

Clinical and laboratory determinants of low serum level of 25-hydroxyvitamin D during escalation of pharmacotherapy in heart failure patients



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Abstract

Introduction: The activation of the renin-angiotensin-aldosterone (RAA) system is a main element of the pathophysiology of chronic heart failure (CHF), determining its symptoms and prognosis. Vitamin D is an RAA inhibitor, and its deficiency frequently accompanies CHF. The factors determining the concentration of 25-hydroxyvitamin D [25(OH)D] in CHF are not well understood, although an association has been suggested between the deficiency and the advancement of CHF. Also unknown is the influence of therapeutic escalation using recommended agents on the serum level of 25(OH)D. The aim of this study was to examine the incidence of abnormal 25(OH)D concentrations in CHF patients and to establish the clinical and laboratory determinants of low activity of this metabolite.

Material and methods: The retrospective analysis included the data of 412 CHF patients not receiving optimal pharmacological treatment who were initially in NYHA (New York Heart Association) class III or IV. Over the period of 3 months the therapy was escalated until reaching maximum tolerated doses or those recommended by the current guidelines. After optimizing the therapy, the incidence of 25(OH)D deficiency (< 30 ng/ml) and insufficiency (< 20 ng/ml) was established, and clinical and laboratory determinants for these abnormal concentrations were analyzed.

Results: Normal serum level, insufficiency, and deficiency of 25(OH)D were observed in, respectively, 41.5%, 26.0% and 32.5% of patients. The NYHA class improved by at least 1 class in 63.6% of patients, remained unchanged in 32.8% of patients, and deteriorated in 3.6% of patients. In multivariable analysis, low availability of natural ultraviolet B (UVB) radiation, loss of body mass during the CHF, higher concentrations of phosphates and albumins, and the presence of diabetes increased the risk of 25(OH)D deficiency, while higher concentrations of uric acid reduced this risk. In patients with a positive response to therapy, the concentration of 25(OH)D

Streszczenie

Wstęp: Aktywacja układu renina-angiotensyna-aldosteron (RAA) stanowi zasadniczy element patofizjologii przewlekłej niewydolności serca (PNS) i determinuje jej objawy i rokowanie. Witamina D jest inhibitorem układu RAA. Jej niedobór często stwierdza się w PNS. Czynniki determinujące stężenie 25-hydroksywitaminsy D [25(OH)D] w przebiegu PNS zostały słabo poznane, choć sugeruje się związek niedoboru z zaawansowaniem PNS. Nieznany jest też wpływ natężenia terapii z wykorzystaniem rekomendowanych leków na stężenie 25(OH)D. Celem pracy było zbadanie częstości nieprawidłowych stężeń 25(OH)D u chorych z PNS oraz ustalenie klinicznych i laboratoryjnych determinantów małego stężenia tego metabolitu.

Materiał i metody: Retrospektywnie analizowano dane 412 pacjentów z PNS nieotrzymujących optymalnego leczenia farmakologicznego, wyjściowo w zaawansowanej klasie III lub IV wg *New York Heart Association* (NYHA). W okresie 3 miesięcy prowadzono terapię, zwiększając dawki leków do dawek maksymalnie tolerowanych lub rekomendowanych w zaleceniach. Po optymalizacji terapii określono częstość niedomiaru (< 30 ng/ml) i niedoboru (< 20 ng/ml) 25(OH)D oraz przeanalizowano kliniczne i laboratoryjne determinanty nieprawidłowych stężeń tego metabolitu.

Wyniki: Prawidłowe stężenie, niedomiar i niedobór 25(OH)D stwierdzono u, odpowiednio, 41,5%, 26,0% i 32,5% chorych. Klasa NYHA uległa poprawie o co najmniej 1 klasę u 63,6%, nie zmieniła się u 32,8%, a pogorszyła u 3,6% pacjentów. W analizie wieloczynnikowej mała dostępność naturalnego promieniowania ultrafioletowego w paśmie B (UVB), utrata masy ciała w PNS, większe stężenie fosforanów i albumin oraz cukrzyca zwiększały, a większe stężenie kwasu moczowego zmniejszało ryzyko niedoboru 25(OH)D. Stężenie 25(OH)D było z graniczną istotnością wyższe ($p = 0,055$), a niedobór i niedomiar rzadsze ($p = 0,02$) u chorych z pozytywną – w porównaniu z jej brakiem – odpowiedzią na terapię jedynie u chorych

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was borderline significantly higher ($p = 0.055$), while insufficiency and deficiency were less frequent ($p = 0.02$) than in patients without a treatment response, but this pertained only to patients with higher exposure to UVB. These differences were not observed in patients with low UVB exposure.

Conclusions: The concentration of 25(OH)D in CHF patients is not associated with the advancement of the disease, but is strongly determined by the potential availability of UVB radiation. A positive response to therapy increases the concentration of 25(OH)D only in the case of high UVB exposure; other determinants of 25(OH)D level include the patient's metabolic profile and the presence of diabetes.

Key words: chronic heart failure, vitamin D deficiency.

Introduction

Chronic heart failure (CHF) is one of the most serious medical and social problems. Its growing incidence and still unfavorable prognosis, despite the ongoing development in therapy, constitute a challenge for healthcare systems around the world [1, 2]. Multidisciplinary studies are being conducted in order to reduce the morbidity and mortality associated with CHF [3].

The activity of the renin-angiotensin-aldosterone system (RAAS) is one of the key links in CHF pathogenesis [1]. In recent years, investigators have obtained experimental data pointing to a relationship between vitamin D deficiency and increased activity of this system [4]. The concentration of 25-hydroxyvitamin D [25(OH)D] – the main metabolite in the synthesis pathway of the active hormone, 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] – is reduced in heart failure patients [5]. There are also documented a relationship between 25(OH)D deficiency and pathological remodeling of the left ventricle, lower left ventricular ejection fraction, more advanced NYHA (New York Heart Association) class, increased N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration, and unfavorable prognosis [6-9]. Moreover, a randomized, prospective study has recently revealed that vitamin D supplementation in CHF patients with vitamin D deficiency causes a reduction in the activity of the RAAS [10]. The above facts have raised interest in vitamin D deficiency as a new, modifiable, potential link in CHF pathophysiology.

The studies on CHF patients indicates that plasma renin activity and acute-phase protein concentration are determinants of 25(OH)D deficiency [11]. This may suggest that the progression of heart failure may be associated with low 25(OH)D serum level. This view is confirmed by observations pointing to lower 25(OH)D concentrations in more advanced stages of CHF [9].

The reasons why the concentration of 25(OH)D, the most important biomarker of the activity of the vitamin D endocrine system, is reduced in CHF patients are unknown. The potential causes include limited exposure to ultraviolet (UV) radiation associated with reduced physical activity, improper diet with insufficient vitamin D content, malabsorption, or reduced cutane-

ous synthesis [12]. Other considered factors include increased conversion of 25(OH)D to $1,25(\text{OH})_2\text{D}$ by tissue hydroxylases whose expression and activity is intensified during inflammation [13] and increased sequestration in the adipose tissue of patients in whom the mass of adipose tissue increases as a result of treatment [14].

A positive response to therapy may modify all the above-mentioned processes and influence 25(OH)D serum level more significantly than the stage of CHF itself. As yet, this issue has not been analyzed.

We aimed to study the behavior of 25(OH)D concentrations in CHF patients and to establish the clinical and laboratory determinants of low activity of this metabolite, taking into consideration the level of response to therapy.

Słowa kluczowe: przewlekła niewydolność serca, niedobór witaminy D.

Material and methods

Study group

The study retrospectively analyzed the data of CHF patients who were included in the Prospective Register of Heart Failure (PRHF) maintained since 2003 by 3rd Department of Cardiology of the Silesian Center for Heart Diseases and CHF patients who participated in the SICA-HF (Studies Investigating Comorbidities Aggravating Heart Failure) program [15]. The study included adult CHF patients with impaired left ventricular ejection fraction (LVEF $\leq 40\%$) diagnosed in accordance with the current guidelines of the European Society of Cardiology. The present analysis included patients with a medical history of heart failure longer than 6 months who did not receive the recommended therapy or received $< 10\%$ of the recommended dose of angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) or beta-blockers (BB) and were not treated with aldosterone antagonists (AA). At the beginning of the therapy or the escalation of the applied treatment, the patients included in the analysis were in NYHA functional class III or IV. Over the course of the following 3 months, during 3-5 follow-up outpatient visits, the drug doses were gradually increased until maximum tolerated doses were reached. The maximum tolerated drug dose was defined as a drug dose at which the patient remained free from symptomatic hypo-

tonia or bradycardia with heart rate < 50/min and potassium concentration < 5.5 mmol/l, or a dose recommended by the guidelines.

Only patients whose ACEI/ARB and BB doses were doubled were included in the study; if the ACEI/ARB dose did not meet this criterion, patients with doses of AA ≥ 100 mg (spironolactone or eplerenone) were included. After dose optimization, the therapy was continued for at least 1 month before the inclusion in the PRHF or SICA-HF and the performance of appropriate clinical and biochemical examinations (index day). During this time, the patients remained in the state of circulatory compensation without clinical or laboratory features of fluid retention or reduced organ perfusion.

Patients chronic treated with glucocorticoids, bisphosphonates, vitamin D preparations, or salts of calcium or phosphorus, patients with active infections, active bleeding, diagnosed hyperplasia or storage disease, or liver disease accompanied by an increase in hepatic enzymes by more than 4 times the upper limit of normal, as well as patients who underwent previous bariatric surgery were excluded from observation.

Ultimately, out of 1029 analyzed patients, the inclusion and exclusion criteria were met by a group of 412 patients, who constituted the study group.

Based on medical history and documentation, the onset of heart failure symptoms was defined with accuracy to 1 month. The lowest body mass during the period of 1 year before the occurrence of symptoms (preCHF) and the lowest, overhydrated-free body mass in the course of heart failure (minCHF) were established using the same sources. The presence of comorbidities, such as arterial hypertension, diabetes, or hypercholesterolemia, was diagnosed based on the data from medical documentation or the results of laboratory tests. Comorbidities were also diagnosed in the case of chronic use of therapies dedicated to a given disease. Current or previous use of tobacco was considered a positive medical history.

Blood for laboratory tests was collected from fasted patients between 8:00 and 10:00 a.m., after at least 30 minutes of rest in a recumbent position. The obtained material was centrifuged at a temperature of 4°C, and the acquired serum was frozen at -75°C until further tests. All procedures were conducted in accordance with the Declaration of Helsinki after obtaining written consent for their performance. The study protocol was accepted by the Bioethical Committee at the Medical University of Silesia in Katowice. The study procedures and their chronology are presented in Fig. 1.

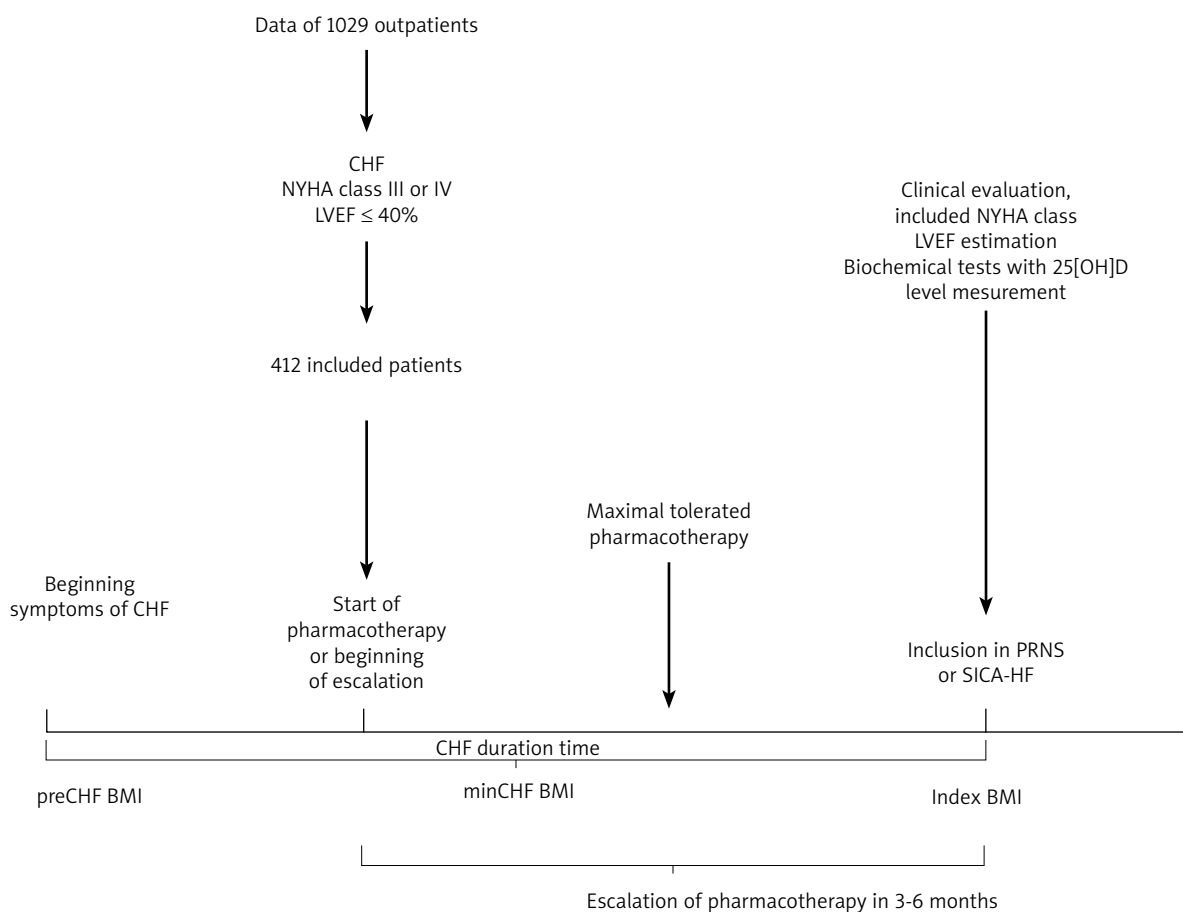


Fig. 1. Scheme of study procedures

Analyzed parameters

Body mass and height measurements were conducted on the day of inclusion in the PRHF or SICA-HF using a certified device (B150L, Redwag, Zawiercie, Poland). Blood drawing, clinical examination included NYHA class, and echocardiography were performed on the same day (index day). By dividing body mass in kilograms by height expressed in meters squared, the body mass index (BMI) was calculated for the period before the heart failure diagnosis, and the lowest BMI in the course of the disease was established; these values were described as preCHF BMI and minCHF BMI. Body mass on the index day was described as indexBMI.

The extent of body mass loss or gain was calculated using the following formulas:

$$\text{Loss of body mass [\%]} = 100 \times (\text{preCHF BMI} - \text{indexBMI}) / \text{preCHF BMI}$$

$$\text{Gain of body mass [\%]} = 100 \times (\text{indexBMI} - \text{minCHF BMI}) / \text{minCHF BMI}$$

The assessment of left ventricular systolic function was conducted using a Sonos-5000 Hewlett-Packard echocardiographic platform (Hewlett-Packard, Andover, MA, USA). Left ventricular ejection fraction was assumed as the measure of heart contractility; it was measured in a four-chamber view, and the calculation was based on the following formula:

$$\text{LVEF} = 100 \times [(\text{end-diastolic volume} - \text{end-systolic volume}) / \text{end-diastolic volume}]$$

Standard biochemical reagents by Roche Diagnostics (Basel, Switzerland) and a Cobas automatic biochemical analyzer were used in the measurement of the level of creatinine, albumin, and NT-proBNP, phosphates, calcium, albumins, and 25(OH)D.

Glomerular filtration rate (GFR) was estimated based on a shortened version of the formula from the Modification of Diet in Renal Disease (MDRD) study:

$$\text{eGFR}_{\text{MDRD}} = 186 \times \text{creatinine concentration} [\text{mg/dl}]^{-1.154} \times \text{age} [\text{years}]^{-0.203} \times 0.742 \text{ (if female)}$$

In the case of albumin level < 40 g/l, we conducted calcium concentration correction using the following formula:

$$\text{Corrected calcium level [mmol/l]} = \text{total calcium} + 0.02 \times (40 - \text{serum albumin concentration [g/l]})$$

Serum level of 25(OH)D were classified into 3 categories in accordance with the literature guidelines: normal concentration: > 30 ng/ml; insufficiency: 20-30 ng/ml; deficiency: < 20 ng/ml [16].

Statistical analysis

Continuous parameters with normal distribution were presented as arithmetic mean \pm standard deviation, while qualitative parameters were presented as percentages.

The parameters whose distribution was found to be different than normal based on the Shapiro-Wilk test were presented as median with interquartile range (IQR). Logarithmic transformation was conducted in order to correct the variables with distribution other than normal (the tables include the variables before the transformation).

The study group was divided into 4 subgroups based on the stage of heart failure in accordance with the NYHA class and, once again, in accordance with the quartiles of NT-proBNP concentration. The presence of differences regarding clinical and laboratory parameters between the CHF stages was compared with the Kruskal-Wallis test or the λ^2 test.

The relative risk of 25(OH)D level below 20 ng/ml in comparison to concentration exceeding 30 ng/ml was examined with regard to all the analyzed clinical and laboratory parameters. The analysis utilized a unifactorial logistic regression model. Multifactorial analysis included the parameters whose significance in the univariable analysis was $p < 0.2$. The odds ratio (OR) with 95% confidence intervals was calculated in univariable and multivariable analyses using logarithmic transformation (log10) with regard to variables with distributions other than normal.

Next, the entire study group was divided into 4 subgroups, depending on the presence of a positive response to the applied treatment or lack thereof as well as on high or limited availability of ultraviolet radiation at the time of the test measuring the concentration of 25(OH)D. The clinical and laboratory characteristics of these subgroups were compared using the abovementioned tests.

Results with bilateral $p \leq 0.05$ were considered statistically significant. The calculations were conducted using the Statistics v.10.0 and NCSS v.2007 software.

Results

25-hydroxyvitamin D concentration ranges

In the study group, normal concentrations of 25(OH)D were found in 171 patients (41.5%), insufficient level (between 20 and 30 ng/ml) occurred in 107 patients (26.0%), and deficiency (concentrations below 20 ng/ml) was revealed in 134 patients (32.5%) (Fig. 2).

Clinical response to therapy

Under the escalation of pharmacotherapy, a positive clinical response described as NYHA class improvement by at

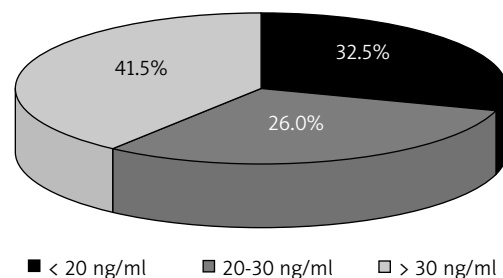


Fig. 2. Incidence of deficient, insufficient, and normal level of 25-hydroxyvitamin D [25(OH)D] in patients with heart failure after the escalation of pharmacotherapy

least 1 class occurred in 262 patients (63.6%); the NYHA class remained unchanged in 135 patients (32.8%), while deterioration occurred in 15 patients (3.6%). Out of the 283 patients (68.7%) who were initially in NYHA class III, improvement, lack of change, or NYHA class deterioration despite the esca-

lation of therapy was observed, respectively, in 155 (54.8%), 113 (40.0%), and 15 patients (5.2%). Among the 129 patients (31.3%) included in the study in NYHA class IV, 107 (82.9%) achieved an improvement, while in the case of 22 patients (17.1%) the NYHA class remained unchanged (Table I).

Tab. I. Clinical characteristics of the study group and comparison of NYHA (New York Heart Association) class. Mean \pm SD, median with interquartile range, or percentage

Parameter	NYHA class				p
	I n = 39	II n = 148	III n = 188	IV n = 37	
Age [years]	51 \pm 10	53 \pm 10	54 \pm 10	54 \pm 11	0.51
Sex [% women]	5.1	14.2	13.4	29.7	0.02
BMI [kg/m ²]	26.6 \pm 3	27.3 \pm 4	26.4 \pm 5	25.1 \pm 5	0.03
Ischemic etiology [%]	89.7	64.2	68.1	59.5	0.006
Initial NYHA class [% NYHA IV]	5.1	20.3	39.9	59.5	< 0.001
Clinical response [% improvement]	100	100	39.9	0	< 0.001
Availability of natural UVB radiation [% analysis of 25(OH)D concentration between April and September]	17.9	40.5	43.6	40.5	0.02
Body mass loss from preCHF BMI to minCHF BMI [% preCHF BMI]	5.0 (8.5)	6.7 (10.6)	11.9 (11.7)	17.8 (15.9)	< 0.001
Body mass gain from minCHF BMI to indexBMI [% minCHF BMI]	3.2 (9.1)	4.8 (8.7)	3.2 (9.0)	2.3 (6.7)	0.33
LVEF [%]	35 \pm 8	29 \pm 8	24 \pm 8	23 \pm 13	< 0.001
Uric acid [μ mol/l]	368 (123)	410 (146)	426 (162)	501 (256)	< 0.001
Albumins [g/l]	42 \pm 3	42 \pm 4	41 \pm 4	40 \pm 5	0.1
Calcium [mmol/l]	2.26 \pm 0.4	2.26 \pm 0.2	2.31 \pm 0.2	2.38 \pm 0.2	< 0.001
Phosphates [mmol/l]	1.02 \pm 0.2	1.06 \pm 0.2	1.12 \pm 0.2	1.24 \pm 0.2	< 0.001
eGFR _{MDRD} [ml/min/1.73 m ²]	101 (38)	93 (33)	87 (33)	77 (39)	< 0.001
NT-proBNP [pg/ml]	480 (828)	917 (1189)	2021 (3110)	3063 (3201)	< 0.001
25(OH)D [ng/ml]	25 (26)	28 (19)	26 (24)	22 (16)	0.41
25(OH)D < 30 ng/ml [%]	61.5	55.4	59.0	64.9	0.71
25(OH)D < 20 ng/ml [%]	35.9	25.7	36.7	35.1	0.17
Concomitant diseases [%]					
Arterial hypertension	20.5	59.5	57.5	56.8	0.93
Type 2 diabetes mellitus	48.7	20.3	33.0	43.2	0.007
Hypercholesterolemia	12.8	61.5	59.0	48.7	0.32
Hypertriglyceridemia	76.9	37.8	46.3	37.8	< 0.001
Nicotinism	76.9	75.7	73.4	67.6	0.50
Therapy					
ACEI/ARB [% treated]	97.4	98.0	93.1	75.5	< 0.001
Percentage of recommended dose in ACEI/ARB-treated patients [%]	61 \pm 52	61 \pm 51	55 \pm 49	34 \pm 34	0.003
BB [% treated]	100.0	99.3	96.3	91.9	0.03
Percentage of recommended dose in BB-treated patients [%]	53 \pm 36	45 \pm 26	46 \pm 26	41 \pm 28	0.31
AA [% treated]	74.4	86.5	95.2	89.2	< 0.001
Percentage of recommended dose in AA-treated patients [%]	83 \pm 41	101 \pm 48	126 \pm 69	155 \pm 80	< 0.001
Loop diuretic [% treated]	51.3	76.4	93.1	94.6	< 0.001
Dose of the loop diuretic in diuretic-treated patients [furosemide equivalent]	25 \pm 32	56 \pm 49	114 \pm 98	143 \pm 64	< 0.001

BMI – body mass index, NYHA – New York Heart Association class, LVEF – left ventricular ejection fraction, eGFR_{MDRD} – estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, 25(OH)D – 25-hydroxyvitamin D, ACEI/ARB – angiotensin-converting-enzyme inhibitor I/angiotensin II receptor blocker, BB – beta blockers, AA – aldosterone antagonists

By the study's definition, all patients who were in NYHA class I or II at the time of the functional and biochemical examinations (index date) fulfilled the criterion of clinical improvement. Out of the 188 patients who were in NYHA functional class III at the time of these examinations, 75 patients (39.9%) improved and 113 (60.1%) stabilized. No improvement was reported among the patients in NYHA class IV; however, there were 15 patients (40.5%) in this group in whom the functional class deteriorated.

Clinical and biochemical characteristics vs. advancement of heart failure

Regardless of the method of staging heart failure (NYHA class or NT-proBNP concentration quartiles), the patients with more advanced CHF had lower values of BMI, left ventricular ejection fraction, and estimated glomerular filtration, and ischemic heart disease was less frequently the cause of their heart failure; they differed in terms of the occurrence of lipid disorders and diabetes. Patients with more advanced CHF were less frequently treated with ACEI/ARB and received lower doses of these agents; they were more often treated with aldosterone antagonists and loop diuretics and received higher doses of these drugs.

Among the patients with more advanced NYHA class, women constituted a higher percentage; this was not observed when the advancement of CHF was expressed using NT-proBNP quartiles. Similarly, the concentration of uric acid increased together with the NYHA class, but not with NT-proBNP quartiles; the opposite was observed in the case of albumin concentration.

Together with an increase in the NYHA class, but not in the case of rising NT-proBNP quartiles, the percentage of patients whose blood was collected for tests in the period of increased availability of UV radiation (between April and October) increased. Regardless of the staging method, the concentrations of calcium corrected by albumin and phosphate concentrations increased together with the advancement of CHF.

Both the average concentration of 25(OH)D and the incidence of reduced serum level of this metabolite did not differ depends on the advancement of CHF (Tables I and II, Fig. 3 and 4).

Risk factors for 25-hydroxyvitamin D concentration below 20 ng/ml

In univariable analysis, the probability of 25(OH)D deficiency in comparison to concentration > 30 ng/ml was increased by low potential availability of UV radiation (Fig. 5), extent of body mass loss during the period of heart failure symptoms, increased concentration of phosphates, higher glomerular filtration, and the presence of diabetes. Positive response to heart failure therapy, expressed as NYHA class improvement after the escalation of pharmacological treatment, decreased the risk of 25(OH)D deficiency (Fig. 5); increased concentrations of uric acid were associated with reduced risk of 25(OH)D deficiency. In the case of treatment

with ACEI/ARB, a tendency a reduction in the risk of deficiency was present (Table III).

The relationship of male sex, body mass gain from the minimum in the period of heart failure to the index day, and albumin concentration with reduced 25(OH)D concentrations did not reach statistical significance in univariable analysis. Due to p -values below 0.2, these parameters were included in the multivariable analysis. Other clinical and biochemical parameters analyzed in the study did not correlate with reduced 25(OH)D concentrations (Table III).

In the multivariable analysis, the low availability of natural UV radiation between October and April, loss of body mass during the period of heart failure, higher concentration of phosphates and albumins, and presence of diabetes increased the probability of 25(OH)D deficiency. Higher concentrations of uric acid reduced this risk. Clinical improvement ceased to be a significant predictor of 25(OH)D concentration in this analysis. Regardless of the staging method, the advancement of heart failure was not associated with the risk of this biochemical irregularity.

Potential availability of ultraviolet B radiation and the influence of clinical improvement on 25-hydroxyvitamin D concentration

The 25(OH)D concentrations in patients with clinical improvement observed in the period of higher availability of UVB radiation were higher than the concentrations found in patients who did not achieve such an improvement; the difference was on the margin of statistical significance ($p = 0.055$). The 25(OH)D concentrations analyzed during periods of low availability of UVB radiation did not differ between the groups exhibiting improvement and lack thereof. Regardless of treatment response, the 25(OH)D serum level analyzed during periods of high availability of UVB were higher in comparison to low availability (Table IV, Fig. 5).

In patients with clinical improvement, the incidence of both insufficiency and deficiency of 25(OH)D during periods of high UVB availability was lower in comparison to patients without a positive response to therapy ($p = 0.02$ for insufficiency and deficiency). The groups did not differ in terms of the incidence of insufficiency and deficiency when 25(OH)D concentrations were analyzed during periods of low availability of UVB radiation. Under high exposure to UVB radiation, as compared to low exposure, the percentage of patients with insufficiency and deficiency was lower regardless of treatment response (Table IV, Fig. 6).

Discussion

25-hydroxyvitamin D insufficiency and deficiency frequently accompany heart failure. The average concentrations of this metabolite in our study group were slightly higher than those reported in some previous studies [17]. In contrast to most researchers reporting lower concentrations of 25(OH)D or 1,25(OH)₂D during more advanced stages of heart failure [9, 18, 19], our observations do not

Tab. II. Comparison between heart failure stage groups based on *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) quartiles. Mean \pm SD, median with interquartile range, or percentage

Parameter	Quartiles of NT-proBNP				<i>p</i>
	Q1 <i>n</i> = 103	Q2 <i>n</i> = 103	Q3 <i>n</i> = 103	Q4 <i>n</i> = 103	
Age [years]	54 \pm 8	55 \pm 9	53 \pm 9	54 \pm 14	0.84
Sex [% women]	12.6	15.5	16.5	12.6	0.80
BMI [kg/m ²]	27.8 \pm 4	27.5 \pm 4	26.4 \pm 5	24.8 \pm 4	< 0.001
Ischemic etiology [%]	73.8	71.8	68.0	58.3	0.08
Initial NYHA class [% NYHA IV]	18.4	29.1	40.0	43.7	0.001
Clinical response [% improvement]	81.6	70.9	53.4	51.5	< 0.001
Availability of natural UVB radiation [% analysis of 25(OH)D concentration between April and September]	35.9	37.9	43.7	41.7	0.66
Body mass loss from preCHF BMI to minCHF BMI [% preCHF BMI]	7.0 (11.8)	8.2 (15.2)	10.3 (11.6)	14.3 (13.8)	< 0.001
Body mass gain from minCHF BMI to indexBMI [% minCHF BMI]	4.9 (10.2)	4.3 (7.9)	2.7 (8.8)	2.5 (7.5)	0.07
LVEF [%]	32 \pm 9	28 \pm 8	26 \pm 11	21 \pm 7	< 0.001
Uric acid [μ mol/l]	409 (117)	400 (117)	432 (152)	444 (206)	0.28
Albumins [g/l]	42 \pm 4	42 \pm 3	41 \pm 4	40 \pm 4	< 0.001
Calcium [mmol/l]	2.24 \pm 0.1	2.26 \pm 0.2	2.30 \pm 0.2	2.35 \pm 0.2	< 0.001
Phosphates [mmol/l]	1.04 \pm 0.2	1.04 \pm 0.2	1.12 \pm 0.2	1.20 \pm 0.2	< 0.001
eGFR _{MDRD} [ml/min/1.73 m ²]	96 (32)	93 (30)	90 (35)	79 (42)	< 0.001
NT-proBNP [pg/ml]	383 (272)	1028 (407)	2014 (973)	5058 (2988)	< 0.001
25(OH)D [ng/ml]	28 (22)	24 (20)	30 (24)	26 (21)	0.35
25(OH)D < 30 ng/ml [%]	54.4	64.1	50.5	65.1	0.09
25(OH)D < 20 ng/ml [%]	31.1	35.9	26.2	36.9	0.33
Concomitant diseases [%]					
Arterial hypertension	61.2	62.1	58.3	49.5	0.24
Type 2 diabetes mellitus	27.2	30.1	24.3	31.1	0.70
Hypercholesterolemia	66.0	56.3	64.1	45.6	0.01
Hypertriglyceridemia	36.9	47.6	43.7	29.1	0.04
Nicotinism	75.7	73.8	76.7	69.9	0.81
Therapy					
ACEI/ARB [% treated]	97.1	95.2	90.3	92.2	0.17
Percentage of recommended dose in ACEI/ARB-treated patients [%]	69 \pm 58	54 \pm 44	57 \pm 51	43 \pm 40	0.02
BB [% treated]	99.0	95.2	97.1	98.1	0.35
Percentage of recommended dose in BB-treated patients [%]	51 \pm 32	47 \pm 26	45 \pm 24	41 \pm 26	0.10
AA [% treated]	87.4	85.4	90.3	95.2	0.09
Percentage of recommended dose in AA-treated patients [%]	95 \pm 48	113 \pm 60	135 \pm 78	122 \pm 63	< 0.001
Loop diuretic [% treated]	68.0	75.7	90.3	99.0	< 0.001
Dose of the loop diuretic in diuretic-treated patients [furosemide equivalent]	50 \pm 53	72 \pm 61	96 \pm 70	133 \pm 115	< 0.001

BMI – body mass index, NYHA – New York Heart Association class, LVEF – left ventricular ejection fraction, eGFR_{MDRD} – estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula, NT-proBNP – *N*-terminal prohormone of brain natriuretic peptide, 25(OH)D – 25-hydroxyvitamin D, ACEI/ARB – angiotensin-converting-enzyme inhibitor I, angiotensin II receptor blocker, BB – beta blockers, AA – aldosterone antagonists

confirm this relationship. Regardless of the method of staging heart failure (NYHA graduation or NT-proBNP quartiles), neither the average concentrations of 25(OH)D nor the frequency of abnormal serum level differed between the stages of CHF.

The percentage of our patients who had an optimal 25(OH)D concentration was 41.5% in comparison to only

8.8% in a study on the population of Israel [20], 25% in a Dutch study [11], and 29.5% in a Brazilian population study [21]. In the Israeli study, some patients with normal 25(OH)D concentration had previously received vitamin D supplementation [20]. In another study, the percentage of elderly heart failure patients (mean age: 78 years) who had normal 25(OH)D concentration was even lower at only 2.2% [22].

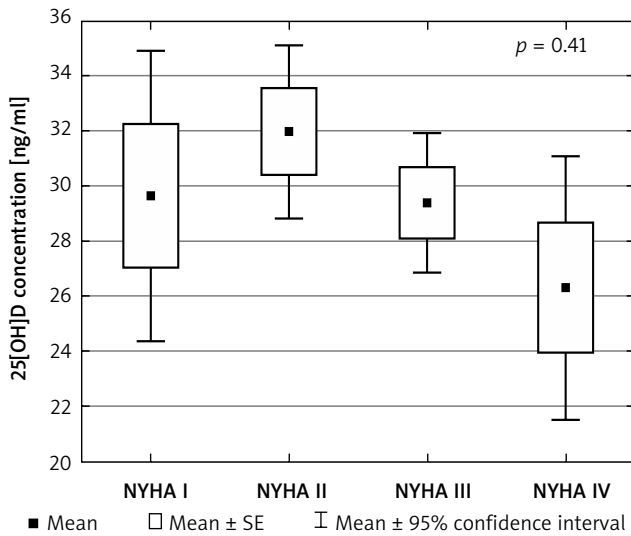


Fig. 3. 25-hydroxyvitamin D concentrations in relation to NYHA (New York Heart Association) class after escalation of pharmacotherapy

The reasons for this high percentage of patients with normal 25(OH)D concentration found in our study are difficult to explain. The study excluded patients receiving vitamin D or calcium supplements, and, although we cannot exclude the possibility that some individual patients did take supplements, it is unlikely that this factor played a significant role in the whole group.

Among heart failure patients, the use of loop diuretics was more frequent in patients with reduced 25(OH)D concentration than in patients with a normal concentration of this metabolite [20]. In our study, a contrary phenomenon took place as both the frequency of use and the doses of these agents were higher than those documented in European Registries [23] and studies on the Polish population [24]. One should bear in mind that the cited data pertain to populations undergoing stabilized pharmacological treatment, while our results concern patients during a period of therapy escalation. This factor may be important for several reasons. Using higher doses of diuretics may result in increased appetite and absorption of vitamin D from nutritional sources. Improved quality of life after diuretic treatment may be associated with increased physical activity and exposure to sunlight, resulting in increased synthesis of vitamin D in the skin. The above possibilities are only hypotheses and should be verified by separate studies.

The research of recent years indicates a bidirectional relationship between the system of vitamin D and the renin-angiotensin-aldosterone system. Both experimental and animal model studies point to the activation of parathormone (PTH) synthesis by angiotensin II and aldosterone [25]. Inhibition of this system during the escalation of therapy including, among other elements, the administration of higher ACEI/ARB and AA doses may lead to the inhibition of PTH synthesis and relative hypoparathyroidism. This may result in a reduction in 25(OH)D conversion to 1,25(OH)₂D

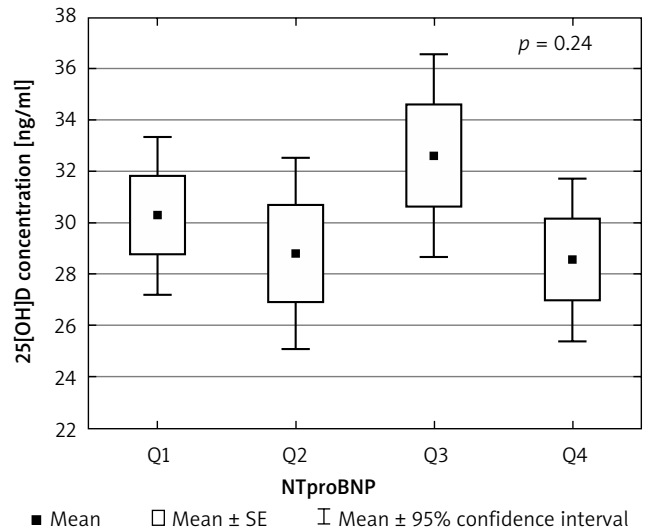


Fig. 4. 25-hydroxyvitamin D concentrations in relation to *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) quartiles after escalation of pharmacotherapy

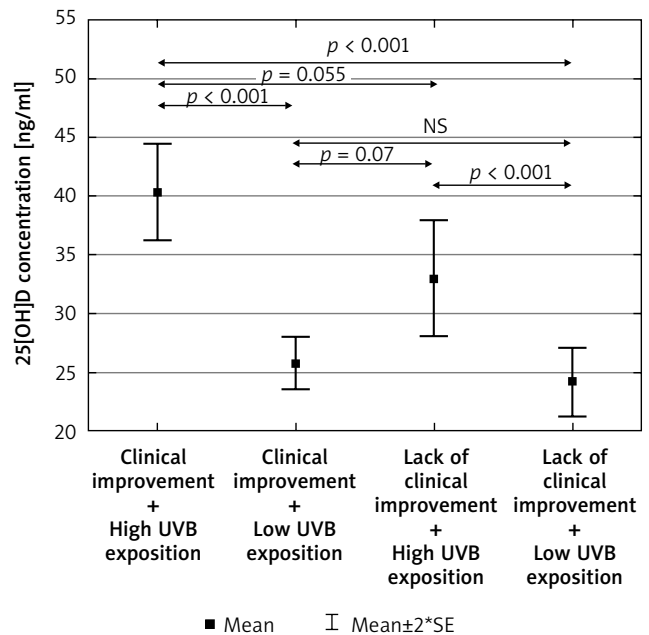


Fig. 5. 25-hydroxyvitamin D concentrations in groups characterized by various response to therapy achieved in periods of low and high availability of UVB radiation, respectively

under the influence of PTH and, consequently, leave an increased pool of 25(OH)D in the plasma. This hypothesis is confirmed by studies in which patients with low serum level of both PTH and 25(OH)D were characterized by better left ventricular ejection fraction, quality of life, and results of 6-minute walking tests, as well as lower NT-proBNP concentrations [26]. Another argument for the above hypothesis is the fact that the frequency of use and doses of ACEI/ARB and particularly AA were significantly higher in our study than in other reports [23, 24].

The risk factors for vitamin D deficiency have been a subject of few studies [10]. Their authors pointed to a negative correlation of 25(OH)D with renin activity and the concen-

Tab. III. Risk factors of reduced 25-hydroxyvitamin D [25(OH)D] concentration in univariable and multivariable analysis

Parameter	Probability of 25(OH)D concentration < 20 ng/ml vs. > 30 ng/ml			
	Relative risk ±95% confidence interval			
	Univariable analysis	<i>p</i>	Multivariable analysis	<i>p</i>
Sex [men vs. women]	0.78 (0.56-1.08)	0.13		
Low vs. high availability of natural UVB radiation [October – March vs. April – September]	2.13 (1.65-2.55)	< 0.001	2.36 (1.77-3.14)	< 0.001
Improvement vs. no improvement or NYHA class deterioration	0.79 (0.64-0.97)	0.03		
Body mass loss to minimum in HF [for every 5% of loss]	1.16 (1.05-1.29)	0.005	1.15 (1.02-1.30)	0.02
Body mass gain from minimum in HF to index day [for every 5% of gain]	1.09 (0.97-1.24)	0.14		
Uric acid [higher concentration for every 100 µmol/l]	0.79 (0.66-0.96)	0.02	0.69 (0.54-0.89)	0.004
Phosphates [higher concentration for every 0.2 mmol/l]	1.23 (0.99-1.52)	0.05	1.38 (1.07-1.78)	0.01
eGFR _{MDRD} [increased filtration for every 10 ml/min × 1.76 m ²]	1.08 (1.01-1.16)	0.03		
Albumins [higher concentration for 1 g/l]	1.04 (0.98-1.09)	0.19	1.08 (1.00-1.16)	0.04
ACEI/ARB treatment [yes vs. no]	0.64 (0.38-1.07)	0.08		
Diabetes [yes vs. no]	1.28 (1.02-1.60)	0.03	1.36 (1.02-1.82)	0.03

eGFR_{MDRD} – estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula, ACEI/ARB – angiotensin-converting-enzyme inhibitor I/angiotensin II receptor blocker

trations of natriuretic peptides, CRP, and interleukin 6. Our study did not confirm any relationship between inflammatory parameters and NT-proBNP. The strongest determinant turned out to be the potential availability of UVB radiation. This suggests that, in CHF patients, the dependence of 25(OH)D on intestinal absorption and diet quality may be small in comparison to the dependence on cutaneous synthesis and, indirectly, physical activity which is required to leave closed quarters and be exposed to sunlight.

The concentration of 25(OH)D was higher in patients examined during the period of increased UVB availability, and it was higher in patients who achieved clinical improvement in comparison with those in whom no improvement from therapy escalation was observed. In multivariable analysis, clinical improvement was no longer a significant predictor of reduced 25(OH)D concentration, which suggests that clinical improvement may increase the concentration of 25(OH)D by increasing effective exposure to sunlight. The significance of body mass loss as a risk factor for reduced 25(OH)D serum level may serve as additional validation of this hypothesis: cachexia is associated with poor exercise tolerance, which suggests lower exposure to sunlight among such patients.

The association between 25(OH)D deficiency and higher phosphate concentrations constitutes another argument for this interpretation because, in a CHF patient, the catabolic profile is an independent determinant of phosphate concentration [27]. Alternatively, the increased phosphate concentration may be a reflection of relative hypoparathyroidism and resulting reduced phosphaturia.

The issue most challenging to explain is the protective significance of uric acid concentrations on the devel-

opment of 25(OH)D deficiency. Its association with higher doses of diuretics appears unlikely because, in multivariable analysis, it was uric acid and not diuretic treatment that proved to be a significant determinant of 25(OH)D. One hypothesis could be that the increase of uric acid concentration is a result of a purine-poor diet, but we find no rational arguments to confirm this interpretation. The role of increased concentration of albumins as a factor increasing the probability of 25(OH)D deficiency is also intriguing. Here, a possible interpretation could consist in the synthesis of vitamin-D binding protein increasing along with albumin production, which could lower its bioavailability and result in reduced synthesis of 25(OH)D.

The presence of diabetes turned out to be a determinant of low 25(OH)D concentration, and this relationship has been confirmed by numerous studies [28].

Limitations

The overview character of this study precludes drawing credible conclusions concerning cause and effect relationships. The lack of 25(OH)D measurements from before the escalation of therapy precludes an assessment of changes in this compound's concentration in relation to the metabolic and functional changes occurring as a result of the therapy. Determining the concentrations of parathormone would be required to analyze the causes of 25(OH)D insufficiency and deficiency in more detail.

Conclusions

1. The incidence of 25(OH)D insufficiency and deficiency in the study group patients is lower than in previous re-

Tab. IV. Comparison of groups with different response to treatment and varying availability of ultraviolet B radiation. Mean \pm SD, median with interquartile range, or percentage

Parameter	Quartiles of NT-proBNP concentration				<i>p</i>
	Clinical improvement/ High UVB exposition <i>n</i> = 101	Clinical improvement/ Low UVB exposition <i>n</i> = 161	No clinical improvement/ High UVB exposition <i>n</i> = 63	No clinical improvement/ Low UVB exposition <i>n</i> = 87	
Age [years]	53 \pm 11	54 \pm 10	54 \pm 9	54 \pm 10	0.54
Sex [% women]	11.9	9.9	17.5	20.7	0.12
BMI [kg/m ²]	26.9 \pm 5	27.0 \pm 4	26.0 \pm 4	26.1 \pm 5	0.12
Ischemic etiology [%]	59.4	73.9	69.8	65.5	0.1
Initial NYHA class [% NYHA IV]	48.5	36.0	14.3	14.9	< 0.001
Clinical response [% improvement]	100.0	100.0	0.0	0.0	< 0.001
NYHA functional class change [mean \pm SD]	1.22 \pm 0.4	1.30 \pm 0.5	-0.10 \pm 0.3	-0.10 \pm 0.3	< 0.001
High availability of natural UVB radiation [% analysis of 25(OH)D concentration between April and September]	100.0	0.0	100.0	0.0	< 0.001
Body mass loss from preCHF BMI to minCHF BMI [% prePNS BMI]	9.4 (11.0)	7.7 (12.5)	14.3 (15.0)	12.0 (12.8)	< 0.001
Body mass gain from minCHF BMI to indexBMI [% minCHF BMI]	4.2 (8.5)	2.9 (8.5)	5.0 (10.2)	2.7 (8.3)	0.27
LVEF [%]	26 \pm 8	29 \pm 10	22 \pm 6	26 \pm 12	< 0.001
Uric acid [μ mol/l]	408 (170)	389 (133)	422 (190)	415 (184)	0.09
Albumins [g/l]	41 \pm 4	41 \pm 4	41 \pm 4	41 \pm 4	0.75
Calcium [mmol/l]	2.30 \pm 0.2	2.27 \pm 0.2	2.31 \pm 0.2	2.31 \pm 0.2	0.15
Phosphates [mmol/l]	1.11 \pm 0.2	1.06 \pm 0.2	1.15 \pm 0.2	1.13 \pm 0.2	0.009
eGFR _{MDRD} [ml/min/1.73 m ²]	85 (38)	93 (32)	86 (33)	82 (37)	0.02
NT-proBNP [pg/ml]	1242 (1904)	996 (1951)	2538 (2976)	2117 (3241)	< 0.001
25(OH)D [ng/ml]	36 (22)	23 (16)	39 (22)	20 (19)	< 0.001
25(OH)D < 30 ng/ml [%]	33.7	70.2	52.4	70.1	< 0.001
25(OH)D < 20 ng/ml [%]	12.9	38.5	27.0	48.3	< 0.001
Concomitant diseases [%]					
Arterial hypertension	54.4	59.6	58.7	57.5	0.87
Type 2 diabetes mellitus	19.5	24.2	42.9	34.5	0.004
Hypercholesterolemia	51.5	63.4	63.5	51.7	0.12
Hypertriglyceridemia	38.6	36.6	49.2	37.9	0.37
Nicotinism	67.3	79.5	73.0	72.4	0.60
Therapy					
ACEI/ARB [% treated]	96.0	93.8	93.7	90.8	0.54
Percentage of recommended dose in ACEI/ARB-treated patients [%]	52 \pm 48	63 \pm 54	55 \pm 52	48 \pm 38	0.1
BB [% treated]	98.0	98.8	96.8	94.3	0.2
Percentage of recommended dose in BB-treated patients [%]	48 \pm 26	47 \pm 31	46 \pm 22	41 \pm 23	0.2
AA [% treated]	92.1	84.5	98.4	89.7	0.02
Percentage of recommended dose in AA-treated patients [%]	113 \pm 49	103 \pm 62	128 \pm 65	137 \pm 78	< 0.001
Loop diuretic [% treated]	87.1	72.0	95.2	90.8	< 0.001
Dose of the loop diuretic in diuretic-treated patients [furosemide equivalent]	81 \pm 59	66 \pm 96	119 \pm 70	112 \pm 82	< 0.001

BMI – body mass index, NYHA – New York Heart Association class, LVEF – left ventricular ejection fraction, eGFR_{MDRD} – estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula, NT-proBNP – N-terminal prohormone of brain natriuretic peptide, 25(OH)D – 25-hydroxyvitamin D, ACEI/ARB – angiotensin-converting-enzyme inhibitor I/angiotensin II receptor blocker, BB – beta blockers, AA – aldosterone antagonists

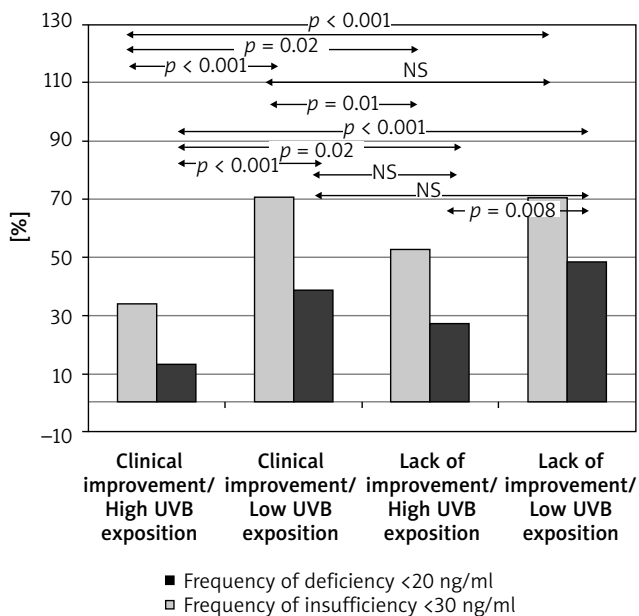


Fig. 6. Incidence of 25-hydroxyvitamin D insufficiency and deficiency in groups characterized by different treatment response achieved during periods of low and high availability of ultraviolet B radiation, respectively

- ports, which may be associated with the metabolic profiles of the patients and the employed therapy.
- In heart failure patients, escalation of pharmacotherapy resulting in improvement of their functional status may influence the concentration of 25(OH)D regardless of CHF progression after treatment optimization. This influence is noticeable only in periods of high UVB availability, which proves that the effect of increased availability of ultraviolet radiation is a stronger factor conditioning the concentration of 25(OH)D than clinical improvement in response to therapy.
 - The patients' metabolic profiles and the presence of diabetes are important determinants of 25(OH)D concentration.

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