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Vitamin D Attenuates Left Atrial Volume Changes in African American Males with Obesity and Prediabetes

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Abstract

Vitamin D deficiency is common among African Americans in the United States and is associated with increased cardiovascular disease risk. In this study, prediabetic African American males who were found to be vitamin D–deficient were randomized to vitamin D supplementation and assessed for changes in left atrial (LA) volume. Prediabetic African American males who were vitamin D–deficient (25(OH)D: 5.0–29 ng/mL) were randomized to high-dose ergocalciferol or placebo. Echocardiography was performed at baseline and at 1 year. Ejection fraction (EF), septal and posterior wall thickness, LA area, LA length, LA volume, E, A, septal and lateral e′ and a′, deceleration time, and isovolumetric relaxation time were collected. Eighty-one of 158 (51%) subjects received vitamin D_2. Baseline characteristics were similar among both groups. In the placebo group, left atrial volume significantly increased on follow-up (LA volume increased 6.3 mL, P = 0.0025). Compared with placebo group, the treatment group with ergocalciferol had attenuated increases in left atrial volume (LA volume increased 2.6 mL, P = 0.29). Changes in left atrial volume persisted when indexed to body surface area. There was no significant difference in other diastolic parameters and blood pressure between groups. In conclusion, vitamin D–deficient prediabetic African American males who were treated with high-dose vitamin D_2 were found to have attenuated increases in left atrial volume compared with controls over 12-month follow-up.

Keywords

vitamin D; left atrium; diabetes; supplementation

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Left atrial enlargement is well known to be a strong prognostic factor in cardiovascular outcomes. Left atrial volume increases as a result of either pressure or volume overload. The increase in left atrial size as a response to increased filling pressures has been documented on invasive studies,[1] while chronic volume overload states also result in chamber enlargement. Increased left atrial volume is a marker of diastolic dysfunction, and these patients have been shown to have higher rates of cardiovascular events, including atrial fibrillation, stroke, heart failure, hypertension, and all-cause mortality.[2] In patients with type 2 diabetes mellitus, left atrial dysfunction has been found to be significantly greater than controls.[3]

While vitamin D deficiency is typically thought to involve the musculoskeletal system, there has been significant evidence linking it with adverse cardiovascular events.[4] In the Framingham Offspring Study, individuals with vitamin D deficiency (25(OH)D3 < 37.5 nmol/L) had a hazard ratio of 1.62 for development of cardiovascular disease compared with those with normal levels.[5] Vitamin D–deficient individuals have been found to have over a twofold increased risk of MI, even after adjustment for common risk factors.[6] Patients with low 25-hydroxy vitamin D levels have a higher risk of sudden cardiac death, heart failure, cardiovascular mortality, and all-cause mortality.[7] Patients with newly diagnosed type 2 diabetes have been found to have lower levels of 25-hydroxy vitamin D as compared to healthy controls,[8, 9] and low 25(OH)D is a risk factor for hyperglycemia.[10] Diabetes has long been known to be a significant risk factor for cardiovascular disease, but the effect of vitamin D supplementationon cardiovascular parameters has not been studied in this population. In this study, prediabetic African American males who were found to be vitamin D–deficient were randomized to vitamin D supplementation and assessed for changes in left atrial area and volume.

Methods

This study was ancillary to a vitamin D supplementation study conducted in veterans between 2011 and 2013. Vitamin D Intervention in Veteran Administration (DIVA Study) has been described elsewhere.[11] Briefly, DIVA was a double-blind placebo-controlled randomized clinical trial conducted to test the effect of supplementation with high doses of vitamin D for 12 months on oral glucose insulin sensitivity in African American males with obesity and prediabetes. Secondary outcomes included changes in left atrial area and volume. The study was approved by the University of Illinois Institutional Review Board and by the Jesse Brown VA Medical Center (JBVAMC) Research and Development Committee. The study was registered at clinicaltrials.gov (NCT01375660).

Subjects were recruited from JBVAMC in Chicago, and eligible participants were randomized to placebo or vitamin D groups. They had follow-up every 3 months and the final assessment after 12 months of treatment. The subjects provided written informed consent prior to participation.

Inclusion Criteria

The main inclusion criteria were as follows: African American male veterans, age 35–85 years, BMI 28–39 kg/m^2, fasting glucose 95–125 mg/dL and/or A1c 5.7–6.4%, and

25(OH)D 5.0–29 ng/mL. Participants who were diagnosed with diabetes during screening or intervention were allowed in the study if they did not need to take antidiabetic medications and A1c remained <7%.

The main exclusion criteria were diabetes and any medical conditions that would be expected to interfere with the study or increase risk to the subject, such as kidney stones, hypercalcemia, hyperparathyroidism, sarcoidosis, and chronic kidney disease (CKD) beyond stage 3a (eGFR < 45 mLs/min/1.73 m^2).

A total of 2067 subjects were prescreened, 205 randomized, and 173 (84%) came for the final visit. Of these 173 subjects, 158 (91%) had successful baseline and exit echocardiograms and were analyzed for the present study.

Vitamin D

All subjects received cholecalciferol (D3) 400 IU as multiple vitamins and in addition either weekly ergocalciferol (D2) 50 000 IU (Pliva Co., Zagreb, Croatia) or placebo. Out of n = 158 subjects included in the present ancillary study, n = 77 received weekly placebo and n = 81 received vitamin D2 50 000 IU. Serum vitamin 25(OH)D was measured at baseline and 12 months.

Outcomes

The main outcome of interest involved the change in left atrial dimensions, specifically left atrial area, length, and volume. Other parameters measured were left ventricular ejection fraction, septal and posterior wall thickness, and markers of LV diastolic function (early [E] and late [A] mitral inflow wave velocities, early [E′] and late [A′] mitral annular relaxation velocity, isovolumetric relaxation time [IVRT], and E-wave deceleration time). Biplane Simpson's method was used to calculate left atrial volume from apical four- and two-chamber views at end-systole. All parameters were measured by a single sonographer in accordance with the American Society of Echocardiography guidelines.[12, 13]

Statistical Analysis

The sample size for the study was calculated according to general recommendations and previously published study.[14] Before statistical analysis, normal distribution and homogeneity of the variances were tested. Baseline characteristics were compared with independent *t*-tests. The mean circulating 25(OH) vit D was across five measurements: baseline and follow-up at 3, 6, 9, and 12 months. Values were represented as means and standard deviations (SD). The significance was determined at $P < 0.05$ (two tailed). Statistical analysis was conducted using IBM SPSS 21 (Armonk, NY, USA).

Results

Baseline Characteristics

Baseline characteristics were similar between groups (Table I). All subjects were African American males and had equivalent hemoglobin A1c, BMI, and blood pressure values. Average age of those in the therapy arm was 58.1 ± 7.3 years, while those in the placebo arm

were 59.6 ± 8.5 years. There was also similar prevalence of major cardiovascular risk factors including hypertension, hyperlipidemia, peripheral vascular disease, obstructive sleep apnea, and tobacco use.

Baseline echocardiographic measurements were similar between the two groups (Table II). Both groups had a normal ejection fraction. Left atrial volume indexed to body surface area (LaVi) was mildly abnormal, and left atrial diameter was moderately abnormal. Wall thickness was similar between the two groups. Isovolumetric relaxation time (IVRT) and deceleration time (DT) were prolonged, and both septal and lateral early diastolic mitral annular velocity (septal E′ and lateral E′) were decreased, suggesting abnormal diastolic function.

Serum Vitamin D Concentration

At 12 months, the mean serum 25(OH) vit D level had increased to 50.5 ± 24.1 ng/mL in the treatment group and to 20.18 ± 9.6 ng/mL in the placebo group (between groups $P < 0.001$).

Left Atrial Change

Follow-up echocardiographic results are shown in Table III. In the placebo group, left atrial volume significantly increased on follow-up (LA volume increased 6.3 mL, $P = 0.0025$). Compared with placebo group, the treatment group with ergocalciferol had attenuated increases in left atrial volume (LA volume increased 2.6 mL, $P = 0.29$). Changes in left atrial volume persisted when indexed to body surface area. Left ventricular ejection fraction and wall thickness did not change significantly in either group, as well as parameters evaluating diastolic function (IVRT, DT, septal E′, lateral E′). Of note, there was no significant difference in blood pressure between groups at 12-month follow-up ($P = 0.941$). Univariate predictors of left atrial volume change are shown in Table IV, with no variable reaching statistical significance.

Discussion

In this trial, vitamin D–deficient prediabetic African American males who were treated with high-dose vitamin D_2 were found to have attenuated increases in left atrial volume compared with controls over 12-month follow-up, despite similar blood pressure control. This is significant because in this high-risk population, abnormal cardiac structure is very prevalent and a marker of worse outcomes.[15] While vitamin D supplementation has been studied in various groups, our study is unique in that the population was prediabetic African American males, a cohort that has not been investigated to date. Prediabetics have an increased risk of cardiovascular diseases,[16] stemming from early pancreatic β-cell dysfunction and insulin resistance.[17] Early intervention has been shown to reduce long-term vascular complications in these patients, [18] and our study suggests that early supplementation in those who are vitamin D–deficient may slow deleterious changes in cardiac structure.

The vitamin D receptor (VDR) is present in numerous tissues, many of which could play a role in the changes seen in our patient population. The VDR is present in endothelium,[19] and in diabetics, vitamin D supplementation has been shown to improve endothelial function,[20] possibly through improving vascular resistance, reducing inflammation, or by activating

vascular endothelial growth factor (VEGF) which in turn increases nitric oxide synthesis in endothelial cells.[21] Vitamin D suppresses pro-inflammatory cytokines and causes an increase in IL-10 levels.[22] The VDR is also known to inhabit cardiac myocytes.[23] In animal models, vitamin D regulated myocyte growth 24 and it has been proposed that the presence of the VDR in sarcolemma may regulate myocyte relaxation.[25] Left atrial remodeling may also be affected by vitamin D regulation of extracellular matrix metalloproteinases which would inhibit collagen deposition.[26] Possibly most significant is the effect that vitamin D has on inhibiting the renin–aldosterone–angiotensin system (RAAS).[27] Atrial wall tension activates RAAS, and subsequent increases in angiotensin II would typically cause fibroblast proliferation and fibrosis formation, but these are attenuated with vitamin D.[28] Inhibiting RAAS and PTH also has positive effects on blood pressure regulation, which ultimately impacts left atrial volume.[29] It is notable that while increases in left atrial volume were attenuated, Doppler measurements of diastolic function did not significantly change throughout the study. This could possibly be because our sample size was too small to detect a difference in these parameters. However, elsewhere vitamin D levels were also not associated with left ventricular diastolic performance.[30]

Our study builds on prior work investigating the echocardiographic changes associated with vitamin D. Vitamin D deficiency has been shown to be an independent predictor of left ventricular hypertrophy [31] and in patients with heart failure is associated with left ventricular dilation.[32] Even in children, vitamin D deficiency has been associated with increased left ventricular mass and diastolic dysfunction.[33] Regarding the left atrium, it has been shown that patients with atrial fibrillation have lower vitamin D levels and larger left atrial diameters than age-matched controls.[28] In patients with left ventricular hypertrophy and chronic kidney disease, vitamin D supplementation has been shown to decrease LaVi.[27] Our study adds to these findings in a different but similarly at-risk cohort.

There are a few limitations to our study. While left atrial size and volume is a marker of worse cardiovascular outcomes, it is just a surrogate for cardiovascular events. Due to our study size, it is difficult to say whether vitamin D supplementation would affect cardiac hospitalizations and mortality in our population. In addition, our inclusion criteria were quite rigorous, and while this provided a very homogenous sample, caution should be made when applying these results to patients outside of this group.

In summary, vitamin D–deficient prediabetic African American males who were treated with high-dose vitamin D_2 were found to have attenuated increases in left atrial volume compared with controls over 12-month follow-up. Further studies are warranted to investigate whether vitamin D supplementation in this population has effects on long-term cardiovascular outcomes.

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TABLE I

Baseline Characteristics

	Placebo (n = 77)	**Therapy (n = 81)**	**P**
Age (years)	59.6 (±8.5)	58.1 (±7.3)	0.3
BMI (kg/m^2)	31.6 (±3.1)	32.4 (±3.4)	0.15
A1c (%)	6.1 (±0.3)	6.1 (±0.3)	0.16
Vitamin D [25-OHD] (ng/mL)	13.8 (±5.9)	14.9 (±5.9)	0.19
Hypertension (%)	65.2	71.6	0.62
Hyperlipidemia (%)	60.6	50.6	0.39
Coronary artery disease (%)	7.6	11.5	0.5
Stroke (%)	3.0	9.9	0.08
Congestive heart failure (%)	3.0	6.2	0.2
Peripheral vascular disease (%)	0.0	2.5	0.17
Obstructive sleep apnea (%)	10.6	18.5	0.18
Tobacco use (%)	45.2	51.9	0.57

TABLE II

Baseline Transthoracic Echocardiogram Measures

Measures	Placebo (n = 77)	Therapy (n = 81)
EF (%)	61.1 (±6.0)	61.5 (±8.3)
SWT (cm)	1.0 (±0.2)	1.0 (±0.2)
PWT (cm)	1.1 (±0.15)	1.0 (±0.2)
LVEDd (cm)	4.7 (±0.6)	4.7 (±0.7)
LVEDs (cm)	2.5 (±0.7)	2.5 (±0.8)
LA Area (cm^2)	18.5 (±3.7)	18.6 (±4.9)
LA Length (cm)	4.9 (±0.6)	4.8 (±0.8)
E (m/sec)	0.7 (±0.2)	0.7 (±0.2)
A (m/sec)	0.6 (±0.2)	0.6 (±0.2)
DT (ms)	230.1 (±51.9)	225 (±52.5)
IVRT (ms)	104.3 (±18.1)	104 (±21.1)
Sep E′ (m/sec)	0.07 (±0.02)	0.07 (±0.03)
Sep A′ (m/sec)	0.09 (±0.02)	0.1 (±0.09)
Lat E′ (m/sec)	0.09 (±0.03)	0.09 (±0.02)
Lat A′ (m/sec)	0.1 (±0.03)	0.1 (±0.09)
LA Vol (mL)	62.8 (±17.8)	62.9 (±19.4)
LAVI (mL/m^2)	28.0 (±7.6)	28.93 (±9.0)

TABLE III

Change in Transthoracic Echocardiography Measures from Baseline to 1 year

	Placebo (n = 77)		Therapy (n = 81)	
Measures	**Change**	**P**	**Change**	**P**
EF (%)	−0.3 (±5.7)	0.61	−0.1 (±5.3)	0.84
SWT (cm)	0.0 (±0.2)	0.55	0.0 (±0.2)	0.41
PWT (cm)	−0.1 (±0.1)	0.56	0.0 (±0.1)	0.36
LVEDd (cm)	0.1 (±0.5)	0.38	0.0 (±0.5)	0.62
LVEDs (cm)	−0.1 (±0.8)	0.38	−0.2 (±0.8)	0.18
LA Area (cm^2)	0.6 (±3.2)	0.04	0.8 (±4.6)	0.18
LA Length (cm)	0.0 (±0.6)	0.49	0.2 (±0.6)	0.02
E (m/sec)	0.0 (±0.2)	0.70	0.0 (±0.2)	0.61
A (m/sec)	0.1 (±0.1)	0.37	0.1 (±0.1)	0.09
DT (ms)	−1.8 (±40.8)	0.49	6.1 (±64.6)	0.23
IVRT (ms)	−2.4 (±26.3)	0.27	−1.9 (±22.6)	0.41
Sep E′ (m/sec)	0.0 (±0.1)	0.50	0.0 (±0.2)	0.26
Sep A′ (m/sec)	0.0 (±0.02)	0.86	0.0 (±0.0)	0.95
Lat E′ (m/sec)	0.0 (±0.02)	0.37	−0.1 (±0.0)	0.08
Lat A′ (m/sec)	0.0 (±0.03)	0.09	0.0 (±0.0)	0.85
LA Vol (mL)	6.3 (±16.3)	0.0025	2.6 (±16.8)	0.29
LAVI (mL/m^2)	2.9 (±7.35)	0.0022	0.8 (±8.6)	0.36

TABLE IV

Univariate Predictors of Left Atrial Volume Change

Variable	β	P
Baseline 25D (ng/mL)	−0.332	0.2
EF (%)	−0.571	0.06
SWT (mm)	−0.241	0.7
PWT (mm)	−0.015	0.99
LVIDd (mm)	−0.068	0.81
IVIDs (mm)	0.195	0.38
E (cm/sec)	−11.847	0.16
DT (ms)	−0.028	0.36
IVRT (ms)	0.06	0.52
Sep E′ (cm/sec)	−127.625	0.11
Lat E′ (cm/sec)	−99.386	0.11
Average E′ (cm/sec)	−138.479	0.08