

Vitamin D deficiency and anemia is highly prevalent and dependent on the etiology of heart failure: A pilot study

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Abstract

Background: Anemia and vitamin D deficiency are common factors in chronic heart failure (CHF). The aim of this study was to assess vitamin D levels as well as its binding protein and anemia in relation to a cause of CHF: coronary heart disease, valvular disease and cardiomyopathy.

Methods: One hundred and sixteen consecutive patients (36 females and 80 males) with CHF were admitted for percutaneous coronary interventions (PCI). Hemoglobin concentration, serum creatinine, B-type natriuretic peptide (BNP), 25-hydroxyvitamin D [25(OH)D] and its binding protein-VDBP were measured.

Results: The prevalence of anemia was 22%. BNP was the highest in the group with coronary artery disease. Ejection fraction was the lowest in cardiomyopathy group. 25(OH)D was lowest in valvular disease group, significantly lower than in the coronary artery group. A similar pattern of change showed vitamin D binding protein. The prevalence of vitamin D deficiency (level below 20 ng/mL) in the whole group was 95%, in 49% of the patients 25(OH)D was below 10 ng/mL. In univariate analysis 25(OH)D correlated with hemoglobin, red blood cell count, hematocrit, mean corpuscular volume and BNP in patients with CHF in the whole group. In multiple regression analysis, predictors of 25(OH)D were estimated, glomerular filtration rate, BNP and valvular disease.

Conclusions: 25(OH)D deficiency is common in CHF patients. Valvular disease is associated the most severe vitamin D deficiency and worsened kidney function. A higher prevalence of anemia in CHF due to coronary heart disease may be associated with wider use of angiotensin converting enzyme inhibitors and acetylsalicylic acid. Heart and kidney function are predictors of 25(OH)D level in the patients of this study. (Cardiol J 2021; 28, 2: 262–270)

Key words: vitamin D deficiency, anemia, heart failure

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Introduction

Heart failure (HF) is a common clinical syndrome caused by a variety of cardiac diseases [1]. HF prevalence has been increasing recently due to an aging population and prolongation of life by modern therapeutic innovations. Despite improvements in therapy, the mortality rate in patients with HF has remained unacceptably high [1]. In the 1970s, hypertension and coronary disease, particularly myocardial infarction (MI), were the primary causes of HF in the United States and Europe [1–3]. However, coronary artery disease (CAD) and diabetes mellitus have become increasingly responsible for HF while hypertension and valve disease have become less common because of improvements in diagnosis and therapy [4–7]. Risk factors for HF include coronary heart disease, cigarette smoking, hypertension, obesity, diabetes, and valvular heart disease [5, 8]. Vitamin D deficiency and anemia are frequent findings in HF [1–4]. It was previously shown that the prevalence of anemia in a cohort undergoing percutaneous coronary intervention (PCI) was 21% and related to the New York Heart Association (NYHA) class [9].

Taking all these data into consideration, including fact that studies on anemia and 25-hydroxyvitamin D [25(OH)D] in HF are scarce and equivocal, this cross-sectional study was designed to investigate: a) the prevalence of anemia and vitamin D deficiency in patients with HF due to CAD, cardiomyopathy or valvular disease undergoing PCIs; b) relation between 25(OH)D, its binding protein and anemia in these three subpopulations.

Methods

The study was performed on 116 consecutive patients: 36 females and 80 males with chronic HF with reduced ejection fraction admitted to the Department of Invasive Cardiology for PCIs. The criteria for patients with HF to be included in the study were according to the European Society of Cardiology (ESC) guidelines from 2016 [10]: 1) age \geq 18 years; 2) documented history of HF of \geq 6 months; 3) left ventricular ejection fraction (LVEF) \leq 40% as assessed by echocardiography (performed at the beginning of the study, using the Simpson planimetric method); 4) clinical stability and unchanged medications for \geq 1 month prior to the study. Patients were divided into three subgroups: group I — patients with chronic HF due to CAD (n = 40); group II — patients with HF due to cardiomyopathy (n = 31); and group III — patients

with HF due to valvular disease without signs or symptoms of CAD (n = 45).

Exclusion criteria included: 1) acute coronary syndrome or coronary revascularization within 3 months before the study; 2) unplanned hospitalization due to HF deterioration or any other cardiovascular reason within 1 month before the study; 3) any acute or chronic illness that might influence iron metabolism (including malignancy, infection, chronic kidney disease [CKD] requiring renal replacement therapy, and hematological diseases); 4) any anemia and/or iron deficiency treatment either at the beginning or during 12 months prior to the study. The study protocol was approved by the local ethics committee and all subjects gave informed written consent. The study was conducted in accordance with the Declaration of Helsinki. In all patients, venous blood samples were taken in the morning following an overnight fast and after lying supine at rest for at least 15 min. Hematological parameters were assessed from fresh venous blood sampled with ethylenediaminetetraacetic acid (EDTA). Biochemical parameters were assessed in clotted samples. After centrifuging, serum was collected and frozen at -80°C until laboratory analysis.

The following blood biomarkers were measured directly: hemoglobin concentration, serum creatinine, B-type natriuretic peptide (BNP) were assayed by standard laboratory methods in the central laboratory at the University Hospital. Estimated glomerular filtration rate (eGFR) was assessed using Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) [11]. Creatinine clearance was estimated using the Cockcroft-Gault formula (creatinine clearance = $(140 - \text{age}) \times \text{body weight} / \text{serum creatinine} \times 72$ if female $\times 0.85$) [12]. 25(OH)D was assayed using commercially available kits from Gentaur, Kampenhout, Belgium and its binding protein (VDBP) using assays from R&D, Minneapolis, MN, USA. Kidney function was assessed either by serum creatinine or creatinine clearance according to Cockcroft-Gault formula.

Anemia was defined according to the World Health Organization (WHO) criteria, i.e., hemoglobin below 12 g/dL in females and 13 g/dL in males [13]. According to the WHO, vitamin D insufficiency is defined as serum 25(OH)D below 20 ng/mL (50 nmoL/L) [14]. However, Holick [15] defined vitamin D deficiency as serum 25(OH)D level below 20 ng/mL and vitamin D insufficiency as less than 30 ng/mL (75 nmoL/L). The rationale to change the definition was based on the finding that serum

parathyroid hormone, which correlated negatively with serum 25(OH)D, declined as serum 25(OH)D raised and achieved a plateau at a serum 25(OH)D of approximately 30 ng/mL (75 nmol/L) [16, 17].

Statistical analysis

The statistical significance of differences between the groups was tested using either analysis of variance with F statistics, the Student t test, or χ^2 test, where appropriate. The associations between variables were assessed using the univariate Pearson correlation coefficients or the Spearman rank correlation coefficients. A value of $p < 0.05$ was considered statistically significant. The multiple regression analysis was used to determine independent factors affecting the dependent variables. Factors showing linear correlation with 25(OH)D ($p < 0.1$) were included in the analysis. All statistical analyses were performed using Statistica 13.1.

Results

According to the definition, the prevalence of anemia in the studied cohort was 22% (18% in females and 25% in males). In NYHA class I prevalence of anemia was 11%, in class II — 22%, in class III — 23%, and 31% in class IV ($p < 0.01$ for trend). Baseline clinical and biochemical characteristics of the population studied is presented in Table 1. The group with cardiomyopathy was significantly younger than the two other groups. The degree of HF is reflected by NYHA class (median value was 2 in all groups) and did not differ between groups studied, however BNP was the highest in the group with CAD and LVEF was the lowest in the cardiomyopathy group. Kidney function assessed either by serum creatinine or creatinine clearance according to the Cockcroft-Gault formula, which included body weight, which were similar, whereas eGFR was significantly higher in the cardiomyopathy group when compared to the valvular disease group. 25(OH)D was lowest in valvular disease and cardiomyopathy group, significantly lower than in the coronary artery group. VDBP was significantly lower in group III relative to group I. When the definition of Holick was adopted [15], the prevalence of vitamin D deficiency in the whole group was 95%, only 6 patients had vitamin levels higher than 20 ng/mL, all of them in group I. Serum 25(OH)D below 10 ng/mL was found in 49% of the patients studied, 40% in group I, 45% in group II and 60% in group III, respectively. When patients were classified as anemic/non-anemic it was found that in group I, serum iron was lower in anemic

relative to non-anemic patients (39 ± 17 vs. $80 \pm 33 \mu\text{g/dL}$, $p < 0.01$), as well as eGFR by CKD-EPI (69 ± 33 vs. $86 \pm 31 \text{ mL/min/1.73 m}^2$, $p < 0.05$). In group II in anemic patients eGFR by CKD-EPI was lower relative to non-anemic patients (69 ± 33 vs. $93 \pm 37 \text{ mL/min/1.73 m}^2$, $p < 0.05$). In group III, NYHA class was higher in anemic patients when compared to their non-anemic counterparts (3 ± 1 vs. 2 ± 0.5 , $p < 0.05$). In univariate analysis vitamin D correlated with hemoglobin ($r = 0.61$, $p < 0.01$; Fig. 1), red blood cell count ($r = 0.42$, $p < 0.05$), hematocrit ($r = 0.44$, $p < 0.01$), mean corpuscular volume (MCV; $r = 0.25$, $p < 0.05$) and BNP ($r = 0.30$, $p < 0.01$; Fig. 2) in patients with HF (in the whole group). Vitamin D binding protein was related to age ($r = 0.21$, $p < 0.05$; Fig. 3). In the multivariable-adjusted logistic regression analyses on the etiology of HF, predictors of 25(OH)D were eGFR ($r = 0.38$, $p = 0.004$), BNP ($r = 0.41$, $p = 0.003$) and valvular etiology ($r = 0.29$, $p = 0.005$), adjusted R^2 was 45%, $F(4,53)$, $p < 0.001$, $SE = 6.82$.

Discussion

In the present study, 25(OH)D concentration was assessed together with its binding protein in patients with HF referred for coronary angiography. The main finding in the current study was a high prevalence of vitamin D deficiency (almost 100% in the whole group) and an especially profound vitamin D deficiency ($< 10 \text{ ng/mL}$) in HF patients. 25(OH)D was lowest in patients with HF due to valvular disease, significantly lower than in patients with CAD. In the present study, all patients had 25(OH)D lower than 30 ng/mL. Almost 50% of the population studied had 25(OH)D lower than 10 ng/mL. It was also found that VDBP was lowest in the valvular disease group relative to the coronary artery group. Measurements were done in the winter time. 25(OH)D levels in 24 healthy age and sex matched volunteers were also assessed and it was found that 8 of them had 25(OH)D levels below 20 ng/mL, but higher than 10 ng/mL. Mean level was $22 \pm 7 \text{ ng/mL}$, and the VDBP level was $337 \pm 55 \mu\text{g/mL}$. It was highly significant, above ($p < 0.001$) than in the studied population. As reported in the literature, the bone-centric guidelines recommend a target 25(OH)D concentration of 20 ng/mL (50 nmol/L), and age-dependent daily vitamin D doses of 400–800 IU. The guidelines focused on pleiotropic effects of vitamin D recommend a target 25(OH)D concentration of 30 ng/mL (75 nmol/L), and age, body weight, disease status,

Table 1. Clinical and biochemical characteristics of groups studied.

	Group I Coronary heart disease	Group II Cardio- myopathy	Group III Valvular disease	P
Age [years]	68 ± 11	61 ± 10	67 ± 10	I vs. II: p < 0.01 II vs. III: p < 0.01
Anemic patients	29%	20%	21%	I vs. II: p < 0.05
Hemoglobin [g/dL]	13 ± 12	14 ± 2	13 ± 2	NS
Hematocrit [%]	40 ± 5	42 ± 5	40 ± 5	NS
Erythrocyte count [$\times 10^{12}/\mu\text{L}$]	4.5 ± 0.5	4.7 ± 0.5	4.5 ± 0.6	NS
MCV [fL]	89 ± 5	90 ± 5	89 ± 4	NS
Iron [$\mu\text{g}/\text{dL}$]	65 ± 33	88 ± 33	89 ± 44	I vs. II: p < 0.01 I vs. III: p < 0.001
Ferritin [ng/mL]	167 (79;246)	175 (113; 276)	115 (75;193)	II vs. III: p < 0.05
Transferrin saturation [%]	23 ± 12	29 ± 13	28 ± 14	I vs. II: p < 0.05 I vs. III: p < 0.05
Functional iron deficiency	7%	8%	11%	NS
Absolute iron deficiency	5%	6%	9%	NS
Vitamin D [ng/mL]	13 ± 6	10 ± 5	10 ± 3	I vs. II: p < 0.05 I vs. III: p < 0.05
Vitamin D binding protein [$\mu\text{g}/\text{mL}$]	281 ± 106	262 ± 51	245 ± 81	I vs. III: p < 0.05
Vitamin D deficiency	85%	100%	100%	I vs. II: p < 0.05 I vs. III: p < 0.05
Creatinine [mg/dL]	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.3	NS
Creatinine clearance [mL/min]	70 ± 22	72 ± 21	67 ± 17	NS
eGFR by CKD-EPI [mL/min/1.72 m ²]	81 ± 31	88 ± 34	71 ± 21	II vs. III: p < 0.05
CKD prevalence	27%	30%	25%	NS
Ejection fraction [%]	29 ± 8	24 ± 7	40 ± 16	I vs. II: p < 0.05 I vs. III: p < 0.01 II vs. III: p < 0.01
BNP [pg/mL]	328 (210; 723)	263 (125; 599)	227 (81; 466)	I vs. III: p < 0.05
Hypertension	61%	57%	61%	NS
Diabetes	32%	19%	28%	NS
Atrial fibrillation	23%	33%	38%	NS
ACEI	94%	97%	76%	I vs. III: p < 0.001 II vs. III: p < 0.001
ASA	94%	64%	55%	I vs. II: p < 0.001 I vs. III: p < 0.001
Thienopyridines	60%	24%	22%	I vs. II: p < 0.001 I vs. III: p < 0.001
Anticoagulants	11%	33%	31%	I vs. II: p < 0.01 I vs. III: p < 0.001
Diuretics	79%	87%	67%	I vs. III: p < 0.05 II vs. III: p < 0.001

Data given are percentages, means ± standard deviation or median and interquartile ranges. ACEI — angiotensin converting enzyme inhibitors; ASA — acetylsalicylic acid; BNP — B-type natriuretic peptide; CKD — chronic kidney disease; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration equation; eGFR — estimated glomerular filtration rate; MCV — mean corpuscular volume

and ethnicity-dependent vitamin D doses ranging between 400 and 2000 IU/day [18, 19].

Kolaszko et al. [20] assessed 25(OH)D levels in patients hospitalized in the cardiology ward

with regard to a presence or absence of HF. It was found that these groups did not differ with regard to 25(OH)D levels. In addition, 25(OH)D levels were similar in patients with or without CAD,

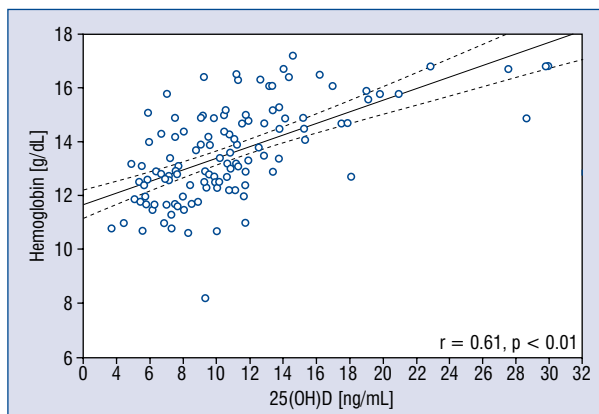


Figure 1. Correlation between hemoglobin and 25(OH)D in heart failure patients.

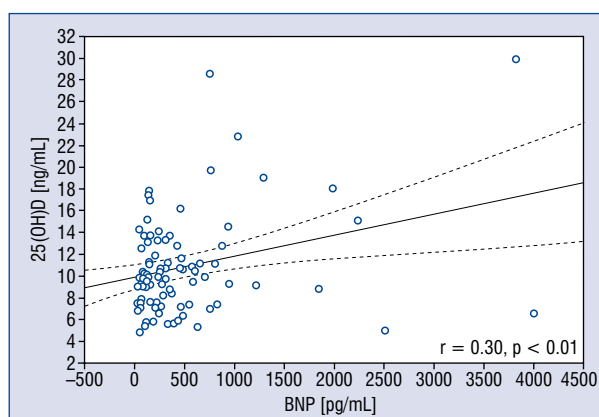


Figure 2. Correlation between B-type natriuretic peptide (BNP) and 25(OH)D in heart failure patients.

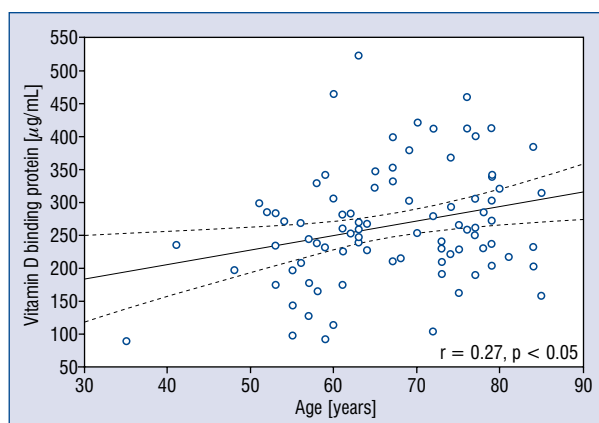


Figure 3. Correlation between vitamin D binding protein and age in heart failure patients.

however, the prevalence of vitamin D deficiency or insufficiency was not reported. The mean level of 25(OH)D in the present study was 12 ± 5 ng/mL in HF and samples were taken in the winter time, similar to the paper by Kolaszko et al. [20]. Being fully aware of seasonal variations [21] data was not collected on dietary supplements of vitamins and other nutrients as well as medications affecting bone health (i.e. steroids). The population herein was slightly older than those studied by Kolaszko et al. [20]. Moreover, 25(OH)D was assessed and its binding protein in HF patients of three different etiologies, while in previous studies etiology was not taken into account. Renal function as reflected by eGFR was comparable to the Kolaszko et al. [20] study. Polat et al. [22] reported that lowered 25(OH)D concentration in HF due to cardiomyopathy was related to severity of the disease. In the present study, there was no correlation between LVEF and 25(OH)D in any group studied.

In the Pandey et al. [23] study more than 90% of HF patients with preserved ejection fraction had 25(OH)D insufficiency, and 30% were deficient. It was also associated with exercise intolerance as reflected by lower peak VO_2 and 6-minute walk distance in HF with preserved ejection fraction. Saponaro et al. [24] evaluated the levels of vitamin D in patients with HF and were compared to a control group to assess the effects of vitamin D on HF outcome. They reported that patients with HF had statistically lower 25(OH)D levels ($p < 0.001$) and a statistically higher prevalence of vitamin D insufficiency (61.1% vs. 39.5%, $p < 0.001$) and deficiency (24.7% vs. 6.6%, $p < 0.001$), relative to the healthy controls. In addition, a significant inverse relationship was observed between baseline 25(OH)D and risk of HF-related death, having a hazard ratio of 0.59 (95% confidence interval 0.37–0.92, $p = 0.02$), and was confirmed in a multivariate adjusted analysis. In corroboration with this study, Walker et al. [25] in a prospective cohort study of 1802 patients with chronic HF and $LVEF \leq 45\%$ found that sepsis was the major cause of death in their study. As sepsis death was independently associated with lower log serum vitamin D than non-sepsis death, and vitamin D supplementation was suggested to possibly be one of the targeted preventative strategies.

Pludowski et al. [26] evaluated the 25(OH)D concentration in a representative group of 5775 adult volunteers in 22 Polish cities. Conducted

in late winter, mean and median concentration of 25(OH)D were 18 ± 10 ng/mL and 16 ng/mL, respectively. In the whole group (spring and winter measurements) serum 25(OH)D levels lower than 20 ng/mL were found in 66%. Also reported, 16% of the participants had surprisingly low levels of 25(OH)D i.e. below 10 ng/mL. In the current study, 49% of the participants had 25(OH)D lower than 10 ng/mL. In the study performed in northern Poland on 448 adults from February to mid-April, the mean 25(OH)D level was 14 ± 7 ng/mL and 84% had a concentration of less than 20 ng/mL (< 50 nmol/L) [27]. Similar data came from a study on 274 elderly (mean age 69 years) postmenopausal women living in Warsaw [28]. The mean 25(OH)D level was 14 ng/mL (winter time) and 83% had 25(OH)D deficiency. A debate continues on the lower limit of normal for 25(OH)D levels, which depends upon geographic location and sunlight exposure of the reference population. Moreover, there is no consensus on optimal 25(OH)D concentration for skeletal or extraskeletal health. The Institute of Medicine concluded that a serum 25(OH)D concentration of 20 ng/mL (50 nmol/L) is sufficient for most individuals [29], but other experts (Endocrine Society, National Osteoporosis Foundation [NOF], International Osteoporosis Foundation [IOF], American Geriatrics Society [AGS]) suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults to minimize the risk of falls and fractures [30–32]. Zhang et al. [33], reported a plateau above 20 ng/mL for incidence, but much higher for mortality. In the Moli-sani study vitamin D deficiency was associated, independently of known HF risk factors, with an increased risk of hospitalization for HF in an Italian adult population [34].

In the present study, a vast majority of patients had vitamin D deficiency, could not be solely ascribed to impaired kidney function. Other causes of 25(OH)D deficiency include: decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis (via decreased 25-hydroxylation in the liver or 1-hydroxylation in the kidney), or end-organ resistance to 25(OH)D. Winter levels of 25(OH)D mainly depend on food intake and previous liver storage. Dietary assessment was not performed in the present population studied. As cutaneous vitamin D production and vitamin D stores decline with age [35], this explanation may also be considered, at least partially. In addition to reduced endogenous production, vitamin D intake is often low in older subjects. It has been also reported that in hospital-

ized patients, 25(OH)D deficiency defined as level < 15 ng/mL) was found in 57%, of whom 22% were considered severely deficient (serum concentration of 25(OH)D < 8 ng/mL) [36]. As shown, predictors of vitamin D deficiency were inadequate vitamin D intake, winter season, and housebound status. As vitamin D deficiency may be dependent, in part, upon the age of patients on hospital wards [37, 38], it should be stressed that in a subgroup of patients < 65 years without known risk factors, vitamin D deficiency was still detected in 42% [35] of them. As it has been reported previously [39], vitamin D deficiency predisposes up-regulation of renin-angiotensin-aldosterone (RAA) system, causes left ventricle hypertrophy and vascular smooth muscle cell hypertrophy as well.

Anemia was found in 22% of patients studied. Its prevalence rose significantly with NYHA class (from 11% in class I to 31% in class IV). A subclinical inflammatory state was reported, as reflected by elevated levels of cytokines, hemodilution, dietary deficiencies including iron and other microelements, the use of medications affecting RAA system, CKD, poor nutrition and decreased bone marrow perfusion may all contribute to the development of anemia in HF [40–42]. Inflammatory cytokines or high sensitivity C-reactive protein were not studied in the present patients, however, CKD was present in 25–30% of patients as well as iron deficiency (both absolute and functional) was diagnosed in 12–20% depending on the HF etiology, in addition a vast majority of the patients were treated with drugs affecting the RAA system, and as well as acetylsalicylic acid (ASA) and anticoagulants. Therefore, the high prevalence of anemia in the studied group appears to be multifactorial with an important role of CKD as a subclinical inflammatory state and iron deficiency. In addition, therapy of chronic HF with the RAA system blockade and use of other drugs potentially contributed as anticoagulant to the presence of anemia in this population. Higher prevalence of anemia of valvular origin of chronic HF might be associated with a higher prevalence of impaired kidney function as reflected by lower eGFR and creatinine clearance, higher prevalence of iron deficiency (both absolute and functional).

As reviewed previously, angiotensin converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB) can decrease hemoglobin levels by 0.2–0.3 g/dL [43]. ACEI declined vascular resistance in efferent arterioles in glomeruli, increased oxygenation in the peritubular region and thereby lowered the signal for synthesis of erythropoietin.

The tetrapeptide N-acetyl-Ser-Asp-Lys-Pro (Ac-SDKP) named goralatide or seraspenide, a normal inhibitor of entry for pluripotent cells into the S-phase, is metabolized by ACE. During therapy with ACEI, Ac-SDKP can accumulate and cause a decline in erythropoiesis [44].

Findings in the present study show a correlation between 25(OH)D and anemia in patients with HF. It may be due to the fact, that patients with worse kidney function and anemia had a lower 25(OH)D. In other studies associations were found in patients scheduled for cardiac surgery and coronary angiography [45–47]. However, in the randomized controlled trials two studies reported no effect of vitamin D in anemia [48, 49], while two others performed in CKD showed a beneficial effect of vitamin D on the dose of erythropoietin stimulating agents [50, 51]. In Effect of Vitamin D on Mortality in Heart Failure (EVITA) trial vitamin D supplementation had no effect on anemia prevalence in advanced HF patients [52]. In the EVITA trial prevalence of anemia was 17% in the treatment group and 11% in the placebo group, whereas at termination of the study, the prevalence was much higher, reaching 32% in both groups. No data on iron status were provided. In the current study, prevalence of iron deficiency (absolute and functional) was close to 20%. However, no correlations were found between iron parameters, 25(OH)D and its binding protein. It was assumed that there may simply be no causal relationship between anemia, iron status and 25(OH)D in HF. It is well established that vitamin D deficiency is highly prevalent in patients with CKD undergoing renal replacement therapy [53]. This supports the findings that kidney function was a predictor of 25(OH)D in HF. As shown previously, prevalence of CKD was high in patients undergoing PCI despite normal serum creatinine, particularly in higher NYHA class [53, 54]. It corroborates with the present study that BNP was also a predictor of 25(OH)D in HF patients.

Limitations of the study

This study has several strengths and, on the other hand, several limitations. As all patients underwent coronary angiography, we were able to divide the cohort with regard to the etiology of HF. Moreover, vitamin D binding protein as well as detailed iron status data was also assessed. A limitation could be a lack of assessment of parathyroid hormone, calcium, phosphate and cross-sectional design. Other limitations include retrospective data analysis, and no advanced statistical approach to analyze independent associations.

Conclusions

Vitamin D deficiency is very common in HF patients, predominantly in valvular disease. Higher prevalence of anemia in HF due to CAD may be associated with wider ACEI and ASA use relative to other etiologies. Correlation between anemia and 25(OH)D are of interest but require further study to elucidate possible pathogenetic mechanism(s) and also do not provide a rationale for vitamin supplementation. However, heart and kidney function are predictors of 25(OH)D level.

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Conflict of interest: None declared

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