LVMI.[29,30] The forest plot of the pooled estimate is presented in Figure 1. We found that LVMI was higher in

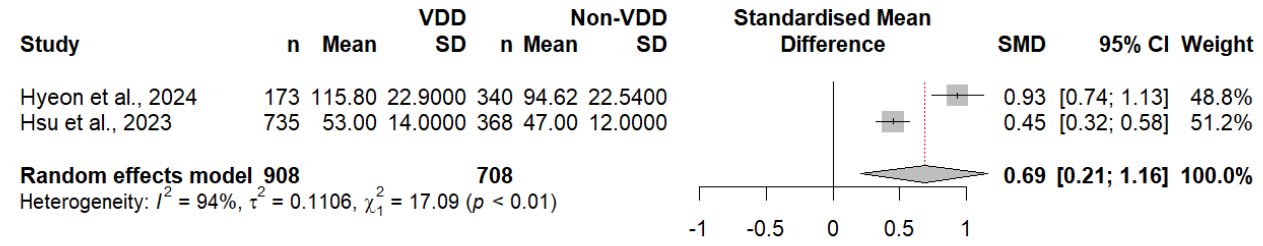

Figure 1. Forest plot for the association between serum vitamin D (25[OH]D) and LVMI. SMD = 0.62 (95%CI: 0.30 to 0.95); *p*-tot=0.01.

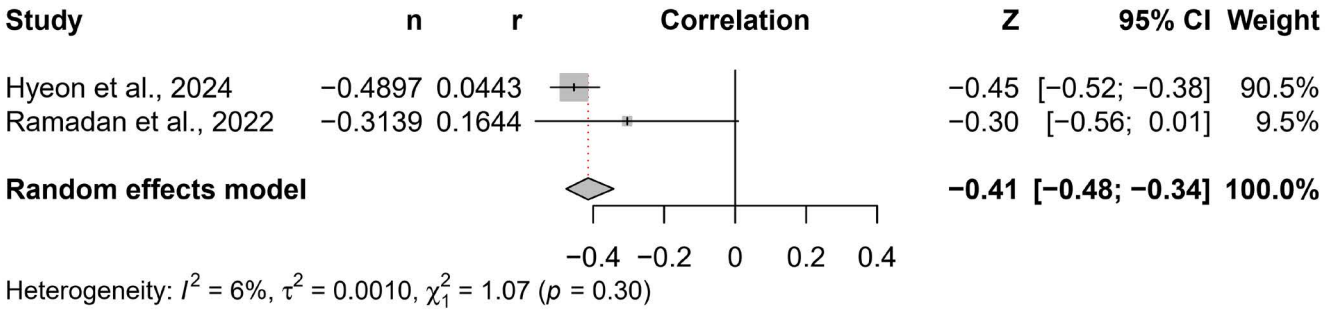

Figure 2. Forest plot for pooled correlation coefficient (*r*) on the correlation between serum vitamin D (25[OH]D) and LVMI. Sum-*r* =-0.414 (95%CI: –0.48 to –0.34); *p*-tot < 0.001.

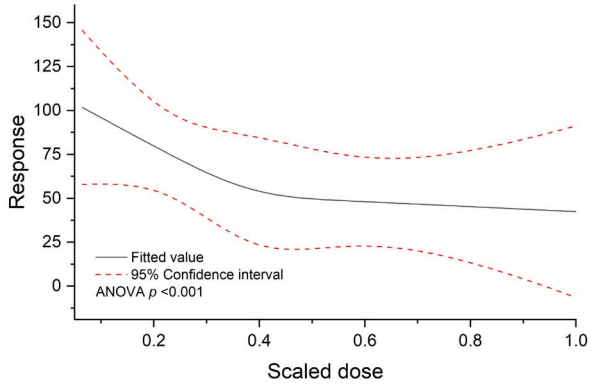

Figure 3. Dose-response plot for vitamin D level and LVMI forming a J-shaped pattern.

individual with hypovitaminosis D than in those without (*p*-tot=0.005), with SMD of 0.69 (95% CI: 0.21–1.16). An additional quantitative analysis was performed to estimate the pooled correlation between serum vitamin D levels and LVMI. The pooled analysis was carried out on two studies,[30,32] where the forest plot is presented in Figure 2. Pooled correlation coefficient (*r*) revealed a negative correlation between serum vitamin D level and LVMI (r = –0.414 [95% CI: –0.48 to –0.34]) with a statistical significance (*p*-tot < 0.001). Heterogeneity was found to be significant in the pooled association analysis (I^2=89%; *p*-Het<0.001), but not in the correlation pooled analysis (I^2=6%; *p*-Het=0.30).

4.5. Dose-response effect

For the dose-response analysis, we included the data from three studies.[29–31] Circulating vitamin D showed a J-shaped correlation with the LVMI reduction (Figure 3). The correlation between the two variables was significant with p-value less than 0.001. The optimal serum vitamin D level to maintain was found to be more than 46.26 ng/mL (Figure 3).

4.6. Publication bias

Due to the insufficient number of studies (n < 10), the funnel plot analysis was not carried out because the analysis tends to be misleading. This practice is in line with the recommendations from previous meta-analyses.[34,35]

5. DISCUSSION

This is the first systematic review and meta-analysis that emphasizes the relationship between vitamin D levels and left ventricular remodeling, LVMI, in patients with renal impairment. We found that LVMI was significantly higher in patients with VDD than in those without VDD. This finding is further supported by the correlation analysis performed, showing a negative correlation of –0.41 between vitamin D and left ventricular remodeling in patients with renal dysfunction. These results are also consistent with existing original research data.[21,26] Additionally, our findings align with a recent meta-analysis that evaluated the relationship between vitamin D and the incidence of ventricular remodeling in patients with heart failure, specifically in terms of reducing left ventricular end-diastolic diameter (LVEDD) and improving left ventricular ejection fraction (LVEF).[36]

Left ventricular remodeling is understood as an active and maladaptive process involving functional and structural myocardial changes as compensation for hemodynamic

conditions.[37,38] In patients with impaired renal function, left ventricular remodeling is driven by several underlying mechanisms.[39] Hemodynamic changes accompanying renal dysfunction cause mechanical stress on the myocardium, initiating the process of left ventricular remodeling.[37] In addition, impaired renal excretion of sodium results in fluid retention with increased blood volume, a factor forcing the heart to work harder.[40,41] Increased work by the heart then promotes left ventricular remodeling, characterized by an increased LVMI and LVEDD.[2] Inflammation and oxidative stress also affect the elevation of pro-inflammatory cytokines and free radicals, which can damage the vascular endothelium, promote myocardial fibrosis, and accelerate myocardial remodeling.[42] This is also aggravated by activation of the RAAS, which exacerbates vasoconstriction, further aggravating sodium and water retention, and myocardial hypertrophy, all of which support the progression of left ventricular remodeling.[1] Elevated PTH levels also have a role in increased bone resorption and vascular calcification, which also play a role in myocardial remodeling and vasculopathy.[43]

Vitamin D is thought to play a role in inhibiting left ventricular remodeling in patients with renal impairment. Vitamin D plays an important role in regulating the body's calcium and phosphate balance.[44] Recently, the evidence of this interplay is strengthened by proteomics or metabolomics-based approaches.[45] VDD can increase PTH levels, which in turn worsen cardiovascular dysfunction and accelerate the process of left ventricular remodeling.[46] Furthermore, Vitamin D has anti-inflammatory effects that can reduce pro-inflammatory cytokine levels.[47,48] In the RAAS system, vitamin D can inhibit the process of vasoconstriction and hypertension, thereby slowing left ventricular remodeling.[46,48] In a review, vitamin D was proposed as an antihypertensive supplement due to its efficacy in improving RAAS activity and blood pressures along with the administration of antihypertensive drugs.[49] Vitamin D also plays a role in improving vascular endothelial function and reducing oxidative stress. Studies have shown that vitamin D has an effect that inhibits myocardial hypertrophy through better calcium regulation mechanisms and reduced fibrosis.[5,6,50] A study using a mouse model with a cardiomyocyte-specific vitamin D receptor knockout strain further supported the role of vitamin D signaling in regulating pro-inflammatory and pro-fibrotic genes.[51] Findings from the present study along with other previous reports support the supplementation of vitamin D to alleviate left ventricular remodeling among individuals with renal impairment.[46,52]

One of the strengths of this study is that it is the first to evaluate the relationship between vitamin D levels and LVMI. Additionally, it provides a comprehensive explanation of the pathophysiological mechanisms by which vitamin D influences LVMI and the process of left ventricular remodeling. However, there are several limitations to consider. First, the study is constrained by a language barrier, as it only includes studies published in English. Furthermore, some databases were not utilized in the record search, which could have introduced selection bias. The outcomes of the included studies were also limited, with many using the same parameters, which reduces the diversity of the findings. Finally, the study was affected by high heterogeneity and the generally poor quality of the included studies, which may have impacted the robustness of the conclusions.

6. CONCLUSIONS

(1) Serum vitamin D is associated with the left ventricular remodeling among patients with impaired renal function, though some relationship is not consistent across studies.
(2) Quantitative analysis suggests that circulating vitamin D plays a critical role in left ventricular remodeling, as indicated by the change in LVMI.
(3) The optimum maintenance level for circulating vitamin D is 46.26 ng/mL.
(4) Considering the potentially significant modifying effect of intact PTH on this relationship, future studies should include adjustments or conduct targeted analyses to confirm it.

Conflict of interest
None declared.

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