ORIGINAL ARTICLE

Vitamin D deficiency, anxiety and depression correlated with quality of life in patients with chronic heart failure

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Abstract: Introduction – In heart failure (HF) anxiety and depression were relatively ignored by researchers, even if the measurement of quality of life (QoL) in these patients have become important tools to quantify disease severity. The objective of the present study was to quantify psychological stress and QoL in patients with chronic stable HF, and correlate the scores obtained with severity of heart failure and vitamin D levels. **Materials and methods –** The study included 45 patients with HF who performed clinical evaluation, biochemical analysis, echocardiography, determination of quality of life scores according to the Minnesota Living with Heart Failure questionnaire (MLHFQ) and the Hospital anxiety-depression scale (HAD). **Results –** It was found a significant correlation between the severity of HF versus vitamin D levels ($p < 0.001$), HAD-A scores ($p<0.011$), HAD-D scores ($p<0.033$), also for the MLHFQ ($p<0.001$). The results of the study demonstrated a significant correlation between the MLHFQ scores and levels of vitamin D ($p < 0.001$). **Conclusions –** The results obtained in this study showed that vitamin D deficiency in patients with chronic heart failure is significantly correlated with the severity of heart failure and decreased quality of life, anxiety and depression and could be used as a marker of increased risk.
Keywords: vitamin D, heart failure, quality of life, anxiety, depression.

Rezumat: Introducere – La pacienții cu insuficiență cardiacă (IC), anxietatea și depresia au fost relativ ignorate de către cercetători, chiar dacă măsurarea calității vieții (quality of life (QoL)) la aceștia a devenit un instrument important pentru cuantificarea severității bolii. Obiectivele studiului au inclus determinarea stresului psihologic și QoL la pacienții cu IC cronică stabilă și corelarea scorurile obținute cu severitatea bolii și nivelul de vitamina D. **Materiale și metode –** În studiu au fost incluși 45 de pacienți cu IC cronică stabilă, iar protocolul de studiu a urmărit evaluarea clinică, analiza biochimică, ecocardiografia, determinarea scorului calității vieții în conformitate cu chestionarul Minnesota Living with Heart Failure (MLHFQ) și scala de anxietate-depresie (HAD). **Rezultate –** S-a constatat o corelație semnificativă între severitatea IC și nivelul vitaminei D ($p<0,001$), scorurile HAD-A ($p <0,011$), HAD-D ($p <0,033$) și MLHFQ ($p<0,001$). Rezultatele studiului au demonstrat o corelație semnificativă între scorurile MLHFQ și nivelurile de vitamină D ($p <0,001$). **Concluzii –** Rezultatele obținute în acest studiu au arătat că deficitul de vitamina D la pacienții cu insuficiență cardiacă cronică este semnificativ corelat cu severitatea insuficienței cardiace și scăderea calității vieții, cu anxietatea și depresia și ar putea fi folosit ca marker al riscului crescut.
Cuvinte cheie: vitamina D, insuficiență cardiacă, calitatea vieții, anxietate, depresie.

INTRODUCTION

Heart failure (HF) is a chronic condition requiring permanent treatment. Patients with HF are monitored in the ambulatory cardiology departments at regular intervals, based on the severity of disease[1].

The evolution of HF is usually towards worsening, with decreased quality of life and increased mortality in the medium and long term. Prevention of cardiovascular diseases (especially myocardial infarction) and modern methods of treatment have led in the last years to an improvement in the survival of HF patients[2].

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Associations of risk factors (smoking, hypertension, diabetes, dyslipidemia) are consistent for occurrence of heart failure with both preserved and reduced left ventricular ejection fraction (LVEF), the most common sub-phenotypes of these condition[3]. Heart failure prevention is an important public health purpose. Increased physical activity and exercise can help prevent HF, as they are associated with reduced HF incidence and potentially act through a variety of mechanisms to slow disease progression.

The severity of heart failure is associated in numerous studies with vitamin D deficiency[4], and also with a worse prognosis[5]; moreover, supplementation of vitamin D could reduce the mortality rate and increase quality of life in patients with HF[6].

Different questionnaires that measure the quality of life in HF patients have become important assessment tools over the last decades[7,8]. Among these, one of the most well-known and used is the Minnesota Living with Heart Failure questionnaire (MLHFQ), which has demonstrated good psychometric properties in numerous studies, being translated and culturally adapted in at least 34 languages[8-11]. However, there are some concerns about the the homogeneity of its elements and about quantification of anxiety and depression, common comorbidities especially in these patients. Associations between HF and depression\ anxiety increase mortality[17]. Therefore, specific scores can be obtained for a comprehensive quantification of psychologic parameters, by using the HAD questionnaire.

The objective of the present study was to quantify psychological stress and quality of life in patients with chronic stable HF, and correlate the scores obtained with severity of heart failure and vitamin D levels.

MATERIAL AND METHODS

In the present study we correlated the echocardiographic parameters of cardiac performance and the scores obtained from the Minnesota Living with Heart Failure and HAD Questionnaires with vitamin D levels in 45 selected patients with chronic heart failure of different etiologies. The patients were divided into 3 groups according to ejection fraction: group A with preserved EF (≥50%) (n=15), group B with intermediate EF (40-49%) (n=15) and group C with low EF (<39%) (n=15), according to European guidelines1. This study conformed to the Declaration of Helsinki, was approved by the local ethics committee and all patients provided written informed consent.

Table 1. Category of vitamin D_3 levels

Category	ng/mL	nmol/L
Sufficient	>30	>75
Insufficient	21-29	50-75
Deficient	10-20	25-50
Severe decificiency	≤10	≤25

Biochemical analysis

Venous blood sampling was performed during hospitalization. After centrifugation, blood samples were quickly frozen and stored at-80 °C until analysis. 25-OH vitamin D_3 was performed immediately after plasma decompression.The 25-OH vitamin D_3 levels obtained were interpreted according to Table 1.

The glycaemiawas determinedby using a Siemens Dimension RLX-MAX, Dade Behring device.

To determine total cholesterol (TC), triglycerides (TG) and HDL-cholesterol (HDL-c) photometric methods (Dimension RLX-MAX automatic analyzer, Dade Behring) were used. LDL-cholesterol fraction was calculated using the Friedewald's formula:

LDL- C (mg/dL) = CT (mg/dL) – 0,2 x TG (mg/dL) – HDL-C (mg/dL)

Determination of echocardiographic parameters

Transthoracic echocardiography was performed in all patients enrolled in the study on the GE Vivid 9 ultrasound system. M-mode ultrasound was used to accurately measure heart structures. Two-dimensional ultrasound provided morphological and functional information about dimensions, cavities, cardiac wall, valvular lesions, ejection fraction and systolic performance. Doppler with two variants – spectral (for quantitative applications) and color (for qualitative applications) evaluated and quantified valvular regurgitation, left systolic and diastolic ventricular function and pulmonary pressures. Diastolic dysfunction was determined by the E/A ratio, and the left ventricular systolic function by measuring the ejection fraction.

The Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The MLHFQ, a self-administered disease-specific questionnaire for patients with heart failure comprising

Table 2. The severity of the quality of life impairment in patients with HF according to the MLHFQ

The quality of life impairment severity	The MLHFQ
Low	0-35
Medium	36-70
High	71-105

21 items representing the impact of HF on quality of life over the last 4 weeks, from 0 to 5, was applied to all patients. It provides a total score ranging from best to worst (0–105). Scores for emotional wellbeing (5 items, ranging between 0 to 25) and physical performance (8 items, range between 0 to 40) are evaluated. The other eight items are only considered for the calculation of the total score. The questions highlight how much the life of the patients with heart failure is affected regarding sleep, diet, physical condition (tired, exhausted), physical activity (entertainment, sports), sexual activity, or emotional life (restlessness, relating with family/friends, feeling a burden for the family).The severity of quality of life impairment in these patients is interpreted according to the score obtained after applying the MLWHF questionnaire (Table 2).

Table 3. Characteristics of patients (n=45)

Variable	Group	N	Mediate	Deviation Std.	Error Std.	95% Interval de confidentiality of the average		Minimum	Maximum
						Limit inf.	Limit sup.		
Age(years)	A	15	68.43	9.00	1.64	65.07	71.79	44	82
	B	15	71.90	9.11	1.66	68.50	75.30	58	85
	C	15	66.50	8.92	1.63	63.17	69.83	46	80
	Total	45	68.94	9.19	0.97	67.02	70.87	44	85
History of HF (months)	A	15	44.40	44.81	8.18	27.67	61.13	12	144
	B	15	81.67	57.83	10.56	60.07	103.26	12	186
	C	15	66.57	55.23	10.08	45.94	87.19	12	245
	Total	45	64.21	54.54	5.75	52.79	75.64	12	245
SBP at admission (mmHg)	A	15	138.90	18.19	3.32	132.11	145.69	100	185
	B	15	150.17	21.91	4.00	141.98	158.35	100	210
	C	15	140.03	21.39	3.91	132.05	148.02	90	180
	Total	45	143.03	20.96	2.21	138.64	147.42	90	210
DBP at admission (mmHg)	A	15	80.63	12.74	2.33	75.88	85.39	60	105
	B	15	85.60	12.68	2.31	80.87	90.33	60	120
	C	15	83.40	15.52	2.83	77.61	89.19	60	120
	Total	45	83.21	13.71	1.44	80.34	86.08	60	120
HR at admission (bpm)	A	15	83.47	21.50	3.93	75.44	91.49	57	126
	B	15	76.23	13.52	2.47	71.18	81.28	60	120
	C	15	75.53	14.48	2.64	70.13	80.94	60	106
	Total	45	78.41	17.07	1.80	74.84	81.99	57	126
Glycaemia (mg/dL)	A	15	114.23	20.26	3.70	106.67	121.80	84	172
	B	15	112.90	28.85	5.27	102.13	123.67	74	226
	C	15	113.60	28.95	5.29	102.79	124.41	69	210
	Total	45	113.58	26.04	2.75	108.12	119.03	69	226
Creatinine (mg/dL)	A	15	1.26	0.30	0.05	1.14	1.37	0.80	2.10
	B	15	1.45	0.54	0.10	1.25	1.65	0.90	3.20
	C	15	1.41	0.27	0.05	1.31	1.51	0.97	2.00
	Total	45	1.37	0.40	0.04	1.29	1.46	0.80	3.20
LVEF(%)	A	15	53.50	2.90	0.53	52.42	54.58	50	60
	B	15	43.77	3.09	0.56	42.61	44.92	40	49
	C	15	27.60	6.26	1.14	25.26	29.94	15	38
	Total	45	41.62	11.58	1.22	39.20	44.05	15	60
25-OH vitamin D3	A	15	27.19	4.46	0.81	25.52	28.86	21.3	36.1
	B	15	24.65	4.55	0.83	22.95	26.35	14.2	36.1
	C	15	17.24	4.40	0.80	15.59	18,88	10.1	27.2
	Total	45	23.03	6.13	0.65	21.74	24.31	10.1	36.1
The MLHFQ	A	15	52.40	15.92	2.91	46.45	58.35	21	83
	B	15	70.07	18.98	3.47	62.98	77.15	36	98
	C	15	83.73	17.02	3.11	77.38	90.09	45	105
	Total	45	68.73	21.47	2.26	64.24	73.23	21	105

SBP=systolic blood pressure, DBP=diastolic blood pressure, HR=heart rate, LVEF=left ventricular ejection fraction, HR=heart rate, 25-OH vitamin D3=25-hydroxyvitamin D3, MLHFQ=Minnesota Living with Heart Failure Questionnaire scores.

The Hospital anxiety and depression scale (HAD)

HAD scale consists of 14 items and contains two subscales, one for anxiety another for depression. Each item is quantified on a 4-point Likert scale from 0 (no symptoms) to 3 (highest level of symptoms). The maximum score is 21 for each subscale, scores like 0-7 are considered normal, whereas scores above 11 mean a considerable psychological morbidity either in the field of anxiety or depression. Scores like 8-10 indicate a borderline status. Scores were considered if at least five answers were given on each subscale. Missing responses in patients who completed only 5 or 6 items were replaced based on the sum of items filled multiplied by 7/5 respectively 7/6.

STATISTICAL ANALYSIS

The statistical analysis was done using SPSS v.17 software and included descriptive statistics results (mean, standard deviation, standard error, confidence intervals). The differences between the independent groups were obtained by the Mann-Whitney test, the correlations between numerical variables were made using the multivariate regression model and the strength of correlation was obtained with the Spearman's correlation coefficient. Nominal variables were compared and associated with the Pearson's chi-squared test, $p<0.05$ being considered statistically significant.

RESULTS

The characteristics of the 3 groups are represented in Table 3.

In Table 4 are represented the results of the Kruskal-Wallis test (comparisons between the three groups, for each variable).

The mean values of age, glycaemia, creatinine, systolic blood pressure, diastolic blood pressure and heart rate showed no statistically significant difference between the 3 groups.

LVEF values were between 15 and 60%. The mean LVEF values in the three groups were as follows: in group A 53.50±2.90%, in group B 43.77±3.09% and in group C 27.60±6.26%. The LVEF was significantly higher in group A compared to the other two groups ($p <0.001$).

The 25-OH vitamin D_3 values were between 10.1 and 36.1 ng/ml. The mean values in the 3 groups were as follows: in group A 27.19±4.46 ng/ml, in group B 24.65±4.55 ng/ml and in group C 17.24±4.40 ng/ml. The 25-OH vitamin D_3 values were significantly decre-

Table 4. Comparisons between the three groups (n=45)

Variable	p
Age	0.068[is]
History of HF	0.027[s]
SBP at admission	0.071[is]
DBP at admission	0.375[is]
HR at admission	0.137[is]
Glycaemia (mg/dl)	0.981[is]
Creatinine (mg/dl)	0.981[is]
LVEF %	<0.001[s]
E/A	0.007[s]
25-OH vitamin D_3	<0.001[s]
The MLHFQ	<0.001[s]

s=significant difference; is=insignificant difference.

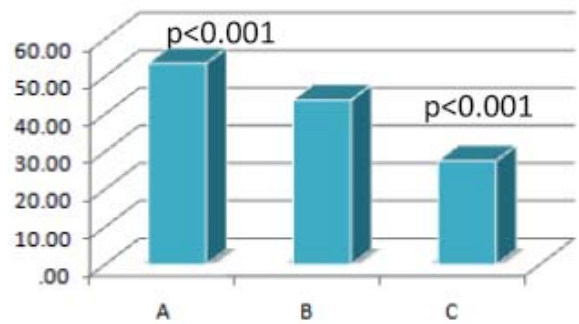

Figure 1. Distribution of mean EF % values in the 3 groups (n=45).

Table 5. Comparative analysis of the psychological test scores in the 3 groups. Nonparametric Kruskal-Wallis test. Heart failure patients (n=45)

Variables	Group	N	Mean	Std. Deviation	Std. Error	95% Confidence		p^{semnif}
						Lower bound	Upper bound	
HAD A	A	15	7.1	3.65	1.10	4.5	9.5	**0.011[s]**
	B	15	8.9	4.66	0.91	7.0	10.8	
	C	15	9.7	4.21	0.90	7.8	11.5	
	Total	45	8.9	4.36	0.55	7.7	10.0	
HAD D	A	15	6.8	3.10	0.61	5.5	8.0	**0.033[s]**
	B	15	7.2	4.45	1.34	4.2	10.2	
	C	15	9.1	3.49	0.74	7.3	10.6	
	Total	45	7.0	3.64	0.46	0.46	8.5	

Table 6. Correlations between psychological tests scores, risk factors and HF severity (n=45)

Total lot (n=45)		Severity of HF Coef.p	TC	HDL-c	LDL-c	TGL	SBP	DBP
HAD A	value r	-0.054	0.108	0.043	**0.133**	-0.023	-0.071	-0.023
	p	0.215	0.063	0.170	**0.025**	0.691	0.239	0.701
HAD D	value r	-0.004	-0.101	-0.086	-0.076	-0.031	0.004	-0.054
	p	0.926	0.082	0.111	0.201	0.593	0.932	0.372

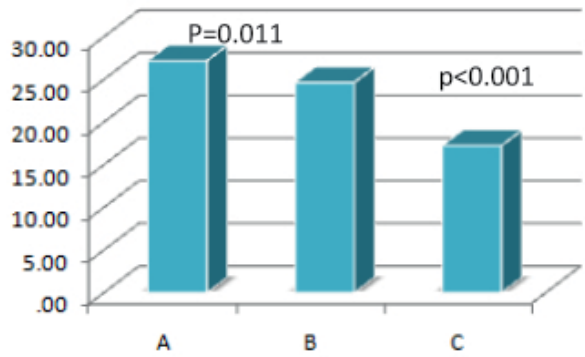

Figure 2. Distribution of mean values of 25-OH vitamin D_3 levels in the 3 groups (n=45).

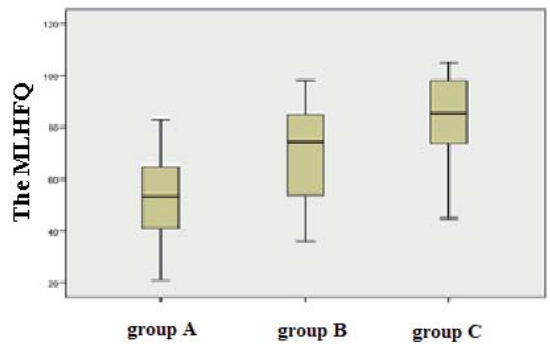

Figure 3. Boxplots representing the MLHFQ scores comparison between groups (n=45).

ased in group C versus A (p <0.001) and group B (p <0.001) (Figure 2).

The MLHFQ scores ranged between 21 and 105. The mean values in the three groups were: in group A 52.40±15.92, in group B 70.07±18.98 and in group C83.73±17.02. The MLHFQ scores were significantly lower in group A vs. group B (p = 0.001) and group C (p <0.001) and in group B vs. group C (p = 0.012) (Figure 3).

A significant negative correlation was found between the MLHFQ scores and LVEF (r = -0.832, p<0.001) and also 25-OH vitamin D_3 (r=-0.493, p <0.001) (Figure 4).

There was a significant correlation between severity of HF and anxiety-depression overall batch scores (Table 5): for HAD A score (p<0.011) and for HAD D score (p<0.033).

The analysis of correlations between HAD A and HAD D scores with severity of heart failure and risk factors (lipid parameters TC, HDL-C, LDL-C and TGL and mean values of SBP and DBP) revealed a significant positive correlation between HAD A scores and LDL cholesterol values (r=0.133, p=0.025) (Table 6).

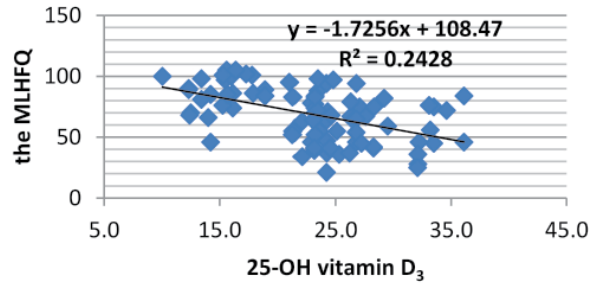

Figure 4. Linear regression plot. Correlation between the MLHFQ scores and 25-OH vitamin D_3 (r = -0.493, p <0.001) in the 45 HF patients.

DISCUSSION

The Minnesota Living with Heart Failure Questionnaire was designed by Rector, Kubo, & Cohn in 1987 as a specific tool for use in clinical and community trials for quality of life assessment in HF[12]. The MLHFQ is a very useful tool because it is cost-free, self-administered and easy to understand even by elderly patients, being validated by clinicians.

In the present study we observed that the MLHFQ scores are significantly increased in HF patients according to severity of disease. Numerous recent studies have demonstrated a relationship between LVEF values and the MLHFQ scores[9,13] or between LVEF and 25-OH vitamin D_3 levels[14,15], but no study has associated this marker with quality of life in heart failure patients.

A transversal multicenter study, conducted by Fotos et al., included 199 patients with HF who were hospitalized at the Department of Cardiology of three general hospitals in Greece over a 1 year period. Clinical data were obtained from the reviewed medical files

and the quality of life of patients was assessed using the Minnesota Living with Heart Failure Questionnaire. The results of this study have shown that patients with associated diabetes had a significantly lower quality of life[16].

The MLHFQ score in our study was 68.73±21.47, higher than reported by the Fotos et al. study, indicating poor health status perceived by patients in our country. This is a matter of concern, given that the mean age of the subjects included in our study, 68.94±9.19, was lower compared to 69.97±9.87 years in Fotos et al. study. The patients completed the questionnaire during hospitalization, not at admission like our patients, when most of them are anxious, a situation generally accompanied by lower scores.

In a recent article Bilbao et al., analyze the constituent parts of the questionnaire, noting that the largest discrepancies are related to the items referring to physical health factors. Although the two initial subscales: physical health (items 2,3,4,5,6,7,12,13) and emotional health (items 17,18,19,20,21) have been validated and applied in many countries (China, Korea, Greece), the authors consider that it is also necessary to validate the social subscale due to the different social situation of HF patients in the world[9]. Heo et al., proposed that this subscale be analyzed separately[17].

Improvement of the MLWHFQ score occurs in all these studies through educational and pharmacological interventions. The results of our study should be interpreted with caution because of the limitations imposed by the small number of patients, but compared with other studies the fact that we included the same number of patients in every group increases the power of comparisons. The validity of the results of this study could have been improved by comparing them with other quality of life questionnaires and by correlation with other objective tests (eg. 6 minutes walk test). The better scores in other studies are correlated with the obedience to complete the questionnaire.

In our study, mean serum 25-OH vitamin D_3 levels were significantly correlated with LVEF ($p<0.001$). These results are in line with similar published findings as confirmed in previous studies[18,19]. Quality of life and vitamin D_3 deficit in heart failure patients are closely linked and can cause HF aggravation[20]. In terms of cardiovascular risk assessment, vitamin D is a marker of increased arterial stiffness, as shown in numerous studies[21]. Vitamin D deficit is also being suggested to play a key role in depression onset in HF patients[22].

These results demonstrate a strong connection between vitamin D deficit and quality of life measured by the MLHFQ, and anxiety and depression measured by HAD scale, suggesting that correction of vitamin D deficit could improve parameters of vascular rigidity, depression and prognosis in heart failure patients.

LIMITATIONS OF THE STUDY

This study had a relatively small sample size. Large multicentre clinical studies are required to confirm our findings.

In conclusion, this study demonstrated that vitamin D deficiency in patients with chronic heart failure is significantly correlated with the severity of heart failure and decreased quality of life, anxiety and depression and could be used as a marker of increased risk. Further studies are needed to confirm the utility of vitamin D supplementation for clinical and functional improvement of these patients.

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