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Relationship between vitamin D status and left ventricular geometry in a healthy population: results from the Baltimore Longitudinal Study of Aging

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Abstract

Objectives—The effects of vitamin D on the heart have been studied in patients with cardiac disease, but not in healthy persons. We investigated the relation between vitamin D status and left ventricular (LV) structure and function in community-dwelling subjects without heart disease.

Design—The relationship between concentrations of 25-hydroxyvitamin D [25(OH)D], a marker of vitamin D reserve, and LV transthoracic echocardiography measures was analysed in 711 participants in the Baltimore Longitudinal Study of Aging who were without cardiac disease.

Results—Mean 25(OH)D in the study population was 32.3±11.4 ng/mL; only 15.5% of subjects had moderate or severe vitamin D deficiency [25(OH)D <20 ng/mL]. Adjusting for age, body mass index, cardiovascular disease risk factors, physical activity, calcium and parathyroid hormone, 25(OH)D was positively correlated with LV thickness (β 0.095, SE 0.039, P <0.05) and LV mass index (β 7.5, SE 2.6, P <0.01). A significant non-linear relation between 25(OH)D and LV concentric remodelling was observed. LV remodelling was more likely in participants with 25(OH)D levels <30 ng/mL [odds ratio (OR) 1.24; 95% confidence interval (CI) 0.83–1.85] or 38 ng/mL (OR 1.73; 95% CI 1.13–2.65), compared with those with 30–37 ng/mL 25(OH)D. Consistently, LV relative wall thickness was significantly lower (P for trend=0.05), and LV diastolic internal diameter index (P for trend<0.05) and end-diastolic volume index (P for trend<0.05) were significantly higher in subjects with 30–37 ng/mL 25(OH)D compared to the rest of the study population. There was a significant interaction between 25(OH)D and hypertension on the risk of LV hypertrophy (P <0.05).

Conclusions—In a population-based sample of predominantly vitamin D-sufficient subjects without heart disease, LV geometry was most favourable at intermediate 25(OH)D concentrations.

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Conflict of interest statement

None of the authors has any conflicts of interest to declare.

Keywords

heart; left ventricular mass; left ventricular remodeling; population; vitamin D

Introduction

In the last decade, there have been several reports of associations between vitamin D deficiency and cardiovascular disease [1]. In particular, it has been shown that low vitamin D levels are common in heart failure (HF) [2] and correlate with more severely impaired left ventricular (LV) structure [3] and function [4] and worse clinical outcomes [2, 5]. However, the studies performed to date, including vitamin D supplementation trials [6, 7], have not answered the question of whether vitamin D deficiency is causally linked or secondary to HF. Similarly, whether vitamin D or its analogues may improve left ventricular hypertrophy (LVH) in chronic kidney disease (CKD) has not been established [8–11].

Animal models have consistently demonstrated that vitamin D can act as an anti-hypertrophic hormone in the heart [12–14]. Nevertheless, it may not be possible to translate these findings to humans. For example, mutations in the vitamin D receptor gene cause an elevation of blood pressure and activation of the renin–angiotensin–aldosterone system in mice, but not in humans [15].

One potential strategy to gain understanding of the effects of vitamin D on the human heart is to analyse the relationship between vitamin D status and LV geometry and function in individuals without cardiac disease. To accomplish this goal, we investigated a population-based sample of subjects free of overt cardiac disease, who underwent transthoracic echocardiography and measurement of vitamin D levels within the Baltimore Longitudinal Study of Aging (BLSA).

Materials and methods

Study population

The BLSA is a prospective study of community-dwelling volunteers who undergo approximately 3 days of medical examinations at regular intervals [16]. Participants are enrolled if they are healthy at baseline, but remain in the study when any disease develops. For the present analysis, we selected subjects for whom comprehensive transthoracic echocardiography, including tissue Doppler imaging, and vitamin D testing had been performed at the same study visit. We then excluded subjects with the following: history of myocardial infarction, surgical or percutaneous cardiac revascularization or HF after study entry; concomitant significant valve disease (moderate or severe aortic and mitral stenosis or regurgitation); and complete left bundle branch block, atrial flutter/fibrillation or pacemaker rhythm shown on the electrocardiogram, as these findings could affect echocardiographic measurements. All participants provided informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the MedStar Research Institute Institutional Review Board.

Assessment of vitamin D status

According to guidelines, vitamin D status was estimated by measuring serum 25-hydroxyvitamin D [25(OH)D] [17]. Normally, the amount of vitamin D in the body is largely determined by dietary sources and cutaneous synthesis stimulated by sunlight [1, 17]. In the present study, serum 25(OH)D concentrations were measured by liquid

chromatography-mass spectrometry at the Mayo Clinic (Rochester, MN, USA). The lower detection limit was 4 ng/mL and the inter-assay coefficient of variation was 10%.

Although there is no formal consensus on the optimal levels of 25(OH)D, it is generally agreed that health benefits are maximal above 30 ng/mL [17]. We therefore divided our sample into three groups as follows: subjects with <30 ng/mL 25(OH)D were categorized as vitamin D deficient, then the median 25(OH)D concentration in the remaining sample was used to create two other groups [30–37 ng/mL and ≥ 38 ng/mL 25(OH)D].

Echocardiographic measures

All echocardiograms were performed by a single cardiac sonographer with the same echocardiographic instrument (HP Sonos-5500; Philips, Andover, MA, USA) following a standardized protocol, and were interpreted by two experienced sonographers.

The LV linear dimensions (interventricular septal wall thickness, posterior wall thickness and LV end-diastolic and end-systolic diameters) were measured from a parasternal long-axis view and LV mass, relative wall thickness (RWT), fractional shortening, end-diastolic volume, end-systolic volume and ejection fraction were calculated using validated formulae [18]. LV wall thickness was defined as the sum of the interventricular septal wall and posterior wall thicknesses.

According to expert recommendations [18], LV concentric remodelling (LVCR) was defined as normal gender-specific LV mass relative to body surface area (95 g/m^2 in women and 115 g/m^2 in men) associated with increased RWT (> 0.42), whereas LVH was defined as the additional increase in LV mass relative to body surface area.

Diastolic parameters (peak E wave, peak A wave, E/A ratio) were assessed by pulse-wave Doppler examination of mitral inflow and by recording and averaging tissue Doppler early diastolic velocity (E_m) of the medial and lateral mitral annulus [19].

Other variables

Height and weight were used to calculate body mass index (BMI, kg/m^2). Smoking was ascertained using a questionnaire and participants who had smoked fewer than 100 cigarettes in their lifetime were considered as non-smokers. Physical activity was quantified by converting the time spent walking, climbing stairs or in any moderate to vigorous activity, as assessed by questionnaires, into calories expended per week [20]. Seasons during which blood samples were collected were treated as categorical variables.

Hypertension was defined as mean systolic blood pressure $\geq 140 \text{ mmHg}$ and/or mean diastolic blood pressure $\geq 90 \text{ mmHg}$ on three consecutive measurements in the brachial artery immediately before echocardiography, or as use of antihypertensive medication. Most subjects with hypertension were receiving antihypertensive drugs (Table 1). As treatment did not necessarily imply controlled blood pressure, we also included systolic blood pressure in the analysis as an indicator of the actual LV afterload at the time of evaluation. Heart rate was recorded by electrocardiography at the same time as echocardiography.

Diabetes mellitus was defined according to the American Diabetes Association criteria or as use of antidiabetic therapy, and hypercholesterolaemia as total serum cholesterol $\geq 200 \text{ mg/dL}$ or ongoing lipid-lowering treatment. Glomerular filtration rate was calculated from serum creatinine using the MDRD equation, and renal failure was defined as glomerular filtration rate $< 60 \text{ mL/min/1.73 m}^2$.

Medications with Anatomical Therapeutic Chemical classification codes related to the cardiovascular system (C codes) were considered for the analysis. Participants taking vitamin D and analogues (A11CC), vitamins D and A in combination (A11CB), and vitamin D with other vitamins (A11A, A11B, A11H and A11JC) were considered as taking vitamin D supplementation.

Serum intact parathyroid hormone (PTH) concentration was determined by chemiluminometric immunoassay (ADVIA Centaur iPTH, Siemens Medical Solutions Diagnostics, New York, NY, USA); the inter-assay coefficient of variation was 8%. Automated chemical analysis was used to measure the serum calcium level.

Statistical analyses

Continuous variables are presented as mean $\pm$ SD and categorical variables as absolute and/or relative frequencies. Comparisons between the three vitamin D groups were made by one-way analysis of variance and chi-squared tests, as appropriate. 25(OH)D and PTH concentrations were naturally log-transformed before analysis to achieve normal distribution.

The independent association between 25(OH)D and continuous echocardiographic parameters was examined in stages using linear regression. The first model included age, gender, BMI, season and vitamin D supplementation. The latter was included because it might be a surrogate of a healthier lifestyle with an impact on the heart. In addition, other vitamins within supplements coded A11CB, A11A, A11B, A11H and A11JC might have an effect on cardiac function or morphology. Next, we additionally adjusted for systolic blood pressure, hypertension, diabetes, hypercholesterolaemia, smoking, renal failure and physical activity in a second model (plus heart rate when diastolic parameters were the dependent variable). Finally, we separately included calcium and PTH to specifically examine their potential contribution to the association between 25(OH)D and echocardiographic measures. The same analytical flow was subsequently applied in logistic regressions to study the relationship between 25(OH)D and either LVCR or LVH.

PTH concentrations were not available for 144 subjects (20.3%). To avoid loss of power and the possibility of selective response bias, regression models were also adjusted for complete PTH values obtained by multiple imputation [21]. Five imputed datasets were generated using the Markov chain Monte Carlo method with SAS PROC MI (SAS software version 9.2, SAS Institute Inc., Cary, NC, USA). Missing PTH values were imputed by using information from parameters available for all subjects and all the other covariates. Results from the analyses of the five separate datasets were pooled, correcting the standard errors of the regression coefficients for within-imputation and between-imputation variability [21].

Adjusted means of echocardiographic measures across vitamin D categories were compared by analysis of covariance controlling for all covariates included in model 2; the Tukey-Kramer's test was used for significant *post hoc* differences between two groups.

Because BMI was a covariate in all models, echocardiographic parameters were measured relative to height instead of body surface area to avoid collinearity. In addition, collinearity was assessed in each model calculating the variance inflation factor, which was considered acceptable when ≤ 2 .

The interactions between 25(OH)D and gender, hypertension and vitamin D supplementation were assessed in all models. A quadratic term for 25(OH)D was also added to the final model to test for a potential non-linear association between 25(OH)D and the dependent variable, in both linear and logistic regressions.

All analyses were performed using SAS software. Statistical significance was set at $P < 0.05$.

Results

Table 1 shows the characteristics of the 711 BLSA participants with complete echocardiography and 25(OH)D data. The level of 25(OH)D was lower than 30 ng/mL in 42% of subjects. Moderate [25(OH)D 10–19 ng/mL] and severe [25(OH)D <10 ng/mL] vitamin D deficiency was observed in 69 (9.7%) and 13 (1.8%) individuals, respectively. Women had significantly higher 25(OH)D concentrations than men (34 ± 12.4 vs. 30.4 ± 9.9 ng/mL, $P < 0.0001$).

There was a significant positive correlation between 25(OH)D levels and age (Pearson's correlation coefficient = 0.16, $P < 0.0001$); the group with the highest 25(OH)D values was also the oldest. This finding, paralleled by a significant decrease in serum PTH level, may be explained by the more frequent use of vitamin D supplements at older ages (Table 1). Physical activity, a possible determinant of vitamin D levels if performed outdoors in the sunlight, did not vary significantly across vitamin D categories. Lipid-lowering drugs were the only medications used with a significantly different frequency among vitamin D groups. As hypercholesterolaemia was defined by ongoing lipid-lowering therapy, its prevalence was also significantly different across the three groups. LVCR and LVH were observed in 342 (48.1%) and 46 (6.5%) cases, respectively, with no substantial differences in prevalence among vitamin D categories (Table 1).

Linear regression analysis with adjustment for age, gender, BMI, supplement use and season of evaluation revealed a significant positive correlation between log-transformed 25(OH)D values and both LV thickness ($P = 0.01$) and LV mass index ($P < 0.01$; Table 2, Model 1). These associations persisted in the fully adjusted model accounting also for systolic blood pressure, cardiovascular disease risk factors and physical activity (Table 2, Model 2). Binary logistic regression with LVCR and LVH as dependent variables and log25(OH)D as the explanatory variable did not demonstrate any significant association (Table 2). However, when log25(OH)D-squared was entered into the fully adjusted model, a significant non-linear relation between vitamin D status and LVCR was observed ($P = 0.01$). In addition, there was a significant interaction between log25(OH)D and hypertension on the risk of LVH ($P < 0.05$). No other tested interactions were statistically significant (data not shown).

Further adjustment for calcium and PTH levels, which may mediate the cardiovascular effects of vitamin D [22, 23], did not change the results of the regression analyses (online supplemental Table 1). As PTH concentrations were only available for 567 (79.7%) subjects, values obtained by multiple imputation were substituted for the missing data. Linear and logistic regression analyses were then repeated adjusting for imputed PTH, and again no differences were found compared to the results obtained without accounting for PTH (online supplemental Table 1). We therefore concluded that neither PTH nor calcium influenced the relation between vitamin D status and LV echocardiography parameters and so did not include them in analyses thereafter.

To better understand the meaning of the quadratic relationship between log25(OH)D and LVCR, we analysed the change in RWT across the three vitamin D categories. Despite a linear increase in LV thickness and LV mass index (P for trend = 0.02 for both), LV end-diastolic diameter index and LV end-diastolic volume index were higher in the intermediate vitamin D group [30–37 ng/mL 25(OH)D] than in the lowest and highest groups (P for trend = 0.01 and 0.02, respectively; Figure 1). Furthermore, the opposite trend was observed for RWT (P for trend = 0.05; Figure 1).

As shown in Figure 2, the odds ratios for LVCR, relative to the intermediate vitamin D group, were 1.24 (95% CI 0.83–1.85, $P=0.29$) and 1.73 (95% CI 1.13–2.65, $P=0.01$) for the vitamin D-deficient and the highest vitamin D groups, respectively.

Discussion

We have shown in the present study that serum 25(OH)D, a circulating marker of vitamin D stores, was directly correlated with LV mass and non-linearly associated with LVCR in an elderly cohort of the BLSA, most of whom had sufficient vitamin D levels and were without cardiac disease. A significant interaction between 25(OH)D and hypertension on the risk of LVH was also found. Adjustment for calcium and PTH levels did not modify these associations.

Whether, and to what extent, vitamin D affects the human heart remains unclear. In HF, vitamin D status has been associated with LV dilatation [3] and impaired function [4], as well as with HF-related outcomes, such as distance walked in 6 min [24], New York Heart Association class [4], natriuretic peptides [5, 22], hospitalization due to HF [5], and mortality [2, 5]. Altered vitamin D signalling has also been implicated in development and progression of LVH in CKD [8–11]. A flaw inherent to such studies, however, is that it is not possible to determine whether vitamin D deficiency has an impact on the heart or, on the other hand, is the consequence of HF and CKD. In fact, because of limited functional capacity in HF, patients spend most of their time indoors, thereby preventing sunlight-induced vitamin D synthesis in the skin [2, 25]. In addition, intake and absorption of dietary vitamin D may be decreased in HF patients [26]. Similarly, renal failure, which frequently accompanies HF, is a risk factor for vitamin D deficiency [27].

Trials of vitamin D supplementation in HF patients have yielded contradictory results, showing both an improvement [6] and no effect [7] on LV ejection fraction and end-diastolic and end-systolic diameters. Findings of studies of the change in LV mass in CKD patients following therapy with native vitamin D [8, 9] and the vitamin D analogue paricalcitol [10, 11] have also been inconsistent.

We investigated the relationship between 25(OH)D concentrations and echocardiography-derived LV measures in community-dwelling individuals without cardiac disease. This minimizes the possibility that reverse causation may underlie any association between vitamin D levels and heart morphology or function. To our knowledge, this is the first such study following this approach. To date, only one study of the relation between vitamin D status and echocardiography outcomes in the general population has been reported, but more than 40% of participants had cardiovascular disease [28].

As a result of the high degree of use of vitamin D supplements in the well-educated BLSA sample, vitamin D sufficiency was more common than deficiency, and cases of moderate to severe vitamin D deficiency amounted to only approximately 10%. Therefore, the results of the present study are especially informative with regard to heart structure and function when vitamin D levels are close to or above the generally agreed adequate threshold. Studies like the present one must be performed before recommending vitamin D for everyone to improve their cardiovascular health [1].

In our cohort, LV thickness and LV mass progressively increased across vitamin D categories and were positively correlated with 25(OH)D levels. This finding is inconsistent with those of some earlier analyses [3, 10, 29], but in agreement with others [11]. Notably, previous studies differed from ours by including populations with highly prevalent and often severe vitamin D deficiency.

Precisely defining the mechanisms that underlie the positive correlation between 25(OH)D levels and LV mass is beyond the aims of the present work. However fibroblast growth factor 23, which increases in parallel with vitamin D levels [30] and is positively associated with LV mass [31], may have an indirect effect on this relationship.

In animal models, vitamin D has been mostly shown to prevent increases in the size of individual cardiomyocytes [12] and the cardiac extracellular matrix [13], and thus prevent an increase in whole heart weight [12–14]. However, conclusions from studies in mice may not apply to humans, as exemplified by the striking differences in renin–angiotensin system activity, blood pressure and cardiac size between vitamin D receptor-knockout animals and patients with hereditary 1,25-dihydroxyvitamin D-resistant rickets, despite theoretically sharing a similar phenotype [15].

We found a non-linear relationship between 25(OH)D concentrations and LVCR, which is associated with a higher risk of cardiovascular disease events than normal LV geometry [32–34]. This finding was clarified by comparing adjusted mean values of LV thickness, LV mass index, LV end-diastolic diameter and volume index, and RWT across vitamin D groups (Figure 1). Compared to the vitamin D-deficient group, there was an increase in both LV wall thickness (and mass) and cavity measures during diastole in the intermediate group, reminiscent of the situation in physiological LVH, in which chamber size and LV mass increase together [35]. In this respect, a direct effect of vitamin D to improve the kinetics of myocardial contraction and relaxation might be involved [36].

However, any beneficial effect of vitamin D was lost at 25(OH)D concentrations above 37 ng/mL; similarly unfavourable LV structural changes were observed in this high-vitamin D group as in the vitamin D-deficient group. Mancuso *et al.* demonstrated an increase in RWT in spontaneously hypertensive HF-prone rats fed a high-salt diet and treated with vitamin D for 13 weeks [14]. The findings of two epidemiological studies from the Framingham Offspring Study and the Third National and Nutrition Examination Survey suggested the existence of a U-shaped relationship between 25(OH)D and incident cardiovascular disease, including HF, and mortality [37, 38]. In the Framingham Offspring cohort, there was an interaction between 25(OH)D levels and arterial hypertension in determining the incidence of new cardiovascular events [37]. Our data also highlight a significant interaction between 25(OH)D and hypertension in determining LVH, a further step towards overt cardiac disease compared to LVCR.

Because of its cross-sectional design, the present study does not provide evidence of the (patho)physiological processes linking vitamin D levels to modifications of LV structure. Furthermore, hypertension-stratified analyses of the relationship between 25(OH)D and LVH could not be performed because of the low prevalence of LVH.

In conclusion, our analysis in healthy, community-dwelling individuals indicates that the 30 ng/mL 25(OH)D threshold for vitamin D sufficiency is associated with a reduced risk of LVCR, a desirable cardiac outcome. On the other hand, continued vitamin D supplementation once an adequate level is obtained might not be advisable, at least as far as the heart is concerned, as the safety margin above 30 ng/mL may be quite small.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviation list

25(OH)D	25-hydroxyvitamin D
PTH	parathyroid hormone
BLSA	Baltimore Longitudinal Study of Aging
LV	left ventricular
BMI	body mass index
RWT	relative wall thickness
LVH	left ventricular hypertrophy
LVCR	left ventricular concentric remodelling
HF	heart failure
CKD	chronic kidney disease

References

1. Lavie CJ, Lee JH, Milani RV. Vitamin D and cardiovascular disease will it live up to its hype? *J Am Coll Cardiol.* 2011; 58:1547–1556. [PubMed: 21958881]
2. Gotsman I, Shauer A, Zwas DR, Hellman Y, Keren A, Lotan C, Admon D. 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. [PubMed: 22308011]
3. Ameri P, Ronco D, Casu M, et al. High prevalence of vitamin D deficiency and its association with left ventricular dilation: an echocardiography study in elderly patients with chronic heart failure. *Nutr Metab Cardiovasc Dis.* 2010; 20:633–640. [PubMed: 20399085]
4. Pilz S, Marz W, Wellnitz B, et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. *The Journal of clinical endocrinology and metabolism.* 2008; 93:3927–3935. [PubMed: 18682515]
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. [PubMed: 21543375]
6. Shedeed SA. Vitamin D Supplementation in Infants With Chronic Congestive Heart Failure. *Pediatr Cardiol.* 2012
7. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. 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. [PubMed: 16600924]
8. Matias PJ, Jorge C, Ferreira C, et al. Cholecalciferol supplementation in hemodialysis patients: effects on mineral metabolism, inflammation, and cardiac dimension parameters. *Clin J Am Soc Nephrol.* 2010; 5:905–911. [PubMed: 20203163]
9. Park CW, Oh YS, Shin YS, et al. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis.* 1999; 33:73–81. [PubMed: 9915270]
10. Bodyak N, Ayus JC, Achinger S, et al. Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. *Proc Natl Acad Sci U S A.* 2007; 104:16810–16815. [PubMed: 17942703]
11. Thadhani R, Appelbaum E, Pritchett Y, et al. Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. *JAMA.* 2012; 307:674–684. [PubMed: 22337679]
12. Chen S, Law CS, Grigsby CL, et al. Cardiomyocyte-specific deletion of the vitamin D receptor gene results in cardiac hypertrophy. *Circulation.* 2011; 124:1838–1847. [PubMed: 21947295]
13. Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU. Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. *J Steroid Biochem Mol Biol.* 2007; 103:416–419. [PubMed: 17275288]

14. Mancuso P, Rahman A, Hershey SD, Dandu L, Nibbelink KA, Simpson RU. 1,25-Dihydroxyvitamin-D3 treatment reduces cardiac hypertrophy and left ventricular diameter in spontaneously hypertensive heart failure-prone (cp/+) rats independent of changes in serum leptin. *J Cardiovasc Pharmacol*. 2008; 51:559–564. [PubMed: 18496147]
15. Tiosano D, Schwartz Y, Braver Y, Hadash A, Gepstein V, Weisman Y, Lorber A. The renin-angiotensin system, blood pressure, and heart structure in patients with hereditary vitamin D-resistance rickets (HVDRR). *J Bone Miner Res*. 2011; 26:2252–2260. [PubMed: 21590741]
16. Schillaci G, Pasqualini L, Verdecchia P, et al. Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. *J Am Coll Cardiol*. 2002; 39:2005–2011. [PubMed: 12084601]
17. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2011; 96:1911–1930. [PubMed: 21646368]
18. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. *Eur J Echocardiogr*. 2006; 7:79–108. [PubMed: 16458610]
19. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009; 22:107–133. [PubMed: 19187853]
20. Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG, Lakatta EG. Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation*. 2005; 112:674–682. [PubMed: 16043637]
21. Sinharay S, Stern HS, Russell D. The use of multiple imputation for the analysis of missing data. *Psychol Methods*. 2001; 6:317–329. [PubMed: 11778675]
22. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J Am Coll Cardiol*. 2003; 41:105–112. [PubMed: 12570952]
23. Kestenbaum B, Katz R, de Boer I, et al. Vitamin D, parathyroid hormone, and cardiovascular events among older adults. *J Am Coll Cardiol*. 2011; 58:1433–1441. [PubMed: 21939825]
24. Boxer RS, Dauser DA, Walsh SJ, Hager WD, Kenny AM. The association between vitamin D and inflammation with the 6-minute walk and frailty in patients with heart failure. *J Am Geriatr Soc*. 2008; 56:454–461. [PubMed: 18194227]
25. Zittermann A, Fischer J, Schleithoff SS, Tenderich G, Fuchs U, Koerfer R. Patients with congestive heart failure and healthy controls differ in vitamin D-associated lifestyle factors. *Int J Vitam Nutr Res*. 2007; 77:280–288. [PubMed: 18271283]
26. Hughes CM, Woodside JV, McGartland C, Roberts MJ, Nicholls DP, McKeown PP. Nutritional intake and oxidative stress in chronic heart failure. *Nutr Metab Cardiovasc Dis*. 2012; 22:376–382. [PubMed: 21186107]
27. Dusso AS, Tokumoto M. Defective renal maintenance of the vitamin D endocrine system impairs vitamin D renoprotection: a downward spiral in kidney disease. *Kidney Int*. 2011; 79:715–729. [PubMed: 21270766]
28. Pilz S, Henry RM, Snijder MB, et al. Vitamin D deficiency and myocardial structure and function in older men and women: the Hoorn study. *J Endocrinol Invest*. 2010; 33:612–617. [PubMed: 20208455]
29. Matias PJ, Ferreira C, Jorge C, et al. 25-Hydroxyvitamin D3, arterial calcifications and cardiovascular risk markers in haemodialysis patients. *Nephrol Dial Transplant*. 2009; 24:611–618. [PubMed: 18775809]
30. Hansen D, Rasmussen K, Pedersen SM, Rasmussen LM, Brandt L. Changes in fibroblast growth factor 23 during treatment of secondary hyperparathyroidism with alfacalcidol or paricalcitol. *Nephrol Dial Transplant*. 2011
31. Mirza MA, Larsson A, Melhus H, Lind L, Larsson TE. Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis*. 2009; 207:546–551. [PubMed: 19524924]

32. Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. *Am J Cardiol.* 2006; 97:959–963. [PubMed: 16563894]
33. Lavie CJ, Milani RV, Ventura HO, Messerli FH. Left ventricular geometry and mortality in patients >70 years of age with normal ejection fraction. *Am J Cardiol.* 2006; 98:1396–1399. [PubMed: 17134637]
34. Pierdomenico SD, Di Nicola M, Pierdomenico AM, Lapenna D, Cuccurullo F. Cardiovascular risk in subjects with left ventricular concentric remodeling at baseline examination: a meta-analysis. *J Hum Hypertens.* 2011; 25:585–591. [PubMed: 21412267]
35. Gaasch WH, Zile MR. Left ventricular structural remodeling in health and disease: with special emphasis on volume, mass, and geometry. *J Am Coll Cardiol.* 2011; 58:1733–1740. [PubMed: 21996383]
36. Tishkoff DX, Nibbelink KA, Holmberg KH, Dandu L, Simpson RU. Functional vitamin D receptor (VDR) in the t-tubules of cardiac myocytes: VDR knockout cardiomyocyte contractility. *Endocrinology.* 2008; 149:558–564. [PubMed: 17974622]
37. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation.* 2008; 117:503–511. [PubMed: 18180395]
38. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med.* 2008; 168:1629–1637. [PubMed: 18695076]

Figure 1. Left ventricular structural parameters across vitamin D groups

Mean (with standard error) of LV structural parameters by vitamin D group after adjusting for age, gender, body mass index, vitamin D supplementation, season, systolic blood pressure, hypertension, diabetes, hypercholesterolaemia, smoking, renal failure and physical activity.

LV, left ventricular; RWT, relative wall thickness.

Parameters are relative to height, where indicated.

Figure 2. Probability of left ventricular concentric remodelling across vitamin D groups
 Odds ratio (OR) values are adjusted for age, gender, body mass index, vitamin D supplementation, season, systolic blood pressure, hypertension, diabetes, hypercholesterolaemia, smoking, renal failure and physical activity.
 LV, left ventricular; Ref, reference group.

Table 1

Characteristics of the study population by vitamin D groups

	Levels of 25(OH)D			<i>P</i> for trend
	<30 ng/mL (<i>n</i> =298)	30–37 ng/mL (<i>n</i> =208)	38 ng/mL (<i>n</i> =205)	
25(OH)D	22.2±5.6 range 6.8–29	33.3±2.4 range 30–37	46±8 range 38–89	<0.0001
Age (years)	63.8±12	67.2±13	69.6±11.6	<0.0001
Men (%)	54	45	38	0.001
BMI (kg/m²)	28.4±5.2	26.7±4.5	25.5±3.9	<0.0001
SBP (mm/Hg)	121.6±15.5	120.1±15.1	117.6±14.2	0.01
HR (beats/min)	68.2±11.8	66±10.5	68.6±11.5	0.04
eGFR (mL/min)	78.9±17.1	75.9±15.7	73.6±17.6	0.002
Ca (mg/dL)	9.29±0.4	9.34±0.4	9.42±0.4	0.001
Physical activity (%)				0.35
0 to <500 Kcal/week	29	23	22	
500 to <1500 Kcal/week	16	20	19	
1500 Kcal/week	55	57	59	
Hypertension (%)	47	42	48	0.38
Treated hypertension (%)	43	37	48	0.05
Diabetes (%)	16	14	11	0.27
Hypercholesterolaemia (%)	36	45	54	<0.001
Smoking (%)	44	43	51	0.17
Renal failure* (%)	9	12	17	0.04
Vitamin D supplements (%)	47	68	75	<0.0001
Diuretics (%)	15	12	18	0.22
Beta blockers (%)	14	16	11	0.32
Ca antagonists (%)	11	9	9	0.73
RAAS inhibitors (%)	25	23	28	0.41
Lipid-lowering drugs (%)	36	45	54	<0.001
Blood test season (%)				0.26
Spring	24	25	23	
Summer	27	29	31	
Autumn	21	27	20	
Winter	28	19	26	
PTH (pg/mL) (<i>n</i>=567)	42.1±19.1 (<i>n</i> =237)	36.1±16.1 (<i>n</i> =163)	33.1±16 (<i>n</i> =167)	<0.0001
LV geometry (%)				
LV concentric remodelling	47	44	54	0.14
LV hypertrophy	6	7	7	0.77

* Defined as estimated glomerular filtration rate <60 mL/min/1.73 m².

25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; Ca, calcium; HR, heart rate; LV, left ventricular; PTH, parathyroid hormone; RAAS, renin–angiotensin–aldosterone system; SBP, systolic blood pressure.

Table 2

Association between log25(OH)D and LV echocardiographic parameters

	Model 1			Model 2		
	β	SE	P	β	SE	P
LV structural parameters						
Thickness	0.092	0.037	0.014	0.095	0.039	0.015
RWT	0.010	0.012	0.39	0.012	0.012	0.34
End-diastolic diameter index	0.045	0.033	0.17	0.043	0.034	0.20
End-systolic diameter index	0.021	0.029	0.47	0.026	0.030	0.39
End-diastolic volume index	2.129	1.473	0.15	2.084	1.521	0.17
End-systolic volume index	0.479	0.785	0.54	0.506	0.782	0.52
Mass index	7.693	2.585	0.003	7.855	2.696	0.004
LV systolic parameters						
Fractional shortening	0.313	0.873	0.72	0.161	0.894	0.86
Ejection fraction	0.479	1.166	0.68	0.278	1.187	0.82
LV diastolic parameters						
E/A	0.004	0.028	0.89	0.002	0.027	0.95
Em	-0.034	0.185	0.86	-0.094	0.185	0.61
E/Em	-0.016	0.219	0.94	0.212	0.222	0.34
	OR	95% CI	P	OR	95% CI	P
LV geometry						
LV concentric remodelling	1.18	0.76–1.82	0.47	1.22	0.77–1.92	0.39
LV hypertrophy	1.73	0.70–4.30	0.24	1.91	0.75–4.91	0.18

Model 1: adjustment for age, sex, body mass index, supplementation and season.

Model 2: model 1 + adjustment for systolic blood pressure, hypertension, diabetes, hypercholesterolaemia, smoking, renal failure and physical activity (and heart rate for diastolic parameters). Parameters are related to height. Variance inflation factor was <1.4 in all models.

25(OH)D, 25-hydroxyvitamin D; E/A, ratio between early and late mitral inflow velocities; E/Em, ratio between early mitral inflow velocity and early diastolic velocity of the mitral annulus; Em, early diastolic velocity of the mitral annulus; LV, left ventricular; RWT, relative wall thickness.