Lower serum 25-hydroxyvitamin D level is associated with impaired myocardial performance and left ventricle hypertrophy in newly diagnosed hypertensive patients

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ABSTRACT

Objective: Vitamin D deficiency is an independent risk factor for cardiovascular mortality. The relationship between vitamin D level and left ventricle (LV) myocardial performance index (MPI=Tei index), which incorporates both LV systolic function and diastolic function, was not investigated in previous studies. We hypothesized that vitamin D level may be associated with LV function and geometry. We aimed to investigate the association between serum 25-hydroxyvitamin D (25 [OH] D) levels and MPI and LV hypertrophy in hypertensive patients with newly diagnosed and preserved ejection fraction.

Methods: We studied 151 sequential newly diagnosed hypertensive subjects who lived in the Çukurova region without known cardiovascular risk factors or overt heart disease (mean age: 62.8±10.4 years). Serum 25 (OH) D was measured using a direct competitive chemiluminescent immunoassay. The patients were divided into two groups according to serum 25 (OH) D level: vitamin D-non-deficient group (vitamin D≥ 20.00 ng/mL, n=53) and vitamin D-deficient group (vitamin D< 20.00 ng/mL, n=98). MPI was defined as the sum of isovolumic contraction and relaxation times divided by the ejection time. LV mass index (LVMI) was calculated by using the Devereux formula and body surface area.

Results: MPI and LVMI values were lower and low-density lipoprotein (LDL) levels were higher in patients who were vitamin D-non-deficient than patients who were vitamin D-deficient (p<0.05 for all). Multivariate linear regression analysis showed that serum 25 (OH) D was independently associated with MPI (β=-0.426, p<0.001), LVMI (β=-0.345, p<0.001), and LDL (β=0.140, p<0.026).

Conclusion: Lower serum 25 (OH) D levels are significantly associated with impaired myocardial performance and LVMI.

Keywords: vitamin D, Tei index, myocardial performance index, hypertension

Introduction

Hypertension is an established major independent risk factor for cardiovascular disease (1). Serum 25 (OH) D deficiencies or insufficiency is a substantially prevalent condition in the general population (2). Furthermore, vitamin D deficiency is independently associated with cardiovascular morbidity and mortality in the general population and hypertensive patients (3, 4). Lower serum 25 (OH) D levels are associated with a higher prevalence of hypertension (5, 6). Moreover, vitamin D suppresses the renin-angiotensin-aldosterone system (RAAS), which has an effect on blood pressure (7).

Vitamin D receptors are found in many cells of the cardiovascular system (8). Vitamin D affects left ventricular structure by increasing left ventricle mass and myocardial contractility by affecting calcium flux and calcium homeostasis (9). Left ventricle (LV) myocardial performance index (MPI) combines the indices of contraction and relaxation in an overall index of LV function (10, 11). We hypothesized that vitamin D level may be associated with LV function and geometry. In present study, we aimed to investigate the association between 25 (OH) D and MPI and LV hypertrophy in newly diagnosed hypertensive patients.

Methods

Study population

Between January 2013 and July 2013, 151 sequential patients (mean age: 62.8±10.4 years) who were admitted to the Adana
Body surface area of all subjects was computed as weight divided by height squared (kg/m²). The institutional Ethics Committee approved the study, and written informed consent for participation in the study was obtained from all individuals. None of the patients was taking calcium or vitamin D supplements. The patients were divided into two groups according to serum 25 (OH) D level: vitamin D-non-deficient group (vitamin D≥20.00 ng/mL, n=53) and vitamin D-deficient group (vitamin D<20.00 ng/mL, n=98). Exclusion criteria were malignant HT (high blood pressure with acute impairment of one or more organ systems), evidence of secondary HT (diabetic nephropathy, polycystic kidney disease, renovascular hypertension, Cushing syndrome, thyroid diseases, hyperparathyroidism, coarctation of the aorta, obesity etc.), diabetes mellitus, systolic heart failure (left ventricle ejection fraction (LVEF) <55%), positive history or clinical signs of ischemic heart disease, cerebrovascular disease, valve disease, atrial fibrillation, smoking, receiving any drugs (lithium, NSAID, prednisolone, etc.), moderate and severe renal insufficiency (eGFR formulated by MDRD <60 mL/min/1.73 m²), evidence of hypercalcemia (normal range: 9-10.5 mg/dL or 2.2-2.6 mmol/L), severe hepatic dysfunction, and major non-cardiovascular diseases, such as autoimmune disease, cancer, and systemic inflammatory conditions. The Echocardiography

Echocardiography

Transthoracic echocardiographic examination was performed in the left lateral position. Standard 2-dimensional and Doppler echocardiographies were performed using a commercially available echocardiography machine (Vivid 7R GE Medical System, Horten, Norway). LV end-diastolic diameter (LVDd), LV end-systolic diameter, and left atrial (LA) diameter were measured according to established standards of the American Society of Echocardiography (14). LVEF was calculated by Simpson’s method (14). All measurements were calculated from an average of 5 consecutive cardiac cycles.

LV mass (LVM) was calculated according to the Devereux formula (15): LVM=1.04 [(LVDd+IVSth+PWT)-(LVDd)²]-13.6. Thereafter, LV mass index (LVMi) was obtained by the following formula: LVM/body surface area (g/m²) (13). Intra- and inter-assay CV were below 4.3% and 7.2%, respectively. We also recorded the dates of the 25-hydroxyvitamin D measurements and categorized them into 2 seasons: winter (Jan-Mar) and spring-summer (April-July). In this study, 20 ng/mL 25-hydroxyvitamin D was used as a cut-off for vitamin D sufficiency according to the recommendations from the WHO and, more recently, the Institute of Medicine (12, 13).

Tissue Doppler measurements and calculation of the tissue Doppler-derived myocardial performance index

The tissue Doppler (TD) of the mitral annulus movement was obtained from the apical 4-chamber view. A 2-mm sample volume was placed sequentially at the lateral and septal annular sites. Pulse wave tissue Doppler was performed with a 2-mm sample volume placed at the lateral and septal corner of the mitral annulus from the apical 4-chamber view. Filters were set to exclude high-frequency signals and gain minimized. Doppler ultrasound scanning intervals were measured from the mitral annular velocity intervals. The isovolumetric relaxation time (IVRT) was measured from the onset of closure of the aortic valve until the onset of opening of the mitral valve. The isovolumetric contraction time (ICT) was measured from the onset of closure of the mitral valve until the onset of opening of the aortic valve. The ejection time (ET) was calculated from the opening until the closure of the aortic valve (10). All parameters were measured from the same cardiac cycle. Tissue Doppler measurements were calculated from an average of 5 consecutive cardiac cycles. The TD-derived MPI value was calculated by adding ICT and IVRT and dividing the sum by the ET: (ICT + IVRT)/ET (10). We used the averages of the septal and lateral annulus of the mitral ICT, IVRT, and ET for calculating the MPI. The method of MPI is...
shown in Figure 1. The intra-assay CV was less than 5%, and the inter-assay CV less than 6% for measurements of the MPI.

Statistical analyses

All analyses were conducted using SPSS 17.0 (SPSS for Windows 17.0, Chicago, IL, USA). Continuous variables were expressed as mean±SD, and categorical variables were expressed as percentages. Analysis of normality was performed with the Kolmogorov-Smirnov test. Comparison of categorical variables between the groups was performed using the chi-square (χ²) test. Independent-samples t-test was used in the analysis of continuous variables. Non-normally distributed variables (hs-CRP and triglyceride) were compared with Mann-Whitney U test. The correlations between 25 (OH) D and laboratory, hemodynamic, and echocardiographic parameters were assessed by Pearson correlation analysis. Multivariate, stepwise linear regression analysis was performed to identify the independent associations of serum 25 (OH) D. All significant parameters in the univariate analysis were selected in the multivariate analysis. To avoid overfitting and collinearity in assessing the multivariate model, independent variables were tested for intercorrelation. Collinearity between variables was excluded before modeling. Finally, MPI, LDL, LVMII, LVID, Cr, and parathyroid hormone levels were selected in the multivariate model. A p <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics

The median serum 25 (OH) D value was 14.35 ng/mL. The vitamin D concentrations measured in winter were similar to in spring-summer (13.91±5.9 ng/mL vs. 14.79±7.4 ng/mL, p=0.132) in patients.

The comparison of baseline characteristics of patients is shown in Table 1. Age, gender, BMI, SBP, DBP, heart rate, fasting blood glucose, triglyceride, HDL, hs-CRP, and calcium were simi-

| Variables | Vitamin D-non-deficient (n=53) | Vitamin D-deficient (n=98) | P |
|-----------|-------------------------------|----------------------------|---|
| Age, years | 60.9±9.7                     | 63.9±10.7                  | 0.09 |
| Gender, male | 28 (52.8%)                 | 48 (49.0%)                 | 0.734 |
| BMI, kg/m² | 30.5±4.4                     | 29.0±4.7                   | 0.07 |
| SBP, mm Hg | 147.8±18.5                   | 145.9±12.6                 | 0.509 |
| DBP, mm Hg | 92.0±9.8                     | 91.5±8.4                   | 0.721 |
| Heart rate, beats/minute | 76.3±14.3              | 76.4±12.3                  | 0.978 |
| Glucose, mg/dL | 93.1±12.5              | 94.9±13.8                  | 0.424 |
| Total cholesterol, mg/dL | 205.94±42.64              | 187.87±41.18               | 0.012 |
| TRG, mg/dL median (25th-75th) | 168 (123-228)            | 148 (102-202)              | 0.325 |
| HDL, mg/dL | 42.9±9.3                     | 42.2±11.5                  | 0.657 |
| LDL, mg/dL | 136.3±32.7                   | 117.4±34.6                 | 0.001 |
| hs-CRP, mg/dL median (25th-75th) | 0.4 (0.2-0.8)          | 0.4 (0.2-1.1)              | 0.1 |
| Creatinine, mg/dL | 0.74±0.18                   | 0.79±0.19                  | 0.044 |
| MDRD, mL/min/1.73 m² | 108.1±28.8                 | 97.8±26.7                  | 0.034 |
| Vitamin D, ng/mL | 25.9±4.3                   | 11.8±3.9                   | <0.001 |
| Parathyroid hormone, pg/mL | 40.2±15.7                | 49.4±25.4                  | 0.006 |
| Calcium, mg/dL | 9.3±0.6                    | 9.2±0.5                    | 0.439 |

Vitamin D- body mass index; DBP - diastolic blood pressure; HDL - high-density lipoprotein cholesterol; hs-CRP - high-sensitivity C-reactive protein; LDL - low-density lipoprotein cholesterol; SBP - systolic blood pressure; TRG - triglyceride; Vit D - vitamin D

Data are n (%) for categorical variables, means±SD for continuous variables, or median (25% and 75% interquartiles) for non-normally distributed variables

Comparison of echocardiographic parameters

The comparison of echocardiographic parameters of patients is demonstrated in Table 2. LVEF and LA diameter were similar between groups (p>0.05). However, patients who were vitamin D-deficient had higher values of IVSth, PWT, LVMII, TD-IVRT, TD-IVCT, TD-ET, and MPI values compared with patients who were vitamin D-non-deficient (p<0.05 for all).

Bivariate and multivariate relationships of vitamin D

On Pearson’s correlation analysis, serum 25 (OH) D level was significantly positively associated with LDL-cholesterol (r=0.234, p=0.004) and significantly negatively associated with LVMII (r=-0.500, p<0.001), MPI (r=-0.562, p<0.001), and LVID (r=-0.282, p<0.001). The relationships between 25 (OH) D with MPI and LVMII are shown in Figures 2 and 3.

Multivariate relationships of vitamin D are shown in Table 3. Multivariate linear regression analysis showed that 25 (OH) D
was independently associated with MPI (β=-0.426, p<0.001), LVMI (β=-0.345, p<0.001), and LDL (β=0.140, p<0.026).

### Discussion

The main findings of our study were as follows: (1) patients who were vitamin D-deficient had higher creatinine value, parathyroid hormone level, MPI, and LVMI and lower total cholesterol and LDL compared with patients who were vitamin D-non-deficient and (2) serum 25 (OH) D level was independently associated with MPI, LVMI, and LDL values. The study findings confirmed our hypothesis. Recent clinical studies showed that low levels of vitamin D are associated with hypertension and cardiovascular diseases, such as myocardial infarction and congestive heart failure (5, 6, 16-19). The antihypertensive effects of vitamin D include suppression of renin and parathyroid hormone levels and renoprotective, anti-inflammatory, and vasculoprotective properties (20, 21).

Low vitamin D and high PTH level have been associated with clinical cardiovascular disease (CVD) outcomes, including incident hypertension, myocardial hypertrophy, heart failure, and CVD death (22, 23). Left ventricular mass and LVEF are both important predictors of heart function decline and mortality (24).

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**Table 2. Comparison of echocardiographic parameters**

| Variables          | Vitamin D-deficient (n=53) | Vitamin D-non-deficient (n=98) | P       |
|--------------------|---------------------------|-------------------------------|---------|
| LVID, cm           | 4.31±0.63                 | 4.55±0.53                     | 0.020   |
| LA, cm             | 3.55±0.32                 | 3.61±0.33                     | 0.212   |
| LVF, %             | 64.7±3.6                  | 63.2±5.1                      | 0.501   |
| IVSth, cm          | 0.98±0.20                 | 1.13±0.19                     | <0.001  |
| PWth, cm           | 1.00±0.15                 | 1.12±0.20                     | <0.001  |
| LVMI, g/m²         | 89.1±32.9                 | 125.9±46.9                    | <0.001  |
| TD-IVRT, msec      | 84.3±9.5                  | 95.8±15.8                     | <0.001  |
| TD-IVCT, msec      | 45.9±6.3                  | 55.0±10.4                     | <0.001  |
| TD-ET, msec        | 258.1±25.6                | 266.3±37.9                    | <0.045  |
| TD-MPI             | 0.47±0.11                 | 0.63±0.16                     | <0.001  |

Values are means±SD.

ET - ejection time; IVCT - isovolumic contraction time; IVRT - isovolumic relaxation time; IVSth - interventricular septal thickness; LA - left atrial diameter; LVEF - left ventricular ejection fraction; LVID - left ventricle internal diameter; LVMI - left ventricle mass index; MPI - myocardial performance index; PWth - posterior wall thickness; TD - tissue Doppler

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**Table 3. Multivariate Relationships of Vit D**

| Variables | Standardized β-regression coefficients | P       |
|-----------|----------------------------------------|---------|
| MPI       | -0.426                                 | <0.001  |
| LDL mg/dL | 0.140                                  | 0.026   |
| LVMI g/m² | -0.345                                 | <0.001  |

LDL - low-density lipoprotein cholesterol; LVMI - left ventricle mass index; MPI - myocardial performance index

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**Figure 2. Scattergraph showing strong inverse correlation between 25-hydroxyvitamin D (ng/mL) and myocardial performance index**

**Figure 3. Scattergraph showing relationship between 25-hydroxyvitamin D (ng/mL) and left ventricle mass index (g/m²)**

Improvements in LVEF have been associated with improved prognosis, and this may point to a potential role for PTH as a determinant of cardiac remodeling (24). According to the ICELAND-MI substudy of AGES-Reykjavik, PTH was associated with measures of cardiac structure and function by using cardiac MRI (25). In our study, PTH level was significantly higher in patients with vitamin D deficiency but was not independently associated with MPI. We think that one of the most important reasons of the difference between our results and the previous study results is the technical difference of evaluating left ventricular function.

Vitamin D deficiency is prevalent in chronic heart failure and is associated with poor outcomes (16). However, the effect of vitamin D on myocardial performance in patients with preserved left ventricular systolic function (LVEF>50%) has not been studied previously. Our results showed that 25 (OH) D levels were independently associated with impaired MPI. The MPI has been...
Vitamin D supplementation is significantly associated with better survival, specifically in patients with documented vitamin D deficiency (39). Moreover, vitamin D supplementation regresses both LV hypertrophy and LV dysfunction (38-42). In our study, we found an inverse relationship between 25 (OH) D and MPI. Vitamin D supplementation is simple, safe, and inexpensive. However, larger trials are needed to confirm our results and to determine whether vitamin D interventions prevent the development of impaired myocardial performance in hypertensive patients with newly diagnosed and preserved LVEF.

Study limitations

The present study has some limitations. Firstly, our study is a cross-sectional design and does not provide any insight into the mechanisms that are responsible for the observed associations. Secondly, it has been known that serum vitamin D levels vary with region, seasonality, and altitude due to possible effects of sunlight. Thirdly, the half-life of vitamin D is approximately 3 weeks, but serum vitamin D levels may change throughout the day and season of the year. So, a single measurement may not reflect the actual vitamin D status. Lastly, the Tei index is dependent on heart rate (43). In our study, the heart rates of the groups were similar.

Conclusion

The present study showed that lower serum 25 (OH) D levels were significantly associated with impaired myocardial performance, as well as LV hypertrophy and LDL level, in hypertensive patients with newly diagnosed and preserved EF. Lower 25 (OH) D levels may play a role in the pathogenesis of myocardial dysfunction, even if EF is normal.

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