



Effect of Vitamin D Supplementation on Postoperative Outcomes in Cardiac Surgery Patients: A Systematic Review

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Abstract

Background Vitamin D deficiency is a very common occurrence in cardiac patients. It has been proved that cardiac surgery and cardiopulmonary bypass accelerate the deficiency further. The postoperative outcomes of patients deteriorate in the presence of vitamin D deficiency. Perioperative supplementation of vitamin D is the only solution to the problem. Hence, the present systematic review was conducted to derive the efficacy and safety of vitamin D supplementation on postoperative outcomes in cardiac surgery patients.

Method Publications over duration of last 10 years was searched from different database and web sites. The data from full-text research articles were analyzed for the effect on different postoperative outcomes and side effects.

Result Eight randomized control trials were retrieved on the effect of perioperative vitamin D supplementation in cardiac surgery patients and their postoperative outcomes. Six articles (75%) were found to be in favor of improvement in postoperative outcome. Two articles (25%) did not find any difference of outcome between the control and treatment group. All the studies observed the restoration of vitamin D to normal and no adverse effects from supplementation.

Conclusion Perioperative vitamin D supplementation improves the postoperative outcomes after cardiac surgery. It is effective and safe to supplement vitamin D in cardiac surgery patients.

Keywords

- ▶ cardiac surgery
- ▶ postoperative outcome
- ▶ systematic review
- ▶ vitamin D supplementation
- ▶ vitamin D deficiency

Introduction

Vitamin D deficiency (VDD) is highly prevalent worldwide due to the environmental pollution, minimal exposure to sunlight, dietary deficiency, and lifestyle changes of man-

kind.¹ It is detected in all the age groups. Commonly VDD has been associated with infection, respiratory illness, cardiovascular diseases, cancer, preeclampsia, dental caries, and neurological diseases.¹ Greater proportions of people with cardiovascular disease have low vitamin D level compared

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with general populations. Patients undergoing cardiac surgery are at risk of arrhythmia, myocardial ischemia, ventricular dysfunction, bleeding, and infections. The risks may be aggravated by VDD.² Many patients have low vitamin D levels before and after open heart surgery, but those levels can be restored to normal with supplementation with vitamin D.³ Vitamin D supplementations taken by patients with chronic heart failure are associated with improved cardiac function.⁴ Low blood levels of vitamin D have increased risks of heart disease like stroke, hypertension, and aortic dissection that create problems in postoperative outcome. Low vitamin D level may be a potential risk to respiratory complications in intensive care unit (ICU).⁵ Low levels of vitamin D have been linked to high blood pressure. The postoperative ICU stay and complications are higher in pediatric cardiac surgery patients with VDD.³

However, a few recent articles have not detected any difference in postoperative outcome of VDD patients related to atrial fibrillation and other parameters,⁶ In the hospital setup, perioperative vitamin D therapy is the way forward to normalize the serum level. Hence, the outcome of the therapy needs to be systematically reviewed for clinical recommendation.

In the present systemic review, all the available literatures related to impact of vitamin D therapy on postoperative outcomes in cardiovascular surgical patients over duration of 10 years are analyzed. The efficacy, safety, and public health impact of vitamin D therapy in cardiac surgical patients on postoperative period were assessed.

Methodology

Inclusion criteria: Only original articles were included. The original papers were from clinical trials, observational, cross-sectional, and cohort studies. The studies were both prospective and retrospective. Studies with all age groups and all types of cardiac surgery were included. The full-text articles with complete data on postoperative outcome were chosen.

Exclusion criteria: Review, systematic review, meta-analysis, case report, letter to editor, editorial papers, and stand-alone abstract were excluded. Papers of the patients with emergency surgeries, redo surgeries, transplantation, New York Heart Association class 4, and multisystem illness undergoing cardiac surgery were also excluded.

Publications search method: Published full-text studies were searched in PubMed, Embase, Google Scholar, and Cochrane database with the keywords of vitamin D supplementation, VDD, postoperative cardiac outcome, cardiac surgery, cardiac anesthesia, perioperative period, ICU, and hospital stay for 10 years during year 2012 to 2022. One independent person was involved in searching the literatures. The details of literature search are mentioned in **Fig. 1**.

Data analysis: The data collected from the articles were processed and evaluated to conclude the study. The articles related to the VDD in cardiac surgery patients and the impacts of vitamin D supplementation and therapy on postoperative outcomes were assessed.

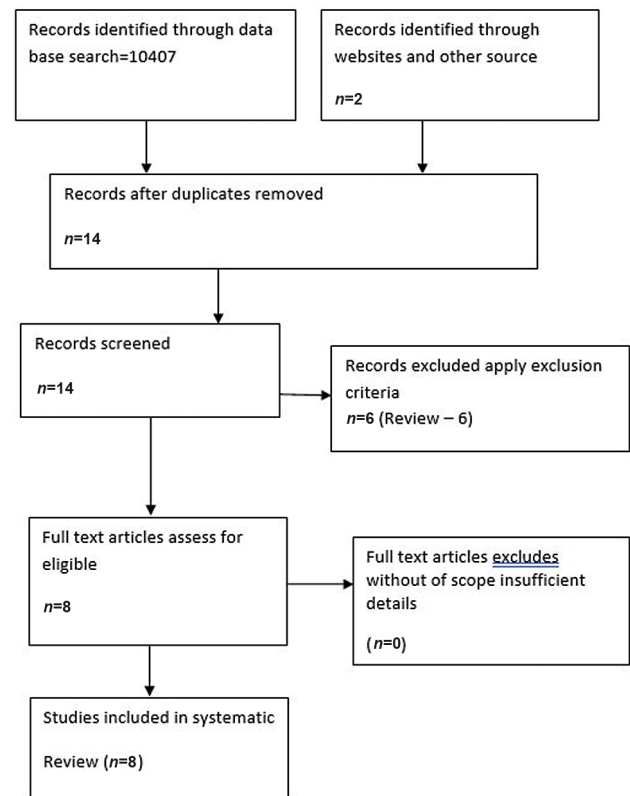


Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the systemic review procedure.

Result

Total 10,407 articles were retrieved. Out of which eight full-text original studies were found suitable for the systemic review and critical analysis after applying the study protocol and exclusion criteria (**Fig. 1**). All the eight articles were randomized control trials (RCT). The authors' name, year of publication, study type, sample size, and outcomes are mentioned in **Table 1**.

Most of the studies reported a significant fall in vitamin D level in the patients during and after cardiac surgery. Valve and congenital heart surgery patients had maximum fall in vitamin D level. All the RCTs detected restoration of vitamin D level back to normal value after supplementation of vitamin D. Six studies (75%) showed more than or equal to 1 parameter improvement in postoperative outcome after cardiac surgery because of vitamin D supplementation (**Table 2**). Two studies (25%) reported no significant difference on postoperative outcomes.^{7,8} Three studies (37.5%) detected significant reduction in postoperative atrial fibrillation (POAF) by vitamin D therapy.^{9,10} Two studies (25%) detected significant reduction in inotrope requirement postoperatively compared with control group.¹¹ One study (12.5%) observed marked reduction in duration of ICU and hospital stay in vitamin D supplementation group compared with control.⁹ One study (12.5%) detected small reduction of interleukin-10 in vitamin D supplementation group compared with placebo without any difference in postoperative acute kidney injury.¹² One study (12.5%) observed anti-

Table 1 Different Studies on Vitamin D with sample size and their outcomes

Authors reference	Study type	Sample size	Outcome of the study
Cerit et al ¹⁹ 2018	RCT	136 CABG	The occurrence of POAF was not significantly different among treatment and control groups in patients with vitamin D insufficiency (31 vs. 33%, $p = 0.538$); however, there was a significant difference between the two groups regarding POAF in patients with vitamin D deficiency (18 vs. 29%, $p = 0.02$)
Barker et al ⁷ 2021	RCT	150 Adult cardiac surgery	Perioperative vitamin D supplementation protects against the immediate decrease in plasma 25(OH)D induced by open-heart surgery. In patient outcomes and serious adverse events did not differ significantly between vitamin D and placebo-treated groups postoperatively and after 6 months. However, there tended (both $p = 0.06$) to be fewer heart failure hospitalizations, and other serious adverse events (i.e., atrial fibrillation, pacemaker, cardiomyopathy) in the vitamin D-treated group
Jelveh-Moghaddam et al ¹¹ 2020	RCT	318 CHD	A significant increase in post-CPB levels of IL-10 and IL-6 in all groups ($p < 0.002$) regardless of vitamin D treatment status; however, no significant difference was seen in levels of IL-1 and TNF- α . Groups B (abnormal vitamin D levels, vitamin D treatment up to normal serum vitamin D levels before surgery) had more patients with critical levels of VIS compared with groups A (abnormal vitamin D levels, no vitamin D treatment) and C (normal baseline vitamin D levels, no supplemental vitamin D treatment) ($p < 0.002$). Furthermore, no differences in hemodynamic and metabolic parameters were observed. A significant reduction in the amounts of inotropes was used in vitamin D deficient patients who were treated with vitamin D before the operation
Talasaz et al ⁹ 2022	RCT	196 CABG	The occurrence of POAF was significantly lower in group B as compared with group A (9.68 vs. 20.39%, $p = 0.038$). The length of ICU stay and hospital stay was reduced in group B patients (2.21 vs. 3.86 days, $p < 0.001$ and 7.40 vs. 9.58 days, $p = 0.022$, respectively). The study demonstrated that vitamin D supplementation reduces the incidence of POAF, duration of ICU, and hospital stay following CABG surgery
Kara and Yasim ¹⁰ 2019	RCT	116 CABG	The ratio of POAF occurrence found in the treatment and control groups were 12.07 and 27.59%, respectively. Vitamin D treatment was found to reduce the risk of POAF development by 0.24 times ($p = 0.034$). In this study with sufficient sample size, preoperative short-term high-dose vitamin D supplementation was found to be significantly preventive to the occurrence of POAF in patients with vitamin D insufficiency and deficiency who underwent CABG surgery
Sahu et al ⁸ 2019	RCT	60 CHD	Prevalence of severe vitamin D deficiency was 93.1%. When compared with the control group, study group showed higher serum vitamin D levels in the immediate preoperative period ($p = 0.001$), postoperative period following CPB ($p = 0.012$), and on the first postoperative day ($p = 0.003$). No statistically significant difference was observed in postoperative mechanical ventilation ($p = 0.35$), ICU stay ($p = 0.15$), and inotropic duration ($p = 0.19$) Children with TOF are highly deficient of vitamin D, its level falls further after CPB, and supplementing vitamin D preoperatively does not influence postoperative recovery pattern. Supplementation of vitamin D as "stoss therapy" was useful in raising serum levels before and after cardiac surgery
McNally et al ²⁵ 2020	RCT	41 CHD	The high-dose group had higher 25-hydroxyvitamin D concentrations both intraoperatively (mean difference + 25.9 nmol/L; 95% CI: 8.3–43.5) and postoperatively (mean difference + 17.2 nmol/L; 95% CI: 5.5–29.0). Fewer participants receiving high-dose supplementation had postoperative serum 25-hydroxyvitamin D concentrations under 50 nmol/L, compared with usual care (RR: 0.31, 95% CI: 0.11–0.87). Postoperative vitamin D status was associated with the treatment arm and the number of doses

(Continued)

Table 1 (Continued)

Authors reference	Study type	Sample size	Outcome of the study
			received. There were no cases of hypercalcemia, and no significant adverse events related to vitamin D Preoperative daily high-dose supplementation improved vitamin D status preoperatively and at time of pediatric ICU admission. Less ARF ; < 0.04, less total mechanical ventilation; <0.03
Eslami et al ¹² 2021	RCT	111 CABG	There was no difference in the incidence of postoperative AKI between the groups. Both of the urinary levels of IL-18 and kidney injury molecule-1 were significantly increased after the operation ($p < 0.001$, for both). Also, the serum level of IL-10 was increased after 3 days of vitamin D supplementation ($p = 0.001$). In comparison with the control group, it remained on a higher level after the operation ($p < 0.001$) and the next day ($p = 0.03$). In conclusion, vitamin D pretreatment was unable to impose any changes in the incidence of AKI and the urinary level of renal biomarkers. However, high-dose administration of vitamin D may improve the anti-inflammatory state before and after the operation. Further studies are needed to assess the renoprotective effect of vitamin D on coronary surgery patients

Abbreviations: AKI, acute kidney injury; ARF, acute respiratory failure; CABG, coronary artery bypass grafting; CHD, congenital heart disease; CI, confidence interval; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IL-10, interleukin-10; LVAD, left ventricular assist device; MI, myocardial infarction; POAF, postoperative atrial fibrillation; RCT, randomized control trial; RR, relative risk; TOF, tetralogy of Fallot.

Table 2 Improvement in postoperative outcomes by vitamin D treatment from studies ($n = 8$)

Parameters	No. of RCT	Percentage (%)
≥ 1 outcome improvement	6	75
POAF	3	37.5
Low VIS	1	12.5
Short duration ICU and hospital stay	1	12.5
Anti-inflammatory effect	1	12.5
Reduction in IL-10 level	1	12.5
Less adverse cardiac events	1	12.5

Abbreviations: ICU, intensive care unit; IL-10, interleukin-10; POAF, postoperative atrial fibrillation; RCT, randomized control trial; VIS, vasoactive inotropic score.

inflammatory effect with high-dose supplementation but without any difference in prevention of acute kidney injury both in control and treatment group.¹² There was an insignificant lesser incidence of adverse cardiac events like pacemaker insertion and cardiomyopathy, POAF, and postoperative heart failure with vitamin D supplementation in one RCT.⁷ All the eight RCT did not found any adverse effects with vitamin D supplementation and detected to be safe in all patients even with high doses.

Discussion

The systemic review of the literatures over past 10 years from the peer reviewed journals with 8 RCTs detected that vitamin D supplementation in perioperative period helped to restore the VDD in all patients. The normal level of vitamin D is important to balance the calcium and other vitamin D-

dependent activity in cardiac patients after surgery, which was achieved by perioperative administration of vitamin D. Improvement in postoperative outcomes from vitamin D treatment in the form of reduction in POAF, lower requirement of inotropes, reduction in duration of ICU, and hospital stay and less cardiac adverse events were detected by six studies. Two studies did not find any significant difference in postoperative outcomes. Supplementation of vitamin D was found to be safe and without any adverse side effects as proved by all RCT.

Vitamin D is not only a fat-soluble vitamin but also has prohormone property and has pleiotropic action.¹³ Commonly known function of vitamin D is for calcium and phosphorus absorption from intestine and kidney with the help of parathormone (PTH).^{13,14} Hence, it is responsible for bone and muscle growth. It is also responsible for genetic regulation of cardiac myocytes, vascular endothelium,

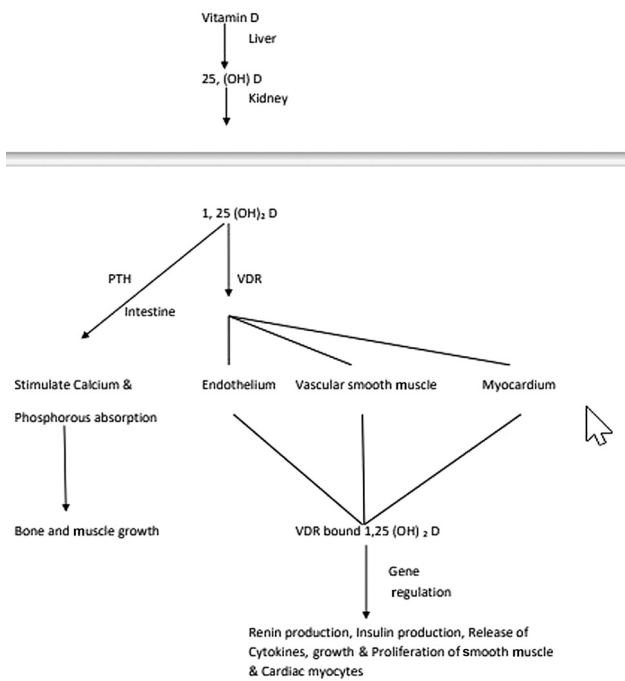


Fig. 2 Mechanism of function of vitamin D (PTH, parathormone; VDR, vitamin D receptor).

insulin secretion, inflammation, and cellular functions by binding to vitamin D receptors (→**Fig. 2**). Vitamin D is classified into five types. The most important are D2 or ergocalciferol and D3 or cholecalciferol. These two forms are produced by ultraviolet light irradiation of calciferol in plant foods to D2 and exposure of epidermis (skin) of human to sun light for D3. Vitamin D is converted to 25, hydroxyl vitamin D (25(OH)D) in liver. 25(OH)D is used to measure vitamin D level and help to detect the deficiency. A value of 25(OH)D less than 20nL/mL is diagnosed as VDD. 25(OH)D is converted to 1,25(OH)2D in kidney. 1,25(OH)2D is the active form for performing all actions but cannot be measured to know the level of vitamin D.

Deficiency of vitamin D is more common after cardiac surgery.^{15,16} Valve surgery patients compared with other adult cardiac surgical cases had significant fall in vitamin D both intra- and postoperative period.¹⁵ The fall is more pronounced in children compared with adult.¹⁷ TekeliKunt et al¹⁸ detected more fall in females compared with male.

POAF: The present systemic review detected three RCTs showing reduction in POAF by vitamin D supplementation.^{9,10,19} However, Sahu et al⁸ did not find any difference. Conflicting results were seen by a prospective cohort study by Ohlrogge et al for POAF with VDD.⁶ Many of the studies commented on VDD and POAF, though they have not conducted the studies with supplementation of vitamin D.

Inotropes requirement: Jelveh-Moghaddam et al¹¹ reported a significant reduction in inotrope requirement in patients after supplementation of vitamin D. The vasoactive inotropic score (VIS) was less compared with placebo treatment. It can be proved by the logic that VDD patients are more dependent on high-dose inotropes, more incidences of

vasoplegia, and high VIS.^{20,21} However, Sahu et al⁸ observed no difference in days of inotropes requirement by vitamin D supplementation.

Major adverse cardiac and cerebrovascular events (MACCE) and kidney function: In this systematic review, Barker et al⁷ reported less MACCE in vitamin D-treated patients. This is supported by Zittermann et al who detected 9.4% incidence of stroke, myocardial infarction, low cardiac output syndrome in postoperative patients of cardiac surgery with VDD compared with normal level.²² None of the RCTs in this review shown any improvement in kidney function by vitamin D therapy. However, in literature some of the studies reported postoperative deterioration of renal function in the presence of VDD.^{23,24}

ICU and hospital stay: Talasaz et al⁹ detected reduced ICU and hospital stay with vitamin D supplementation. This is justified by the study by Ney et al who detected higher incidence of respiratory failure, organ dysfunction, infection, high PTH, neuronal injury, longer ICU, and hospital stay in cardiac surgical patients with low levels of 1,25(OH)2D.²³ However, in another RCT by Sahu et al⁸ detected no difference in duration of mechanical ventilation and ICU stay between supplementation and control group.

The present systematic review recommends the perioperative supplementation of vitamin D in cardiac patients. This is supported by six out of eight RCTs. The supplementation will restore the normal level of vitamin D in VDD cardiac surgery patients and it is without any side effects.

Limitations

The numbers of prospective studies were only eight in number. More RCTs with large sample size will provide clarity on the effects of routine perioperative vitamin D supplementation.

Conclusion

To conclude, VDD is very common after cardiac surgery. Vitamin D supplementation will restore vitamin D level to normal in all patients. The systematic review detected one or more improvement in postoperative outcomes after cardiac surgery from 75% studies. Vitamin D supplementation was found to be safe in clinical practice even with high-dose regime. Further studies, followed by meta-analysis and systematic reviews, will provide more knowledge on the perioperative use of vitamin D supplementation in cardiac surgery patients.

Funding

None.

Conflict of Interest

None declared.

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