

Vitamin D Supplementation in the Treatment of Chronic Heart Failure: A Meta-analysis of Randomized Controlled Trials

Address for correspondence:
Jian-Chang Chen, MD
Department of Cardiology
The Second Affiliated Hospital of
Soochow University
No. 1055 Sanxiang Road
Suzhou, Jiangsu 215004, China
chenjc@medmail.com.cn

Wei-Long Jiang, MD; Hai-Bo Gu, MD; Yu-Feng Zhang, MD; Qing-Qing Xia, MD;
Jia Qi, MD; Jian-Chang Chen, MD, PhD

Department of Respiration (Jiang, Zhang, Xia), Jiangyin Hospital of Traditional Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Jiangyin, China; Department of Cardiology (Gu, Chen), The Second Affiliated Hospital of Soochow University, Suzhou, China; Department of Pharmacy (Qi), Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China

ABSTRACT

Background: In recent years, there has been growing evidence that vitamin D deficiency is associated with the development and progression of chronic heart failure (CHF).

Hypothesis: Additional supplementation of vitamin D may have protective effects in patients with CHF.

Methods: We searched PubMed, Embase, and Cochrane databases through June 2015 and included 7 randomized controlled trials that investigated the effects of vitamin D on cardiovascular outcomes in patients with CHF. Then, we performed a meta-analysis of clinical trials to confirm whether vitamin D supplementation is beneficial in CHF patients. The weighted mean difference (WMD) and 95% confidence interval (CI) were calculated using fixed- or random-effects models.

Results: Our pooled results indicated that additional supplementation of vitamin D was not superior to conventional treatment in terms of left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, and 6-minute walk distance. Moreover, vitamin D supplementation was associated with significant decreases in the levels of tumor necrosis factor- α (WMD: -2.42 pg/mL, 95% CI: -4.26 to -0.57 , $P < 0.05$), C-reactive protein (WMD: -0.72 mg/L, 95% CI: -1.42 to -0.02 , $P < 0.05$), and parathyroid hormone (WMD: -13.44 pg/mL, 95% CI: -21.22 to -5.67 , $P < 0.05$).

Conclusions: Vitamin D supplementation may decrease serum levels of parathyroid hormone and inflammatory mediators in CHF patients, whereas it has no beneficial effects on improvement of left ventricular function and exercise tolerance.

Introduction

Chronic heart failure (CHF) is a complex clinical syndrome that arises secondary to inherited or acquired abnormalities of cardiac structure and/or function that impair myocardial systolic and diastolic function. In the United States, CHF affects approximately 4.7 million people, with nearly 550 000 incident cases of CHF diagnosed annually.¹ The medical treatment of CHF has made remarkable progress in the past few decades. Clinical applications of β -receptor blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone receptor antagonists

have significantly reduced cardiovascular events and improved prognosis in patients with CHF.² However, CHF remains a leading cause of morbidity and mortality throughout the world.

In recent years, epidemiological studies have demonstrated that vitamin D deficiency is associated with increased incidence of hypertension, myocardial infarction, and stroke, as well as chronic kidney disease and type 2 diabetes mellitus.^{3–8} Low vitamin D levels have been found to activate the renin-angiotensin-aldosterone system, induce inflammatory response, and cause endothelial dysfunction.^{9–11} In patients with CHF, vitamin D deficiency is prevalent and is associated with a poor prognosis.^{12–14} Over the past few years, several randomized controlled trials (RCTs) have been carried out to evaluate the effects of vitamin D supplementation in CHF patients.^{15–21} These trials investigated clinical symptoms, cardiac function, quality of life, physical performance, cardiovascular events, and inflammation, comparing vitamin D with placebo. However, some results of clinical studies are inconsistent and the conclusions are

Wei-Long Jiang, MD, and Hai-Bo Gu, MD, contributed equally to this work.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Additional Supporting Information may be found in the online version of this article.

Table 1. Study Characteristics

Study	No. of Patients (Vitamin D/ Control)	Vitamin D Dose	Follow-up Duration	Inclusion Criteria	Endpoints
Dalbeni et al, 2014	36 (18/18)	4000 IU/d	6 mo	Age >40 y, chronic HF, LVEF <55%, NYHA class > II, 25(OH)D <30 ng/mL	LVEF, echocardiographic parameters, NYHA class, NT-proBNP, PTH, renin, aldosterone
Boxer et al, 2014	64 (31/33)	50 000 IU/wk	6 mo	Age ≥50 y, NYHA class II–IV, 25(OH)D <37.5 ng/mL	LVEF, echocardiographic parameters, PTH, NT-proBNP, hsCRP, renin, aldosterone
Schroten et al, 2013	101 (50/51)	2000 IU/d	6 wk	Age ≥18 y, chronic HF, LVEF <45%	Plasma renin activity and concentration, NT-proBNP, fibrosis markers, PTH
Boxer et al, 2013	64 (31/33)	50 000 IU/wk	6 mo	Age ≥50 y, NYHA class II–IV, 25(OH)D <37.5 ng/mL	Peak VO ₂ , exercise duration, 6MWD
Shedeed et al, 2012	80 (42/38)	1000 IU/d	12 wk	Infants with chronic HF, LVEF <40%	LVEF, echocardiographic parameters, TNF-α, IL-10, PTH
Witham et al, 2010	105 (53/52)	100 000 IU at baseline and 10 wk	20 wk	Age ≥70 y, chronic HF, LV systolic dysfunction, NYHA class II–III, 25(OH)D <20 ng/mL	6MWD, renin, aldosterone, BNP, TNF-α
Schleithoff et al, 2006	123 (61/62)	2000 IU/d	9 mo	Chronic HF, NYHA class II–IV	Survival rates, LVEF, NT-proBNP, TNF-α, CRP, IL-10, PTH

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 6MWD, 6-minute walk distance; BNP, B-type natriuretic peptide; CRP, C-reactive protein; HF, heart failure; IL-10, interleukin-10; IU, international units; LV, left ventricular; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PTH, parathyroid hormone; TNF-α, tumor necrosis factor-α; VO₂, oxygen volume.

Table 2. Patient Characteristics

Study	No. of Patients (Vitamin D/ Control)	Age, y	Male Sex, n	Ischemic Cause, n	HTN, n	LVEF, %	25(OH)D, ng/mL	NYHA Class
Dalbeni et al, 2014	36 (18/18)	74.2/74.3	12/10	16/17	17/18	42.3/44.3	17.2/17.6	II–IV
Boxer et al, 2014	64 (31/33)	65.8/66	15/18	8/10	26/28	39.2/36.1	19.1/17.8	II–III
Schroten et al, 2013	101 (50/51)	64/63.5	48/46	35/36	NA	35.7/33.6	27.6/28.8	II–III
Boxer et al, 2013	64 (31/33)	65.8/66	15/18	8/10	26/28	39.2/36.1	19.1/17.8	II–III
Shedeed et al, 2012	80 (42/38)	0.86/0.93	27/22	NA	NA	36.4/37.2	NA	NA
Witham et al, 2010	105 (53/52)	78.8/80.6	34/35	33/34	33/33	33/29	12.3/14.2	II–III
Schleithoff et al, 2006	123 (61/62)	57/54	52/50	47/40	38/32	31/33	14.4/15.3	II–IV

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HTN, hypertension; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association.

Data are expressed as vitamin D/control.

contradictory. We therefore performed a meta-analysis of RCTs to confirm whether vitamin D supplementation is beneficial in patients with CHF.

Methods

Search Strategy

We performed an electronic literature search of PubMed, Embase, and Cochrane databases through June 2015, using the terms vitamin D, cholecalciferol, 1,25-dihydroxy vitamin D₃, 25-hydroxyvitamin D, calcitriol, heart failure, cardiac failure, cardiac dysfunction, cardiac insufficiency,

cardiomyopathy, and ventricular dysfunction. Sensitive filters identified clinical trial or RCT in the PubMed database and the Embase database. The search was limited to human subjects, with no restriction for language.

Study Selection

Clinical trials reporting ≥1 of the outcomes were considered eligible. These outcomes included left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, 6-minute walk distance (6MWD), N-terminal pro-B-type natriuretic peptide (NT-proBNP), tumor necrosis factor-α

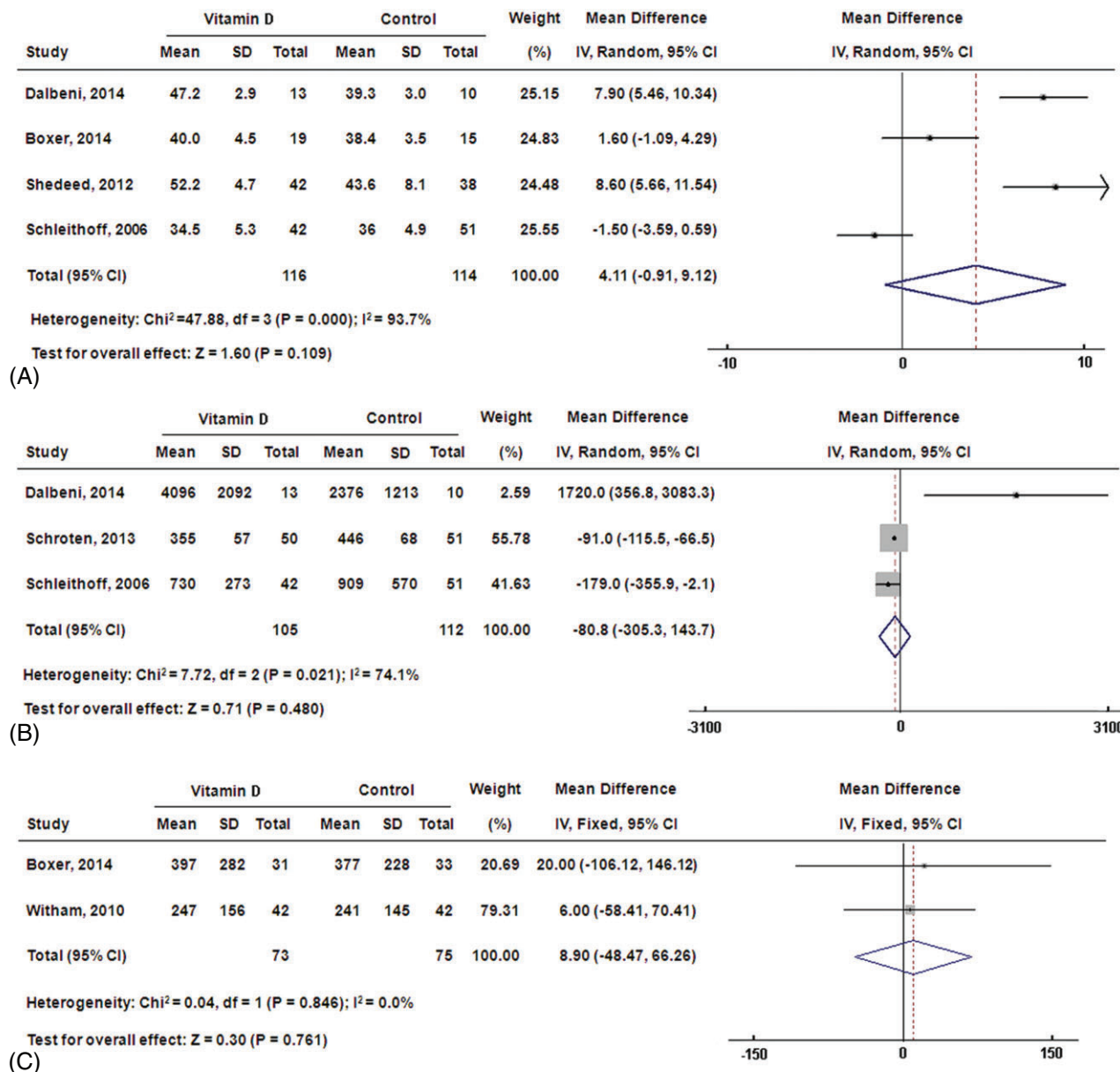


Figure 1. Forest plots for (A) LVEF, (B) NT-proBNP, and (C) 6MWD. Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; df, degrees of freedom; IV, inverse variance; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

(TNF- α), C-reactive protein (CRP), interleukin-10 (IL-10), parathyroid hormone (PTH), and renin.

Data Extraction and Quality Assessment

Two investigators independently reviewed all potentially eligible studies using predefined eligibility criteria and extracted data from the included RCTs. We collected details on study characteristics, patient characteristics, inclusion criteria, intervention strategies, duration of follow-up, and clinical outcomes including LVEF, NYHA class, 6MWD, NT-proBNP, TNF- α , CRP, IL-10, PTH, and renin. The quality of enrolled RCTs was evaluated by the Jadad scale, and a numerical score between 0 and 5 was assigned as a measure of study design.

Statistical Analysis

Continuous variables were analyzed using weighted mean differences (WMD) and 95% confidence intervals (CI). The heterogeneity of results across trials was assessed using the χ^2 -based Q test. A P value >0.1 for the Q test indicated a lack of heterogeneity among the studies. Thus, the pooled effect was calculated using fixed-effects model. Otherwise, a random-effects model was used in case of significant heterogeneity across studies. A sensitivity analysis was performed to evaluate the influence of each individual study on overall estimates by sequential removal of individual studies. Potential publication bias was assessed by the Begg and Egger test. All statistical analyses were conducted using RevMan version 5.0 (the Nordic Cochrane Centre, the

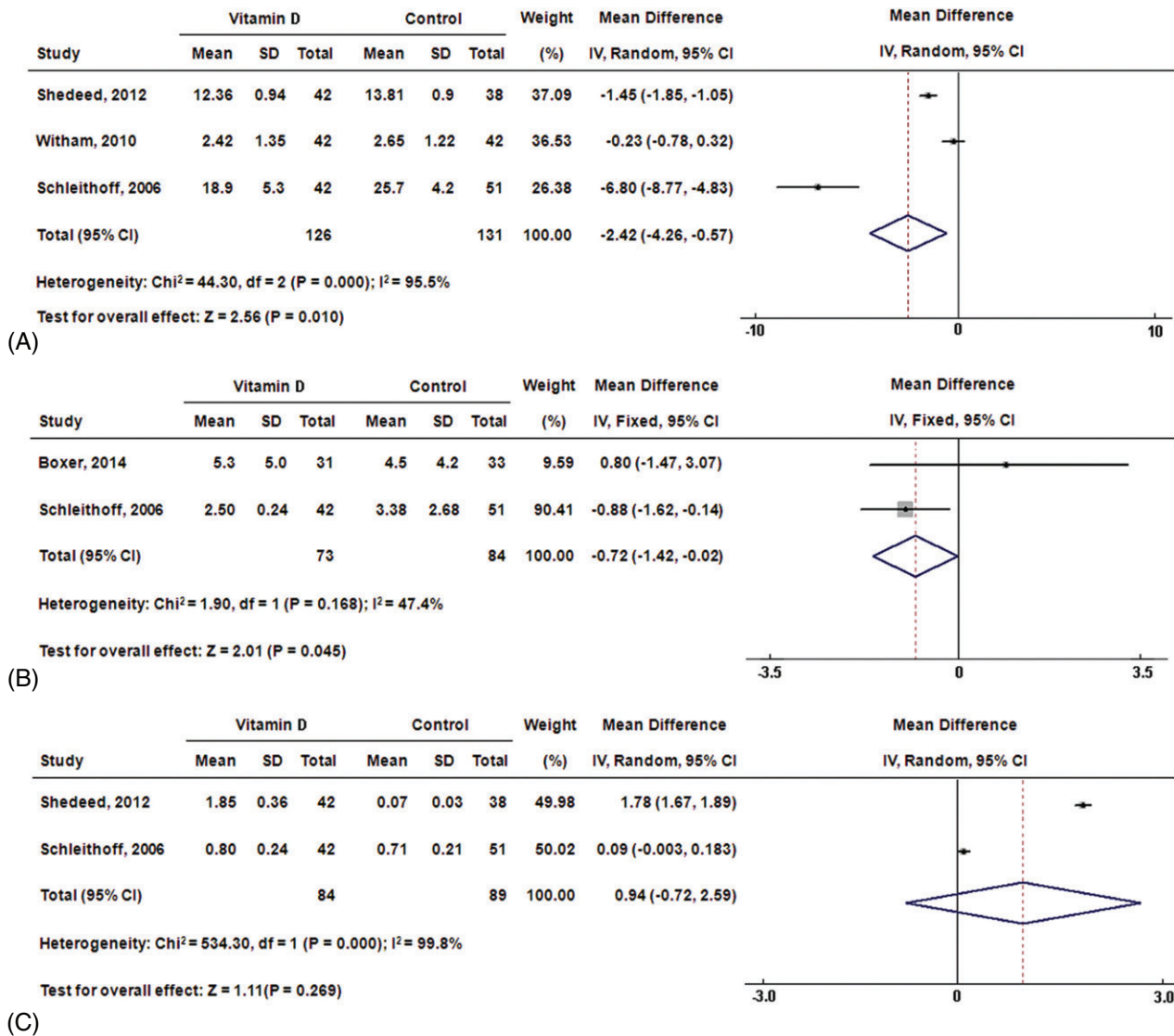


Figure 2. Forest plots for (A) TNF- α , (B) CRP, and (C) IL-10. Abbreviations: CI, confidence interval; CRP, C-reactive protein; df, degrees of freedom; IL-10, interleukin-10; IV, inverse variance; SD, standard deviation; TNF- α , tumor necrosis factor- α .

Cochrane Collaboration, Copenhagen, Denmark) and Stata software version 10.0 (StataCorp LP, College Station, TX).

Results

Among the initial 144 studies, 18 trials were retrieved for detailed evaluation and 7 RCTs satisfying the inclusion criteria were finally included. The baseline characteristics of enrolled studies and patients are shown in Tables 1 and 2. Vitamin D dosage ranged from 1000 IU/d to 50 000 IU/wk and follow-up periods from 6 weeks to 9 months in this meta-analysis. (For the flow of study selection for this meta-analysis and quality assessment of included RCTs by the Jadad scale, see Supporting Information, Figure 1 and Table 1, respectively, in the online version of this article).

Our results indicated that additional supplementation of vitamin D was not superior to conventional treatment in terms of LVEF, NT-proBNP, and 6MWD (WMD: 4.11%, 95% CI: -0.91 to 9.12, $P = 0.11$; WMD: -80.8 pg/mL,

95% CI: -305.3 to 143.7, $P = 0.48$; WMD: 8.90 m, 95% CI: -48.47 to 66.26, $P = 0.76$, respectively; Figure 1). Because a significant heterogeneity across studies was observed for LVEF, we conducted a sensitivity analysis to assess the effect of each study on the pooled estimate under the random-effects model. The results showed that removal of any individual study could not significantly reduce the heterogeneity. In addition, there was no evidence of publication bias for LVEF among the included studies.

The pooled analysis also indicated that serum levels of TNF- α and CRP were markedly decreased in the vitamin D group compared with those in the control group (WMD: -2.42 pg/mL, 95% CI: -4.26 to -0.57, $P < 0.05$; WMD: -0.72 mg/L, 95% CI: -1.42 to -0.02, $P < 0.05$, respectively; Figure 2A and 2B). However, there was no significant difference in serum IL-10 level between patients treated with vitamin D and placebo (WMD: 0.94 pg/mL, 95% CI: -0.72 to 2.59, $P = 0.27$; Figure 2C).

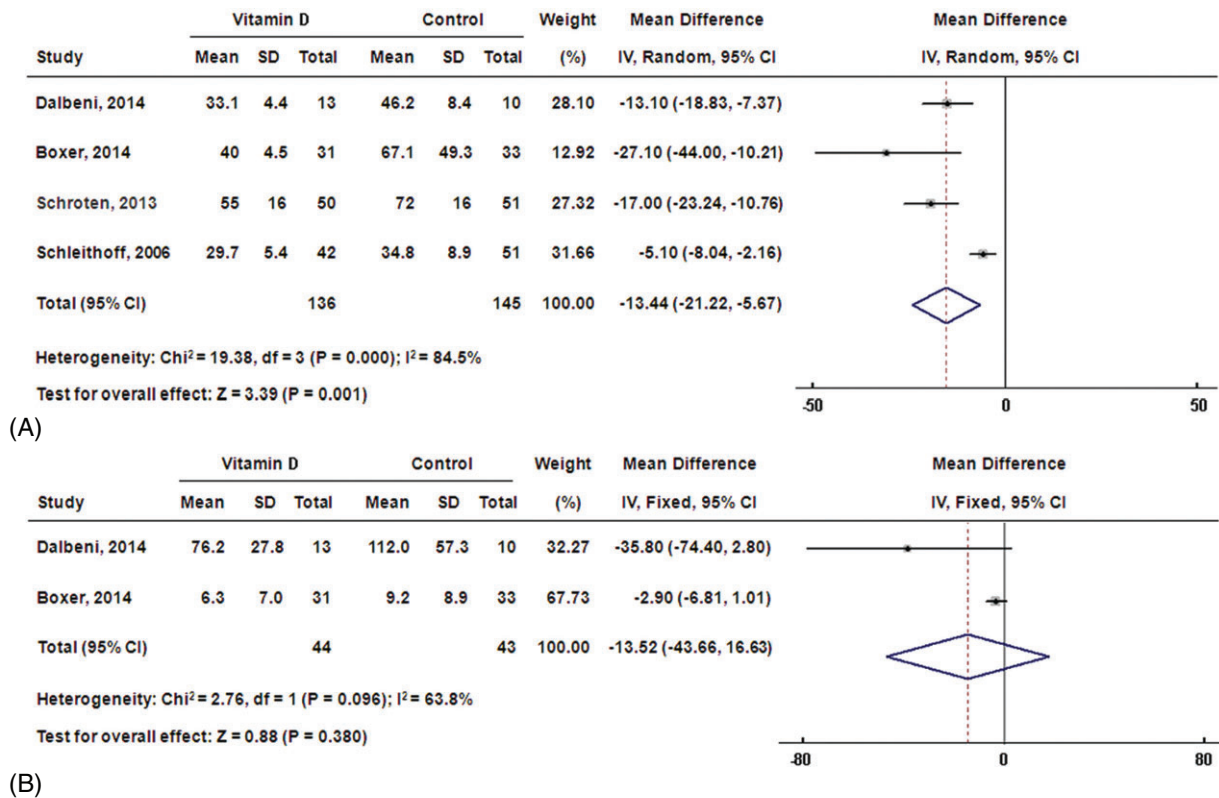


Figure 3. Forest plots for (A) parathyroid hormone and (B) renin. Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Our results revealed that vitamin D supplementation was associated with a marked decline in PTH level in the vitamin D group compared with those in the control group (WMD: -13.44 pg/mL, 95% CI: -21.22 to -5.67 , $P < 0.01$; Figure 3A). However, there was no significant difference in plasma renin concentration between CHF patients treated with vitamin D and placebo (WMD: -13.52 pg/mL, 95% CI: -43.66 to 16.63 , $P = 0.38$; Figure 3B). In addition, we performed Begg and Egger tests and found that there was no publication bias for PTH among the included studies.

Discussion

We carried out a meta-analysis of RCTs to evaluate the effects of vitamin D supplementation on prognosis of patients with CHF. Our results suggested that vitamin D therapy could decrease the serum levels of PTH, TNF- α , and CRP in CHF patients, whereas it had no beneficial effects on improvement of left ventricular function and exercise tolerance.

In recent years, accumulating evidence has demonstrated that vitamin D deficiency is related to the increased occurrence of cardiovascular disease (CVD). Wang et al²² performed a meta-analysis of prospective observational studies and showed a generally linear, inverse association between circulating 25(OH)-vitamin D and risk of CVD. Comparing the lowest with the highest category of 25(OH)-vitamin D concentration, the pooled relative risk for total CVD was 1.52 (95% CI: 1.30 to 1.77). Gotsman et al¹³

reported that vitamin D deficiency was highly prevalent in patients with CHF and was a significant predictor of reduced survival. Fall et al²³ conducted a community-based study among the elderly and found higher circulating vitamin D concentrations to be associated with better ventricular function after adjusting for several cardiovascular risk factors. Liu et al¹² indicated that low 25(OH)-vitamin D concentration was associated with a poor prognosis in CHF patients, and they found that activation of the renin-angiotensin-aldosterone system and inflammation may confer the adverse effects of low vitamin D levels.

Although there is sufficient evidence that vitamin D deficiency is associated with increased incidence and poor prognosis of CHF, it remains unclear whether vitamin D supplementation can reduce cardiovascular events and improve clinical prognosis in CHF patients. In the past decade, several small RCTs have been carried out to evaluate the effects of vitamin D treatment in patients with CHF. Schleithoff et al²¹ reported that additional supplementation of vitamin D in CHF patients decreased proinflammatory cytokine levels, without changes in left ventricular function and NT-proBNP levels. Witham et al²⁰ showed that vitamin D supplementation did not improve functional capacity or quality of life in older patients with CHF. Conversely, Shedeed et al¹⁹ indicated that children with CHF achieved marked improvement in both cardiac function and inflammatory markers after 12 weeks of vitamin D supplementation. Collectively, these RCTs of vitamin D therapy in CHF patients have generated inconsistent results

with regard to cardiovascular outcomes. We therefore performed a meta-analysis of RCTs to confirm whether vitamin D supplementation is beneficial in patients with CHF. The pooled results showed that vitamin D therapy was not associated with improvement in LVEF, NT-proBNP, and 6MWD, suggesting that additional supplementation of vitamin D in CHF patients has no significant effects on cardiovascular outcomes such as left ventricular function and exercise tolerance.

It has been well documented that inflammatory mediators are critically involved in the pathogenesis of ventricular remodeling and may serve as serum biomarkers reflecting the severity and prognosis of CHF.^{24,25} Recently, several studies suggested that circulating concentration of PTH was correlated with the severity of CHF and it could serve as a useful biomarker of the disease.^{26–28} In the present meta-analysis, our pooled results revealed that vitamin D supplementation was associated with a significant decrease in serum levels of TNF- α , CRP, and PTH. We can therefore infer that vitamin D may exert protective effects in patients with CHF by reducing inflammatory factors and PTH levels.

Study Limitations

Although we included relatively high-quality RCTs that investigated the effects of vitamin D supplementation on cardiovascular outcomes in CHF patients, there were also several limitations existing in this meta-analysis. First, the methodological quality of enrolled studies was less than optimal, so we were not able to exclude the potential risk of bias in these trials. Second, the number of patients included in this meta-analysis was relatively small, so further large-sample-size and well-designed RCTs are needed. Third, substantial heterogeneity was observed across studies in this meta-analysis, which might affect the outcomes, although a random-effects model was used.

Conclusion

Our meta-analysis demonstrates that vitamin D supplementation may decrease serum levels of PTH and inflammatory mediators such as TNF- α and CRP in CHF patients, whereas it has no beneficial effects on improvement of left ventricular function and exercise tolerance. Our findings will provide valuable information for the clinicians in the treatment of CHF.

References

- Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2011;123:e240 and *Circulation*. 2011;124:e426]. *Circulation*. 2011;123:e18–e209.
- Krum H, Teerlink JR. Medical therapy for chronic heart failure. *Lancet*. 2011;378:713–721.
- Tamez H, Thadhani RI. Vitamin D and hypertension: an update and review. *Curr Opin Nephrol Hypertens*. 2012;21:492–499.
- Karakas M, Thorand B, Zierer A, et al. Low levels of serum 25-hydroxyvitamin D are associated with increased risk of myocardial infarction, especially in women: results from the MONICA/KORA Augsburg case-cohort study. *J Clin Endocrinol Metab*. 2013;98:272–280.
- Sun Q, Pan A, Hu FB, et al. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. *Stroke*. 2012;43:1470–1477.
- Nigwekar SU, Thadhani RI. Shining light on vitamin D trials in chronic kidney disease. *Kidney Int*. 2013;83:198–200.
- Lim S, Kim MJ, Choi SH, et al. Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects. *Am J Clin Nutr*. 2013;97:524–530.
- Desai CK, Huang J, Lokhandwala A, et al. The role of vitamin supplementation in the prevention of cardiovascular disease events. *Clin Cardiol*. 2014;37:576–581.
- Li YC, Kong J, Wei M, et al. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *J Clin Invest*. 2002;110:229–238.
- Zhang Y, Leung DY, Richers BN, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol*. 2012;188:2127–2135.
- Caprio M, Mammi C, Rosano GM. Vitamin D: a novel player in endothelial function and dysfunction. *Arch Med Sci*. 2012;8:4–5.
- Liu LC, Voors AA, van Veldhuisen DJ, et al. Vitamin D status and outcomes in heart failure patients. *Eur J Heart Fail*. 2011;13:619–625.
- Gotsman I, Shauer A, Zwas DR, et al. Vitamin D deficiency is a predictor of reduced survival in patients with heart failure; vitamin D supplementation improves outcome. *Eur J Heart Fail*. 2012;14:357–366.
- Pourdjabbar A, Dwivedi G, Haddad H. The role of vitamin D in chronic heart failure. *Curr Opin Cardiol*. 2013;28:216–222.
- Dalbeni A, Scaturro G, Degan M, et al. Effects of six months of vitamin D supplementation in patients with heart failure: a randomized double-blind controlled trial. *Nutr Metab Cardiovasc Dis*. 2014;24:861–868.
- Boxer RS, Hoit BD, Schmotzer BJ, et al. The effect of vitamin D on aldosterone and health status in patients with heart failure. *J Card Fail*. 2014;20:334–342.
- Schroten NF, Ruifrok WP, Kleijn L, et al. Short-term vitamin D3 supplementation lowers plasma renin activity in patients with stable chronic heart failure: an open-label, blinded end point, randomized prospective trial (VitD-CHF trial). *Am Heart J*. 2013;166:357.e2–364.e2.
- Boxer RS, Kenny AM, Schmotzer BJ, et al. A randomized controlled trial of high dose vitamin D3 in patients with heart failure. *JACC Heart Fail*. 2013;1:84–90.
- Shedeed SA. Vitamin D supplementation in infants with chronic congestive heart failure. *Pediatr Cardiol*. 2012;33:713–719.
- Witham MD, Crighton LJ, Gillespie ND, et al. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail*. 2010;3:195–201.
- Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83:754–759.
- Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circ Cardiovasc Qual Outcomes*. 2012;5:819–829.
- Fall T, Shiue I, Bergeå af Geijerstam P, et al. Relations of circulating vitamin D concentrations with left ventricular geometry and function. *Eur J Heart Fail*. 2012;14:985–991.
- Gullestad L, Ueland T, Vinge LE, et al. Inflammatory cytokines in heart failure: mediators and markers. *Cardiology*. 2012;122:23–35.
- Hartupée J, Mann DL. Positioning of inflammatory biomarkers in the heart failure landscape. *J Cardiovasc Transl Res*. 2013;6:485–492.
- Gruson D, Lepoutre T, Ahn SA, et al. Increased circulating concentrations of bioactive PTH 1–84 in patients with heart failure. *J Endocrinol Invest*. 2012;35:987–991.
- Altay H, Zorlu A, Binici S, et al. Relation of serum parathyroid hormone level to severity of heart failure. *Am J Cardiol*. 2012;109:252–256.
- Altay H, Colkesen Y. Parathyroid hormone and heart failure: novel biomarker strategy. *Endocr Metab Immune Disord Drug Targets*. 2013;13:100–104.