Biol Trace Elem Res (2010) 135:67–73
DOI 10.1007/s12011-009-8492-9

# Calcium and Vitamin D Status in Heart Failure Patients in Isfahan, Iran

**Mohammad Garakyaraghi · Maryam Kerdegari · Mansour Siavash**

Received: 30 June 2009 / Accepted: 28 July 2009 /
Published online: 19 August 2009


**Abstract** Both calcium and vitamin D play important roles in cardiac muscle contraction and performance. In this cross-sectional study, we evaluated the status of serum calcium, PTH and $25(OH)D_3$ and their correlation with left ventricular Function and NYHA Functional class in 95 heart failure patients referred to Shahid Chamran Hospital, Isfahan, Iran, by colorimetric, immunoradiometric, and Immunochemiluminescent assays, echocardiography and interview respectively. The study was performed between Oct 2007 and Feb 2008. Twenty eight women and 67 men of functional classes 1, 2, or 3 participated in the study. Mean (SD) of age of the participants was 62(11)years. Mean (SD) serum calcium and $25(OH)D_3$ were 2.41 (0.16)mmol/L and 56.78(51.33)nmol/L, respectively. The overall prevalence of low vitamin D status was 84.2%. There was no correlation between serum calcium and $25(OH)D_3$ with LVEF. Interestingly, patients with hyperparathyroidism (serum PTH>65 ng/L) had lower LVEF (27% versus 32.5% $p=0.03$). NYHA functional class was worse in patients with hyperparathyroidism ($p=0.08$). Hypovitaminosis D is very prevalent in heart failure patients. Hyperparathyroidism in these patients may adversely affect cardiac function. Vitamin D3 might serve as an adjunctive treatment for heart failure patients.

**Keywords** Heart failure · Calcium · Hyperparathyroidism · Vitamin D · Left ventricular ejection fraction · NYHA functional class

M. Garakyaraghi
Isfahan University of Medical Sciences, Isfahan Cardiovascular Research Center, Isfahan, Iran

M. Kerdegari
Isfahan University of Medical Sciences, Isfahan, Iran

M. Siavash (✉)
Isfahan University of Medical Sciences, Isfahan Endocrine & Metabolism Research Center, Sedigheh Tahereh Medical Research Complex, Khorram Street, 8187698191 Isfahan, Iran
e-mail: siavash@med.mui.ac.ir

## Introduction

Despite recent advances in management, heart failure thus far carries an unacceptably high mortality rate [1, 2]. It is so prevalent that almost one in three individuals over the age of 55 will develop heart failure during their remaining lifespan. It continues to be a fatal disease, with only 35% surviving 5 years after the first diagnosis [1]. Early and long-term all-cause mortality and hospital readmission rates remain high and have improved little with time. The need to identify optimal management strategies for these clinically complex patients is urgent [3]. The management of patients with heart failure is based upon the understanding of the pathogenic mechanisms at work. Management may focus on optimizing preload, decreasing afterload, and improving contractility. Frequent lines of research are ongoing to address these possible interventions.

Hypovitaminosis D is common in general medical in-patients [4]. Correlation of low vitamin D status and resulting hyperparathyroidism with cardiovascular diseases is under active research.

Several animal and human studies suggest that low vitamin D status may contribute to pathogenesis of heart failure through different mechanisms [5-11].

In a recent study by Kim et al., hypovitaminosis D was highly prevalent in US adults with cardiovascular disorders, particularly those with both coronary heart disease and heart failure [12]. Some studies have shown secondary hyperparathyroidism is also very prevalent in heart failure patients [9].

We evaluated serum levels of calcium, $25(OH)D_3$ and parathyroid hormone (PTH) and their correlation with left ventricular ejection fraction (LVEF) and the New York Heart Association (NYHA) functional class in heart failure patients to investigate the prevalence of hypovitaminosis D, secondary hyperparathyroidism and their relation with cardiac performance.

## Methods

This cross-sectional study was performed between Oct. 2007 and Feb. 2008 in Shahid Chamran Hospital, Isfahan, Iran. Heart failure patients referred to us for evaluation and management were invited to participate in the study. They were included if ambulatory with NYHA Functional Class≤III and LVEF≤45%.

Patients with hypercalcemia, nephrolithiasis, intake of supplements containing vitamin D or calcium, therapy with corticosteroids or anticonvulsants and serum creatinine concentration >176 μmol/L were excluded from the study.

After obtaining written consent, we performed transthoracic echocardiography to evaluate LVEF together with cardiac volumes and obtained fasting blood samples for assessment of serum calcium, phosphorus, albumin, $25(OH)D_3$, creatinine, and PTH concentration.

Transthoracic echocardiography was done by a Wing-Med 800 CF system and LVEF was assessed by Biplane Simpson's method.

Exercise capacity was assessed through a questionnaire based on NYHA functional classification [13].

Blood samples were collected from the antecubital vein of the participants after a 12-h fast. After centrifugation at room temperature for 10 min, serum samples were extracted, frozen, and stored at −20°C until analysis.

Serum $25(OH)D_3$ was measured by Chemiluminescent Immunoassay (DiaSorin, Stillwater, MN). The different stages of vitamin D status were classified as deficiency (0–

25 nmol/L), insufficiency (>25–50 nmol/L), hypovitaminosis (>50–100 nmol/L), adequacy (>100–250 nmol/L), and excess (>250 nmol/L) [14, 15]. Serum PTH (reference range, 16–65 ng/L) was measured by radioimmunoassay (IRMA, Immunotech, Prague, Czech Republic). Serum calcium (nl, 2.2–2.6 mmol/L) concentration was assessed by the use of colorimetric method (Darman Kave, Isfahan, Iran). Albumin, phosphorous, and creatinine were measured by the use of colorimetric method (Pars Azmun, Karaj, Iran).

## Statistical Analysis

Nominal variables are presented as numbers and frequencies. Parametric variables between two groups were compared by *t* test and among more than two groups by ANOVA. Correlations between parametric data were evaluated by Pearson's Correlation. Correlations between nonparametric data were evaluated by Spearman's Correlation. Prevalence of nonparametric data between different groups was compared by chi square. Statistical analysis was performed by SPSS version 15.

The study was approved by the ethics committee affiliated to the chancellor of research of the Isfahan University of Medical Sciences. As mentioned, written consent was obtained from all patients.

## Results

Twenty eight women and 67 men of functional classes 1, 2, or 3 participated in the study. The mean (SD) of age of participants was 62(11)years. The prevalence of patients affected by hypertension, coronary artery disease, diabetes mellitus, and cigarette smoking were 64 (67.4%), 56(58.9%), 29(30.5%), and 17(17.9%) respectively. Ninety patients (94.7%) were current diuretic users. Baseline data of the participants are presented in Table 1.

There were only two patients (2.1%) with mild hypocalcemia. The number (prevalence) of patients with vitamin D deficiency, insufficiency, hypovitaminosis, sufficiency, and excess were 27(28.4%), 36(37.9%), 17(17.9%), 14(14.7%) and 1(1.1%), respectively. The overall prevalence of low serum vitamin D was 84.2%.

There was no correlation between serum $25(OH)D_3$ and LVEF. There was negative correlation between serum $25(OH)D_3$ and LV end diastolic volume ($r=-0.243$, $p=0.048$). After controlling for age and serum creatinine, this negative correlation was more significant ($r=-0.261$, $p=0.036$).

There was non-significant negative correlation between serum $25(OH)D_3$ and LV end systolic volume ($r=-0.209$, $p=0.09$).

**Table 1** Baseline Data of the Participants

| Sex (*n*) | DM | HTN | CAD | Smoking |
|---|---|---|---|---|
| Female (28) | 9 (32.1%) | 23 (82.1%) | 11 (39.3%) | 0 (0.0%) |
| Male (67) | 20 (29.9%) | 41 (61.2%) | 45 (67.2%) | 17 (25.4%) |
| *p* | 0.81 | 0.057 | 0.018 | 0.013 |
| Total | 29 (30.5%) | 64 (67.4%) | 56 (58.9%) | 17 (17.9%) |

*DM* patients with diabetes mellitus, *HTN* patients with hypertension, *CAD* patients with coronary artery disease, *Smoking* patients with cigarette smoking

Patients with hyperparathyroidism (serum PTH>65 ng/L) had lower LVEF (27% versus 32.5% $p$=0.03). NYHA functional class was lower in patients with hyperparathyroidism ($p$= 0.08; Fig. 1), but the prevalence of hypovitaminosis D was not different between NYHA functional classes 1, 2, or 3 ($p$=0.7). Other biochemical findings of the participants are presented in Table 2.

## Discussion

The present study shows high prevalence of hypovitaminosis D in patients with heart failure. Our findings are consistent with other studies, showing reduced circulating levels of $25(OH)D_3$ in heart failure patients [16]. In this setting, hypovitaminosis D may be a consequent of, or contributing factor to heart failure.

There are several explanations for the low circulating vitamin D levels in heart failure patients: inadequate UVB exposure due to reduced outdoor activity, inadequate dietary intake, and malabsorption in these patients. Inflammatory cytokine like TNF$\alpha$, may also suppress calcitriol synthesis [17], as their elevation is a usual feature in heart failure patients [8].

On the other hand, several animal and human studies suggest that hypovitaminosis D may be a contributing factor to heart failure [16]. Probable mechanisms may be: up-regulation of pro-inflammatory and down-regulation of anti-inflammatory cytokines [7, 8, 18, 19], overstimulation of the renin–angiotensin system [5, 6], proliferation of smooth muscle cells, and atrophy, degeneration, and or proliferation of cardiomyocytes [11, 20, 21], defects in heart cell calcium metabolism through regulation of calcium channel activity mediated by the cAMP pathway [22], remodeling of heart extracellular matrix metabolism mediated by matrix metalloproteinases [23], secondary hyperparathyroidism with its cardiac consequences [9, 10], and many other less well-appreciated ones.

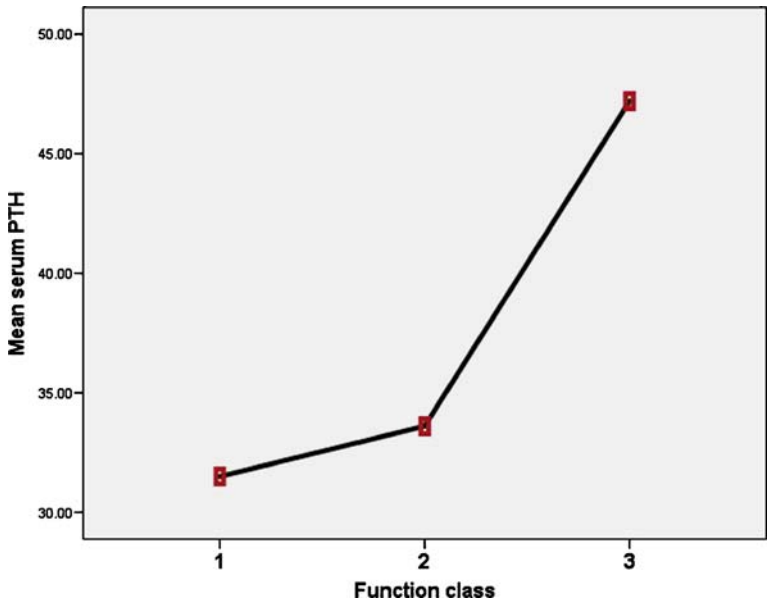


**Fig. 1** Mean serum parathyroid hormone (PTH) in three function classes

**Table 2** Biochemical Findings in the Participants

| NYHA function class (*n*) | Age (years) | Calcium (mmol/L) | Phosp. (mmol/L) | PTH (ng/L) | 25(OH)$D_3$ (nmol/L) | Cr (μmol/L) | LVEF (%) |
|---|---|---|---|---|---|---|---|
| Function class 1(12) | 60.58±12.12 | 2.38±0.16 | 1.19±0.19 | 31.50±14.31 | 46.17±43.86 | 102.28±23.35 | 36.38±3.78 |
| Function class 2(63) | 61.16±9.95 | 2.41±0.16 | 1.21±0.16 | 33.60±19.63 | 60.95±55.37 | 95.87±24.15 | 32.13±7.19 |
| Function class 3(20) | 66.15±13.81 | 2.43±0.15 | 1.24±0.18 | 47.20±38.70 | 50.00±41.74 | 99.78±34.27 | 29.20±6.08 |
| Total (95) | 62.14±11.21 | 2.41±0.16 | 1.21±0.17 | 36.20±24.78 | 56.78±51.33 | 97.50±26.30 | 32.06±6.89 |
| *p* value | 0.195 | 0.722 | 0.626 | 0.078 | 0.533 | 0.679 | 0.015 |

*NYHA* New York Heart Association, *Phosp* serum phosphate, *PTH* serum parathyroid hormone, *Cr* serum creatinine concentration, *LVEF* left ventricular ejection fraction

In our study, there was no direct correlation between serum 25(OH)$D_3$ and its deficiency with LVEF and NYHA functional class. This is not unexpected, as multiple other factors are important determinants of LVEF. Interestingly, we observed an inverse correlation between serum 25(OH)$D_3$ concentration and LVEDV that is suggested to be the strongest predictor of survival for patients with severe heart failure [24].

Heart failure patients are in a state of secondary aldostronism. As a result, they may be affected by secondary hyperparathyroidism because they lose calcium and magnesium in the urine and feces. This leads to relative depletion of serum calcium and provocation of parathyroid hormone secretion [8-10, 25].

In our study, the patients with hyperparathyroidism had lower LVEF and NYHA functional classification independent of their 25(OH)$D_3$ status. This suggests PTH may have some direct effects on cardiac function. Some studies imply that excess levels of the PTH could increase blood pressure and cause cardiomyocyte hypertrophy and interstitial fibrosis of the heart [26-28].

## Conclusion

Suboptimal vitamin D status is very prevalent in heart failure patients. Secondary hyperparathyroidism in these patients may adversely affect left ventricular function. Vitamin D3 might serve as a new agent for the future treatment of heart failure patients.

**Acknowledgments** The authors are grateful both to Dr. Golestanfar and Sattari from Pars medical laboratories for their kind help and the patients who participated in this study.

## References

1. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH (2004) Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J 25:1614–1619

2. Loehr LR, Rosamond WD, Chang PP, Folsom AR, Chambless LE (2008) Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). Am J Cardiol 101:1016–1022
3. Curtis LH, Greiner MA, Hammill BG, Kramer JM, Whellan DJ, Schulman KA, Hernandez AF (2008) Early and long-term outcomes of heart failure in elderly persons, 2001–2005. Arch Intern Med 168:2481–2488
4. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS (1998) Hypovitaminosis D in medical inpatients. N Engl J Med 338:777–783
5. Xiang W, Kong J, Chen S, Cao LP, Qiao G, Zheng W, Liu W, Li X, Gardner DG, Li YC (2005) Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin–angiotensin systems. Am J Physiol Endocrinol Metab 288:E125–E132
6. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J (2004) Vitamin D: a negative endocrine regulator of the renin–angiotensin system and blood pressure. J Steroid Biochem Mol Biol 89-90:387–392
7. Alsafwah S, Laguardia SP, Arroyo M, Dockery BK, Bhattacharya SK, Ahokas RA, Newman KP (2007) Congestive heart failure is a systemic illness: a role for minerals and micronutrients. Clin Med Res 5:238–243
8. Newman KP, Neal MT, Roberts M, Goodwin KD, Hatcher EA, Bhattacharya SK (2007) The importance of lost minerals in heart failure. Cardiovasc Hematol Agents Med Chem 5:295–299
9. Laguardia SP, Dockery BK, Bhattacharya SK, Nelson MD, Carbone LD, Weber KT (2006) Secondary hyperparathyroidism and hypovitaminosis D in African–Americans with decompensated heart failure. Am J Med Sci 332:112–118
10. Khouzam RN, Dishmon DA, Farah V, Flax SD, Carbone LD, Weber KT (2006) Secondary hyperparathyroidism in patients with untreated and treated congestive heart failure. Am J Med Sci 331:30–34
11. Nibbelink KA, Tishkoff DX, Hershey SD, Rahman A, Simpson RU (2007) 1,25(OH)2-vitamin D3 actions on cell proliferation, size, gene expression, and receptor localization, in the HL-1 cardiac myocyte. J Steroid Biochem Mol Biol 103:533–537
12. Kim DH, Sabour S, Sagar UN, Adams S, Whellan DJ (2008) Prevalence of hypovitaminosis D in cardiovascular diseases (from the National Health and Nutrition Examination Survey 2001 to 2004). Am J Cardiol 102:1540–1544
13. The Criteria Committee of the New York Heart Association (1994) Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Little Brown, Boston
14. Witte KK, Clark AL (2006) Micronutrients and their supplementation in chronic cardiac failure. An update beyond theoretical perspectives. Heart Fail Rev 11:65–74
15. Zittermann A, Schleithoff SS, Koerfer R (2006) Vitamin D insufficiency in congestive heart failure: why and what to do about it? Heart Fail Rev 11:25–33
16. Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P (2003) Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? J Am Coll Cardiol 41:105–112
17. Haug CJ, Aukrust P, Haug E, Morkrid L, Muller F, Froland SS (1998) Severe deficiency of 1, 25-dihydroxyvitamin D3 in human immunodeficiency virus infection: association with immunological hyperactivity and only minor changes in calcium homeostasis. J Clin Endocrinol Metab 83:3832–3838
18. Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R (2006) Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 83:754–759
19. Zittermann A, Schleithoff SS, Koerfer R (2005) Putting cardiovascular disease and vitamin D insufficiency into perspective. Br J Nutr 94:483–492
20. Halapas A, Diamanti-Kandarakis E, Kremastinos D, Koutsilieris M (2006) The PTHrP/PTH.1-R bioregulation system in cardiac hypertrophy: possible therapeutic implications. In Vivo 20:837–844
21. Dastur DK, Gagrat BM, Wadia NH, Desai M, Bharucha EP (1975) Nature of muscular change in osteomalacia: light- and electron-microscope observations. J Pathol 117:211–228
22. Selles J, Boland R (1991) Evidence on the participation of the 3', 5'-cyclic AMP pathway in the non-genomic action of 1, 25-dihydroxy-vitamin D3 in cardiac muscle. Mol Cell Endocrinol 82:229–235
23. Rahman A, Hershey S, Ahmed S, Nibbelink K, Simpson RU (2007) Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. J Steroid Biochem Mol Biol 103:416–419
24. Grayburn PA, Appleton CP, DeMaria AN, Greenberg B, Lowes B, Oh J, Plehn JF, Rahko P, St John SM, Eichhorn EJ (2005) Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (BEST). J Am Coll Cardiol 45:1064–1071

25. Frost RJ, Sonne C, Wehr U, Stempfle HU (2007) Effects of calcium supplementation on bone loss and fractures in congestive heart failure. Eur J Endocrinol 156:309–314
26. McGonigle RJ, Fowler MB, Timmis AB, Weston MJ, Parsons V (1984) Uremic cardiomyopathy: potential role of vitamin D and parathyroid hormone. Nephron 36:94–100
27. McCarty MF (2005) Nutritional modulation of parathyroid hormone secretion may influence risk for left ventricular hypertrophy. Med Hypotheses 64:1015–1021
28. Rostand SG, Drueke TB (1999) Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int 56:383–392