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Plasma Vitamin D Binding Protein and Risk of Heart Failure in Male Physicians

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Abstract

Previous studies suggest that vitamin D deficiency may contribute to the pathogenesis of heart failure (HF); however, limited data are available on the association of vitamin D binding protein (VDBP) – a major transport protein for vitamin D – with the development of HF. Thus, we investigated whether plasma VDBP is inversely associated with HF risk. Using a prospective nested case-control design, we selected 464 cases and 464 matched controls from the Physicians' Health Study for current analyses. VDBP was determined using an enzyme-linked immunoassay. Self-reported HF was obtained through annual follow-up questionnaires and validated in a subsample via review of medical records. We used conditional logistic regressions to compute adjusted odds ratios. The mean age was 58.6 years and the median VDBP was 307.8 (IQR: 265.2–354.6) µg/mL. Plasma VDBP was not associated with HF in our study: OR (95% CI): 1.0 (ref), 1.05 (0.66–1.65), 1.28 (0.80–2.06), 1.07 (0.65–1.75), and 1.28 (0.76–2.15) across consecutive quintiles of VDBP, *p* for linear trend 0.41, after adjustment for matching factors, body mass index, diabetes, atrial fibrillation, hypertension, and high sensitivity C-reactive protein. In conclusion, our data showed no significant association between plasma levels of VDBP and HF risk in apparently healthy male physicians.

Keywords

risk factors; epidemiology; heart failure; vitamin D binding protein

Introduction

Heart failure (HF) remains a major public health burden in the United States with a lifetime risk of 1 in 5 at 40 years of age¹ and mortality ranging from 20% to 50%.^{2–4} Emerging research suggests an association between HF risk and vitamin D deficiency. In a prospective study of 41,504 health records, low serum 25-hydroxyvitamin D (25-OHD) was associated with a 31% higher risk of HF compared to normal levels.⁵ Such a relation could be partially explained by the role of vitamin D on parathyroid hormone, renin, vascular endothelial growth factor, calcium influx, inflammation, and platelet aggregation; all of which can

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impact myocardial function and the development of HF.⁶⁻⁹ However, administering vitamin D supplementation in HF patients has produced mixed results.¹⁰⁻¹² One hypothesis for these results is not a lack of 25-OHD, but a low level of vitamin D binding protein (VDBP), an abundant Gc-globulin whose major function is to bind and transport 25-OHD from plasma into target cells.^{13,14} VDBP protects against vitamin D deficiency and is essential for normal vitamin D homeostasis.¹⁵⁻¹⁷ It is currently unknown if the relationship between vitamin D and risk of HF is partly due to low levels of circulating plasma VDBP. If true, VDBP could serve as a novel pharmacological target for new drugs. Therefore, in the current study, we sought to examine whether lower plasma VDBP levels are associated with a higher risk of HF in a prospective nested case-control study of US male physicians.

Methods

This ancillary study was a nested case-control study using data from the Physicians' Health Study (PHS), a completed randomized, double blind, placebo-controlled trial designed to study low-dose aspirin and beta carotene for the primary prevention of cardiovascular disease and cancer among US male physicians. A detailed description of the PHS has been previously published.¹⁸ Of the total 22,071 participants, we randomly selected 464 incident HF cases that occurred after baseline blood collection (1982). We used a risk set technique to match each incident HF case to a control on age at randomization (within 1 year), race (white/non-Hispanic, Hispanic, African-American/black, Asian/Pacific islander, other) – whenever possible given the presence of missing values for this variable, year of birth (within 1 year), and time of blood collection (within 288 days). Each case was eligible to serve as a control prior to HF diagnosis. Similarly, each control was eligible to later become a HF case to assure that controls were representative of the total population that gave rise to the HF cases. Each participant gave written informed consent and the Institutional Review Board at Brigham and Women's Hospital approved the study protocol.

VDBP was determined in human plasma (1:20000) using a sandwich immunoassay from Alpco Diagnostics (Salem, NH). Inter-assay coefficient of variation was 6%. HF outcome in the PHS was ascertained by annual follow-up questionnaires. Specifically, a questionnaire was mailed to each participant every 6 months during the first year and was mailed annually thereafter to obtain information on compliance with the intervention and the occurrence of new medical diagnoses, including HF. Detailed description of HF validation in the PHS using review of medical records in a subsample has been published elsewhere.^{19,20} Information on demographic variables, body mass index, cigarette smoking, exercise, alcohol consumption, and history of diabetes mellitus, atrial fibrillation, and hypertension were collected at baseline. High sensitivity C-reactive protein (hsCRP) was measured in human plasma using a latex-particle enhanced immunoturbidimetric assay (Roche Diagnostics, Indianapolis, IN 46250) and analyzed on a Roche Modular P Chemistry analyzer (Roche Diagnostics). Inter-assay coefficient of variation was 4.5%.

We used conditional logistic regression to calculate odds ratios (OR) with corresponding 95% confidence interval (CI). We created quintiles of VDBP using its distribution in the control series. The lowest quintile of VDBP was used as the reference group. We assessed confounding by body mass index (continuous); history of atrial fibrillation (yes/no), history of diabetes (yes/no), history of hypertension (yes/no), and the natural logarithm of hsCRP (continuous). We obtained a p-value for linear trend by creating a new variable that was assigned the median VDBP value from the control series in each quintile, and fitting the new variable in the conditional logistic regression model. Spearman correlation coefficients between VDBP with hsCRP, age, and body mass index were evaluated. In secondary analyses, we analyzed HF preceded by coronary heart disease (CHD) (n=143) separately from HF without antecedent CHD (n=321), and restricted the study sample to white

participants (n=864). All analyses were completed using SAS, version 9.2 (SAS Institute, Cary, NC). All p-values were 2-tailed and significance level was set at an alpha of 0.05.

Results

Characteristics of the 928 US male physicians obtained at baseline are presented in Table 1 according to quintiles of VDBP. The mean age of study participants at baseline was 58.6 ± 8.2 years (range 39.9 to 82.7 y). Compared to the lowest quintile, the highest quintile of VDBP was associated with higher hsCRP and a lower prevalence of atrial fibrillation (Table 1). VDBP was positively correlated with hsCRP, and the Spearman correlation coefficient was 0.10 ($p < 0.01$). In contrast, no correlation was found between VDBP with body mass index and age ($r = -0.03$, $p = 0.41$ and $r = 0.02$, $p = 0.53$, respectively).

In a conditional logistic regression model adjusting for matching factors, the odds ratios (95% CI) for HF were 1.0 (ref), 1.09 (0.71–1.66), 1.12 (0.72–1.73), 1.02 (0.64–1.62), and 1.15 (0.71–1.87) across consecutive quintiles of plasma VDBP (p for linear trend 0.68). Corresponding values after adjustment for body mass index, and history of atrial fibrillation, diabetes, hypertension, and hsCRP were 1.0 (ref), 1.05 (0.66–1.65), 1.28 (0.80–2.06), 1.07 (0.65–1.75), and 1.28 (0.76–2.15) (p for linear trend 0.41).

In secondary analyses, VDBP was not associated with the risk of HF with antecedent CHD in a model adjusted for matching factors, body mass index, history of atrial fibrillation, diabetes, hypertension, and hsCRP: OR (95% CI): 1.0 (ref), 1.20 (0.44–3.30), 2.22 (0.78–6.31), 1.44 (0.47–4.43), and 2.03 (0.65–6.41) across consecutive quintiles of VDBP (p for linear trend 0.28). For HF without prior CHD, corresponding values were 1.0 (ref), 0.95 (0.56–1.62), 0.94 (0.54–1.64), 1.00 (0.57–1.76), and 1.12 (0.61–2.04) (p for linear trend 0.70). Results did not change when the restricted to white participants (data not shown).

Discussion

In this nested case-control study, we found no association between plasma levels of VDBP and the odds of HF among apparently healthy male physicians.

Vitamin D can be ingested in the diet, or can be formed in the skin via ultraviolet B exposure from the sun, which is then hydroxylated into 25-OHD. This forms a circulating reservoir of vitamin D that is bound to VDBP and distributed to vitamin D receptors (found in endothelial cells, myocytes, and vascular smooth muscle cells).^{7,9} Vitamin D can influence cardiac function via suppression of parathyroid hormone, inhibition of renin, upregulation of vascular endothelial growth factor, and modulation of calcium influx.⁹ Insufficient levels of vitamin D could result from inadequate vitamin D intake, low exposure to solar ultraviolet B, dysfunction of hepatic 25-hydroxylase activity, or increased 25-OHD catabolism.⁶

Approximately 88% of 25-OHD in circulation is bound to VDBP, which transfers 25-OHD into target cells.¹³ Thus, VDBP may protect against vitamin D deficiency and is essential for vitamin D homeostasis,^{15,16} as shown in experiments with VDBP knockout mice.¹⁷ We hypothesized that low levels of VDBP will be associated with a higher risk of incident HF. If such a hypothesis were true and VDBP plays a role in the pathogenesis of HF, then VDBP could serve as a novel pharmacological target for new drugs. However, the lack of an association between VDBP and HF in our study suggests that VDBP may not play a major role in the pathogenesis of HF.

We examined for the first time whether VDBP is associated with HF risk in a large cohort, although previous studies have suggested that vitamin D deficiency is associated with a

higher risk of developing cardiovascular disease and HF. A prospective analysis of electronic medical records of 41,497 individuals found adjusted hazard ratios for HF of 2.01 ($p<0.0001$) and 1.31 ($p=0.005$) comparing very low (<15 ng/mL) and low (16–30 ng/mL) serum 25-OHD, respectively, to normal levels (>30 ng/mL).⁵ Additionally, a prospective analysis of the Ludwigshafen Risk and Cardiovascular Health study showed a decrease in 25-OHD with impaired left ventricular function, and a 2.8 times increased risk of death due to HF in individuals with severe 25-OHD deficiency compared to optimal 25-OHD levels.²¹

Contrary to the above analyses, results from studies evaluating vitamin D supplementation in HF patients have produced mixed results.^{10–12} In a cohort of 1,783 HF patients from a Health Maintenance Organization database, vitamin D supplementation was associated with a 32% reduction in mortality (95% CI: 15%–46%),¹¹ and vitamin D supplementation in a randomized control trial of 93 HF patients showed higher anti-inflammatory cytokines, and lower parathyroid hormone.¹² In contrast, in a randomized placebo-controlled trial of patients with systolic HF and 25-OHD levels <20 ng/mL, supplementation with vitamin D did not improve physical functioning in the intervention group. In fact, there was evidence of a small, but significant, worsening of quality of life 20 weeks into the trial in the intervention arm.¹⁰ Our study did not have data on 25-OHD levels for further exploration.

Our study has additional limitations. First, we cannot exclude residual or unmeasured confounding as a possible alternative explanation of our results given the observational nature of our study design. Second, we had only 1 measurement of VDBP and were not able to account for possible changes in VDBP levels over time. Third, due to assay costs, we were unable to measure biomarkers on all PHS subjects. We were also unable to measure NT-proBNP levels in our subjects. Fourth, data on HF were self-reported and we did not collect data to distinguish HF with and without preserved left ventricular systolic function; hence, we cannot exclude the possibility that some HF cases could have been missed or misclassified. Fifth, we did not have data to estimate renal function – the conversion site of 25-OHD to 1, 25 OHD – which may influence levels of 1, 25 OHD in individuals with renal disease.⁷ Lastly, the fact that our participants were male, mostly Caucasian physicians, may limit the generalizability of our findings. On the other hand, strengths of our study include matching on key variables and the ability to control for residual confounding through collected covariates; the prospective design of the PHS; and a high positive predictive value (91%) of self-reported HF in male physicians.²²

In conclusion, our data showed no association between plasma VDBP and HF risk among US male physicians.

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Table 1
Baseline characteristics of 928 US male physicians according to quintiles of plasma vitamin D binding protein

Characteristics	Quintiles of plasma vitamin D binding protein (median [range] µg/mL)				
	Q1 225.2 (108.5–251.1) (n=179)	Q2 273.4 (251.6–289.4) (n=188)	Q3 307.4 (290.1–324.4) (n=189)	Q4 345.2 (324.5–365.6) (n=181)	Q5 394.8 (365.8–1222.1) (n=191)
Age (years)	58.7 ± 8.0	58.3 ± 8.2	59.0 ± 8.0	58.2 ± 8.0	58.9 ± 8.7
Body mass index (kg/m ²)	25.5 ± 3.2	25.4 ± 3.4	25.3 ± 2.5	25.2 ± 2.7	25.2 ± 2.8
High sensitivity C-reactive protein (mg/dL)	2.7 ± 7.6	2.3 ± 3.3	2.0 ± 2.8	2.4 ± 6.4	3.3 ± 5.9
White race	170 (97.1%)	170 (95.5%)	179 (98.4%)	168 (97.7%)	177 (96.7%)
Current smoker	17 (9.5%)	28 (15.0%)	19 (10.1%)	14 (7.8%)	23 (12.0%)
Never smoked	82 (45.8%)	87 (46.5%)	82 (43.4%)	78 (43.3%)	87 (45.6%)
Current alcohol intake	149 (83.2%)	154 (82.4%)	161 (85.2%)	156 (86.7%)	158 (83.2%)
Atrial fibrillation	11 (6.2%)	10 (5.3%)	12 (6.4%)	1 (0.6%)	4 (2.1%)
Vigorous exercise	127 (71.0%)	143 (76.1%)	136 (72.0%)	143 (79.4%)	131 (70.1%)
Diabetes Mellitus	8 (4.5%)	17 (9.0%)	7 (3.7%)	11 (6.1%)	10 (5.2%)
Hypertension	53 (29.9%)	73 (39.5%)	46 (24.5%)	58 (32.0%)	58 (30.5%)

Data are presented as means ± standard deviation or number (percentage). Few participants had missing data smoking (n=2), exercise (n=5), hypertension (n=7), alcohol use (n=3), and race (38) Q = Quintile