Original Paper

Self-Reported Physical Activity, Quality of Life, and Psychological Status in Relation to Plasma 25-Hydroxyvitamin D Concentration in Patients Treated with Hemodialysis

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Key Words

Hemodialysis • Physical activity • Psychiatric functioning • Quality of life • Vitamin D

Abstract

Background/Aims: Vitamin D status is announced among factors that may influence physical performance and mental health. Our aim was to evaluate self-reported physical activity, quality of life, psychiatric functioning, and affects with respect to plasma 25-hydroxyvitamin D [25(OH)D] concentrations in HD patients. **Methods:** The study was carried out in HD patients not receiving vitamin D supplements (n = 112). IPAQ-L, QLI-D, GHQ-28, and PANAS were used in psychological evaluations. Plasma 25(OH)D concentration was determined by a chemiluminescent microparticle immunoassay. **Results:** Plasma 25(OH)D level was suboptimal in all patients (14.6 ± 4.1 ng/ml). Adjusted correlates of 25(OH)D concentration included the GG genotype of GC rs7041 (β ± SE: 1.77 ± 0.70, P = 0.014), female sex (β ± SE: -2.19 ± 0.75, P = 0.004), and treatment with high flux HD (β ± SE: 2.59 ± 0.69, P = 0.0003). In adjusted analyses, circulating 25(OH)D showed the independent association with total activity related to domestic and gardening domain (β ± SE: 53.2 ± 23.8, P = 0.028), and with moderate-intensity activities (β ± SE: 54.9 ± 27.4, P = 0.048), but not with any of quality of life, psychiatric functioning, or affects measures. **Conclusions:** Vitamin D status is independently positively associated with physical activity in HD patients. Quality of life and mental health do not seem to be associated with circulating 25(OH)D under condition of its suboptimal levels.

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Introduction

Abnormalities in vitamin D metabolism are included into characteristics of chronic kidney disease – mineral and bone disorder [1] as well as attributed to uremic myopathy [2, 3] and altered immunocompetence [4, 5]. Moreover, a higher risk of cardiovascular events and a higher death rate were demonstrated among chronic kidney disease patients showing vitamin D deficiency, including those treated with hemodialysis (HD) [6-8].

25-hydroxyvitamin D [25(OH)D] is a widely accepted biomarker of the vitamin D status, also in dialysis patients [1]. Older studies defined vitamin D deficiency as serum 25(OH)D values below 10 ng/ml, and insufficiency as values ≥ 10 but < 20 –32 ng/ml [9, 10]. However, recent evidence indicates that vitamin D deficiency should be defined as a 25(OH)D level less than 20 ng/ml, and vitamin D insufficiency should be diagnosed at a 25(OH)D concentration of 20 to 30 ng/ml [11-13]. From this currently accepted point of view, vitamin D deficiency in end-stage renal disease (ESRD) population has to be recognized still more common than previously reported [1, 4, 6, 7, 14-18].

Poor physical performance predicts a high risk of mortality, cardiovascular events and hospitalizations in HD patients and those treated with peritoneal dialysis [19]. Lower self-reported physical activity in patients new to dialysis [14] or worse functional capacity according to the Karnofsky index in subjects on chronic HD [15] were shown with respect to vitamin D deficiency in cross-sectional analyses, however not in randomized controlled trial with cholecalciferol supplementation lasting over 6 months in HD subjects [20].

In incident dialysis patients, 25(OH)D deficiency was found to be associated with poorer self-reported mental health [14]. In the non-dialysis population, there are data either showing [21] or not showing [22] poorer mental health in the association with lower 25(OH)D concentrations. However, supplementation with vitamin D did not change mental health composite scores [23].

Previously mentioned data therefore indicate inconsistency in psychological characteristics analyzed in respect to plasma vitamin D concentration in patients treated with HD due to ESRD. The objective of this study was to perform an evaluation of self-reported physical activity, quality of life, psychiatric functioning, and affects with respect to plasma vitamin D concentrations in well-characterized prevalent HD patients.

Patients and Methods

Patients

The prevalent HD patients ($n = 112$) were included into the study. All patients lived in the Greater Poland Voivodship, Poland, and were dialyzed in three dialysis facilities. All dialyses were founded by the National Health Found (NHF), and the principal patient management was provided in accordance with guidelines of NHF that were elaborated on the base of recommendations of the Polish Society of Nephrology and the principal country consultants in nephrology. Patients were using erythropoietin stimulating agents, phosphate binders (predominantly calcium carbonate or calcium acetate), iron and water-soluble vitamin supplements, cinacalcet hydrochloride, and other medication, as appropriate for HD patients. None of patients was administered intravenous vitamin D or its analogues. Among oral vitamin D supplements, alfacalcidol (Alfadiol, GlaxoSmithKline Pharmaceuticals SA, Poland) was the most frequently used. Four patients were receiving paricalcitol. However, patients taking vitamin D (cholecalciferol), its metabolites (calcidiol, calcitriol) or its analogues (22-oxacalcitriol, paricalcitol) were excluded from the study (see below for inclusion criteria). Co-morbid conditions were treated as needed.

Inclusion criteria consisted of age above 18 years, no administration of vitamin D and related pharmaceuticals (see above) at least for one month before enrolment, renal replacement therapy (RRT) vintage at least for 2 years including at least the last 18 months on unchanged dialysis modality [high-flux (HF)-HD or low-flux (LF)-HD], and stable clinical condition at least for one month before enrolment into the study. Exclusion criteria included a diagnosis of dementia, intellectual disability or other conditions

Fig. 1. Flowchart showing enrolment of HD patients to the study.

that might impair the ability to answer questions. Flowchart showing enrolment of HD patients to the study is shown on Fig. 1.

Patients were receiving HD three times a week for 4.0 hours per session. There were differences between dialysis centers in applied HD modality (HF-HD only in one center, LF-HD only in the second center, and both HD modalities in the third center). Differences in the HD methods were taken into account in statistical analyses.

Main characteristics of the patients are shown in Table 1. The studied HD subjects seem to represent the typical HD population: median age exceeded 60 years [24], male sex was slightly more prevalent [24], and diabetic nephropathy was the most common cause of ESRD [24, 25].

Psychological examination

Physical activity and mental health were assessed by the experienced surveyor (psychologist AI). The long version of the International Physical Activity Questionnaire (IPAQ-L) [26-28], the Ferrans & Powers' Quality of Life Index (QLI) – Dialysis Version III (QLI-D) [29-31], General Health Questionnaire (GHQ-28) [32, 33], and The Positive and Negative Affect Schedule (PANAS) [34, 35] were implemented in all study subjects.

Detailed description of abovementioned tests is shown in Supplementary Methods section of online suppl. material, see www.karger.com/doi/10.1159/000452585. Consistent with the International Physical Activity Prevalence Study protocol, all patients were examined in October and November [36].

Table 1. Main characteristics of the HD patients (n = 112)

Characteristics	Value
Age, years	68.0 (29.0 - 91.5)
Female sex, n (%)	52 (46.4)
Total RRT vintage, years	4.82 (2.0 - 21.0)
Life with functioning renal transplant, years ^a	3.75 (0.01 - 17.1)
HD vintage, years	4.73 (2.0 - 18.7)
College education or more, n (%)	30 (26.8)
Genotypes of GC rs7041, n (%) ^{b,c}	GG 40 (36.4), GT 48 (43.6), TT 22 (20.0)
Genotypes of GC rs1155563, n (%) ^{c,d}	TT 45 (40.5), CT 50 (45.0), CC 16 (14.4)
HF-HD vs LF-HD, n (%)	65 (58.0)
Dry body mass, kg	73.9 (43 - 135)
BMI, kg/m ²	26.94 (16.29 - 47.38)
HBsAg positivity, n (%)	0 (0)
HCV RNA positivity, n (%)	8 (7.1)
ALT activity, U/l	13 (2 - 69)
AST activity, U/l	16 (5 - 65)
Type 2 diabetic nephropathy, n (%)	34 (30.4)
Chronic glomerulonephritis, n (%)	21 (18.8)
Chronic tubulointerstitial nephritis, n (%)	8 (7.1)
Hypertensive nephropathy, n (%)	23 (20.5)
Coronary artery disease, n (%)	33 (29.5)
Myocardial infarction, n (%)	14 (12.5)
A habit of sunbathe ^e	5 (4.5)
25(OH)D, ng/ml	14.56 ± 4.08
Total calcium, mg/dl	8.81 (6.65 - 12.8)
Phosphorus, mg/dl	4.7 (2.63 - 8.73)
Total alkaline phosphatase, U/l	102.4 (24.0 - 1,353.3)
Parathyroid hormone, pg/ml	426.6 (30.0 - 2,397.7)
Albumin, g/l	39.0 (27.8 - 47.0)

^a relevant for 8 patients who underwent renal transplantation in the course of renal replacement therapy; ^b available in 110 patients; ^c tested polymorphism was distributed in accordance with Hardy-Weinberg equilibrium; ^d available in 111 patients; ^e only face and hands in all 5 cases

Since QLI-D and GHQ-28 focus on well-being and mental condition, respectively, and PANAS focuses on the assessment of affectivity, they all measure different aspects of psychological functioning. IPAQ-L is a measure of the physical activity, but it might be considered as connected with psychological state of an individual as well [37]. Therefore results of QLI-D, GHQ-28, PANAS, and IPAQ-L will be referred to hereinafter as psychological characteristics.

Anthropometric measurements

Height was measured by a nurse in the upright position of each patient. Body mass was measured and evaluated before and after each dialysis session and recorded. Dry body mass was established by experienced nephrologists (one in each dialysis facility) and used for calculation of body mass index [BMI = weight (kg)/height (m²)].

Laboratory measurements

Fasting blood samples for laboratory testing were drawn before the mid-week dialysis session.

To examine plasma 25(OH)D concentrations, a chemiluminescent microparticle immunoassay was used according to the manufacturer's instructions (Abbot Diagnostic ARCHITECT 25-OH VITAMIN D CMIA®, Mannheim, Germany). The range of the assay is 3.00 – 70.0 ng/mL (7.50 – 175 nmol/l). According to the manufacturer's instruction, the optimal 25(OH)D level for adults is 35 – 80 ng/ml. Other laboratory parameters were measured using standard laboratory assays.

Genotyping

Single nucleotide polymorphisms of the vitamin D binding protein gene, also referred to as the group-specific component gene (*GC*), were chosen for genotyping. The loci selected for this study included *GC* rs7041 and rs1155563.

The genotyping of the *GC* rs7041 polymorphism was conducted by polymerase chain reaction (PCR), followed by digestion of the amplified products with the *Hae*III (GG/CC) restriction enzyme (PCR-RFLP) and 2% agarose gel electrophoresis. The rs7041 T allele remained uncut (493bp), whereas the rs7041 G allele was cleaved by *Hae*III into 414bp and 79bp fragments. The genotyping of *GC* rs1155563 nucleotide variants was conducted by high-resolution melting curve analysis (HRM) on the Bio-Rad CFX96 Real Time PCR system (Bio-Rad, Hercules, California, United States). Primer sequences and conditions for PCR-RFLP and HRM analyses are presented in the earlier study [38].

Statistical analysis

The results are presented as percentage for categorical variables, mean with 1 standard deviation for normally distributed continuous variables, or median (range) for non-normally distributed continuous variables as tested by the Shapiro–Wilk test.

After checking normality of residuals, linear regression method was used to show a magnitude and significance of interactions between tested parameters. However, to explore possible effects of outstanding variables on linear regression output, the Spearman method was additionally used to show correlations between tested variables.

Statistical analyses were performed as follows:

1. Unadjusted correlates were explored for circulating 25(OH)D among patient characteristics that are abovementioned and shown in Table 1. The multivariable analyses adjusted correlates of 25(OH)D for characteristics significant in unadjusted analyses at a P value <0.05.

2. Patient characteristics were used as independent variables in searching correlates for each psychological parameter. Taking into account linear regression analysis, the Spearman correlation, and the correction for multiple comparisons, correlates for self-reported physical activity, quality of life, psychiatric functioning, and affects of the HD patients were established among tested variables.

3. Circulating 25(OH)D as an independent variable was tested for correlation with all psychological characteristics. Adjustment was made using adjusted correlates of 25(OH)D and significant correlates of self-reported physical activity, quality of life, psychiatric functioning, and affects of the HD patients, as appropriate.

For discussion purposes, appropriate comparisons were performed between HD subgroups (females vs. males, chronic glomerulonephritis patients vs. the remaining patients), using appropriate statistical tests for non-paired variables for continuous data, and Chi square test with Yates correction for dichotomous

data. Differences in the examined parameters in relation to tertiles of 25(OH)D plasma concentration were analyzed using ANOVA, ANOVA rang Kruskal-Wallis, and Chi square tests with post hoc tests, as appropriate.

At baseline, a value of P less than 0.05 was considered significant; a borderline significance was mentioned at a P value above 0.05 but less than 0.10. However, the correction for multiple comparisons was applied to avoid a coincidental significance in establishment of correlates of psychological characteristics among patient data. In such cases, a P value less than 0.005 for physical activity correlates, a P value less than 0.010 for correlates of quality of life or psychiatric functioning, and a P value less than 0.025 for correlates of affects were considered significant. In comparisons of parameters separated according to the tertiles of 25(OH)D, only P values with the Bonferroni correction for multiple testing were considered significant.

The previously mentioned statistical analyses were performed using Graph-Pad InStat 3.10, 32 bit for Windows (GraphPad Software, Inc., San Diego, California, United States), CytelStudio version 10.0 (CytelStudio Software Corporation, Cambridge, Massachusetts, United States), and Statistica version 12, 2014 (Stat Soft, Inc., Tulsa, Oklahoma, United States).

Tables with statistical data not shown in the paper are presented in the online supplemental material.

Ethical issues

The study design was approved by the Institutional Review Board of Poznan University of Medical Sciences, Poland (the project identification code 800/15, date of approval September 3, 2015). The written informed consent was obtained from all study participants.

Results

Vitamin D and its correlates

In all prevalent, not vitamin D supplemented HD patients, plasma 25(OH)D concentrations were suboptimal (14.56 ± 4.08 ng/ml). Serum 25(OH)D values corresponding with deficiency by the older definition (< 10 ng/ml [1-3]) were shown in 15.2% of patients, whilst the remaining subjects showed 25(OH)D insufficiency (values ≥ 10 ng/ml but ≤ 32 ng/ml [1, 9]). When vitamin deficiency was diagnosed at the level below 20 ng/ml [13], 90.2% of patients showed deficiency.

Patient characteristics tested as possible correlates of circulating 25(OH)D included both explanatory variables (age, gender, education, *GC* rs7041, *GC* rs1155563, causes of ESRD, dialysis modality, dry body mass, BMI, and serum albumin concentration) and response variables (serum concentrations of calcium, phosphorus, and parathyroid hormone - PTH). Prevalence of coronary artery disease, including myocardial infarction, was also tested for correlation with circulating 25(OH)D as vitamin D deficiency contributes to development of cardiac ischemia [39]. Amongst abovementioned variables, plasma 25(OH)D was positively correlated with the GG genotype of *GC* rs7041, treatment with HF-HD, and dry body mass; a negative correlation was shown for female sex. After adjusting, significant correlates included the GG genotype of *GC* rs7041, female sex, and treatment with HF-HD (Table 2). Patients harboring the GG genotype (major homozygotes) of *GC* rs7041 showed higher plasma 25(OH)D concentration than patients bearing the minor allele (GT and TT individuals) (15.59 ± 3.96 ng/ml vs. 13.82 ± 3.98 ng/ml, respectively, $P = 0.027$). HD women compared to HD men demonstrated lower circulating 25(OH)D ($12.85, 7.6 - 18.9$ ng/ml vs. $16.6, 5.7 - 24.3$ ng/ml, respectively, $P = 0.0001$). The use of more effective dialysis modality (HF-HD vs. LF-HD) was associated with higher plasma 25(OH)D levels (15.50 ± 3.84 ng/ml vs. 13.26 ± 4.08 ng/ml, respectively, $P = 0.004$).

Psychological characteristics and their correlates with patient data

Data of self-reported physical activity, quality of life, psychiatric functioning, and affects of the HD patients are displayed in Table 3.

By IPAQ, none of the HD patients was working or performing vigorous-intensity activities. Transport-related activity was revealed in 44 (39.3%) patients, leisure-time activity was reported by 35 (31.3%), and domestic and gardening activity was shown in 25

Table 2. Demographic, genetic, clinical, and laboratory correlates of 25(OH)D concentration

Characteristics	Unadjusted percent change in 25(OH)D concentration		Spearman correlation		Adjusted ^a percent change in 25(OH)D concentration	
	$\beta^b \pm SE$	P value	R value	P value	$\beta^b \pm SE$	P value
Age (per 10 years)	0.14 $\pm$ 0.27	0.622	0.043	0.656	0.02 $\pm$ 0.26	0.933
Female sex	-3.25 $\pm$ 0.69	0.000008	-0.350	0.0002	-2.19 $\pm$ 0.75	0.004
College education or more	-0.15 $\pm$ 0.87	0.862	-0.002	0.982	-0.54 $\pm$ 0.79	0.491
RRT vintage (per 1 year)	0.042 $\pm$ 0.105	0.694	0.005	0.960	0.88 $\pm$ 0.93	0.350
GG genotype of GC rs7041	1.66 $\pm$ 0.78	0.035	0.213	0.025	1.77 $\pm$ 0.70	0.014
CC genotype of GC rs1155563	-1.66 $\pm$ 1.11	0.137	-0.178	0.061	-1.55 $\pm$ 0.99	0.123
HF-HD vs. LF-HD	2.68 $\pm$ 0.73	0.0004	0.262	0.005	2.59 $\pm$ 0.69	0.0003
Dry body mass, kg	0.59 $\pm$ 0.23	0.011	0.260	0.006	0.03 $\pm$ 0.02	0.195
BMI, kg/m ²	0.48 $\pm$ 0.35	0.178	0.173	0.069	-0.04 $\pm$ 0.16	0.791
Type 2 diabetic nephropathy	-0.047 $\pm$ 0.828	0.955	0.034	0.720	-0.58 $\pm$ 0.75	0.442
Chronic glomerulonephritis	-1.26 $\pm$ 1.01	0.521	-0.149	0.118	-0.14 $\pm$ 0.93	0.880
Chronic tubulointerstitial nephritis	1.37 $\pm$ 1.57	0.383	0.142	0.137	1.64 $\pm$ 1.42	0.251
Hypertensive nephropathy	0.414 $\pm$ 0.914	0.651	0.032	0.739	-0.36 $\pm$ 0.88	0.682
Coronary artery disease	0.995 $\pm$ 0.829	0.233	0.180	0.058	0.37 $\pm$ 0.77	0.636
Myocardial infarction	1.13 $\pm$ 1.15	0.323	0.157	0.099	0.81 $\pm$ 1.06	0.448
Total calcium, mg/dl	0.55 $\pm$ 0.48	0.262	-0.202	0.172	-0.38 $\pm$ 0.80	0.641
Phosphorus, mg/dl	0.055 $\pm$ 0.2821	0.845	0.042	0.781	0.23 $\pm$ 0.41	0.579
Parathyroid hormone (per 200 pg/ml)	18.7 $\pm$ 0.17	0.864	-0.034	0.819	-0.04 $\pm$ 0.26	0.870
Albumin (per 1 g/dl)	0.70 $\pm$ 0.99	0.483	0.057	0.551	-0.80 $\pm$ 0.99	0.417

^a adjustment for female sex, the GG genotype of GC rs7041, treatment with HF-HD, and dry body mass, as appropriate; ^b β coefficient can be interpreted as the percent change expected in 25(OH)D for each unit change in the independent variable; Significant differences are indicated using bold font. Conversion factors to SI units are as follows: for albumin, 10.0; for calcium, 0.2495; for parathyroid hormone, 0.1061; and for phosphorus, 0.3229

(22.3%) patients. Domestic and gardening subdomains equally contributed to total domain (0.0, 0.0 - 2700 metabolic equivalent task (MET)-minutes/week vs. 0.0, 0.0 - 6930 MET-minutes/week, respectively, $P = 0.158$). In respect to forms of physical activity, walking was reported by 45 (40.2%) subjects, and moderate-intensity activities were performed by 39 (34.8%) subjects. As many as 45 (40.2%) patients did not report any physical activity in terms of asked questions.

Unadjusted correlates of psychological characteristics

Table 3. Self-reported physical activity, quality of life, psychiatric functioning, and affects of the HD patients

Parameter	Value
Self-reported physical activity by IPAQ-L	
Total work-related physical activity, MET-minutes/week	0 (0 - 0)
Total transport-related physical activity, MET-minutes/week	0 (0 - 2772)
Total domestic and gardening physical activity, MET-minutes/week	0 (0 - 6930)
Total leisure-time physical activity, MET-minutes/week	0 (0 - 4200)
Total walking, MET-minutes/week	0 (0 - 4158)
Total moderate-intensity activities, MET-minutes/week	0 (0 - 6930)
Total vigorous-intensity activities, MET-minutes/week	0 (0 - 0)
Total physical activity, MET-minutes/week	160.0 (0 - 7969.5)
Total physical activity, MET-kcal/week	151.8 (0 - 10318)
The average time spent sitting (without time spent on HD session and on transportation), minutes/day	300 (51.4 - 720)
Total physical activity level scores	1 (1 - 3)
Quality of life by QLI-D	
Health and functioning subscale	17.4 (4.54 - 24)
Social and economic subscale	19.8 $\pm$ 4.19
Psychological/spiritual subscale	22.9 (5 - 30)
Family subscale	25.5 (9.9 - 30)
Overall quality of life score	19.99 (11.4 - 30)
Psychiatric functioning by GHQ-28	
Somatic symptoms	6 (3 - 21)
Anxiety/insomnia	3 (0 - 19)
Social dysfunction	7 (2 - 21)
Severe depression	0 (0 - 18)
Total score	17 (8 - 65)
Affects by PANAS	
Positive affect	30.5 (15 - 67)
Negative affect	15 (15 - 65)

among demographic, clinical and laboratory data (excluding vitamin D) are shown in online supplemental material, Tables S1-S19. There were no suggestions for correlations of psychological characteristics with dry body weight, BMI, *GC* rs1155563 polymorphism, education, history of myocardial infarction, and serum concentrations of calcium and phosphorus. Correlates significant at a P value less than 0.05 are summarized in online supplemental material, Tables S20 and S21. Taking into account linear regression analysis, the Spearman correlation, and the correction for multiple comparisons, correlates of psychological characteristics were as follows:

1. in the physical activity domain: age (a negative correlation) and chronic glomerulonephritis as a cause of ESRD (a positive correlation) – both at a P value <0.005;
2. in the quality of life domain: age (a positive correlation) and type 2 diabetic nephropathy as a cause of ESRD (a negative correlation) – all at a P value <0.010;
3. in psychiatric functioning: type 2 diabetic nephropathy as a cause of ESRD (a negative correlation), serum PTH concentration (a negative correlation), and serum albumin concentration (a positive correlation) – all at a P value <0.010;
4. in affects: age (a negative correlation), female gender (a positive correlation), and type 2 diabetic nephropathy as a cause of ESRD (a negative correlation) – all at a P value <0.025.

Vitamin D and psychological characteristics

Associations of psychological characteristics with plasma 25(OH)D concentration as an explanatory variable are summarized in Table 4. In adjusted analyses, circulating 25(OH)D was revealed as a significant positive correlate for “total domestic and gardening physical activity” domain. In terms of intensity, a significant association of vitamin D and total moderate-intensity activities was shown. Quality of life, psychiatric functioning, and affects were not significantly associated with circulating 25(OH)D concentrations.

Examined parameters in relation to tertiles of 25(OH)D concentration

Demographic, genetic, clinical, and laboratory data as well as psychological parameters analyzed in relation to tertiles of 25(OH)D are shown in Tables 5 and 6, respectively.

Female gender, GG genotype of *GC* rs7041, and HF-HD which significantly correlated with 25(OH)D after adjustment for possible confounding variables in analyses shown above differed also in tertiles of circulating 25(OH)D, although rs7041 did not reach significance between specific tertiles (Table 5). Additionally, 25(OH)D was higher in patients with higher dry body mass. This relationship lost significance in above presented data after adjustment for female sex, the GG genotype of *GC* rs7041, and treatment with HF-HD (Table 2).

Psychological parameters including total domestic and gardening physical activity as well as total moderate-intensity activities did not yield significant results when analyzed in tertiles of 25(OH)D concentration (Table 6).

Discussion

ESRD is generally associated with suboptimal plasma 25(OH)D concentrations [1, 4, 6, 7, 14-18]. Beyond uremia, additional specific factors may contribute to variations in circulating vitamin D levels. Recognition of variables significantly influencing plasma 25(OH)D concentration may be of relevance for the understanding of 25(OH)D associations with psychological characteristics. Among such variables there are genetic polymorphisms in *GC* (rs2282679, rs7041, rs1155563) [38, 40], gender [16, 38], sunlight exposure [14, 15], dialysis modality [16], and BMI [15, 41].

The GG genotype of *GC* rs7041 was associated in the present study with higher 25(OH)D levels, whereas patients bearing the minor allele of *GC* rs7041 showed lower 25(OH)D concentrations. We confirmed in this respect previous studies [38, 40]. In patients bearing

Table 4. Associations of 25(OH)D with physical activity, quality of life, and psychiatric functioning of HD patients

Parameter	Unadjusted		Adjusted ^b	
	$\beta^a \pm SE$	P value	$\beta^a \pm SE$	P value
Self-reported physical activity by IPAQ-L				
Total work-related physical activity, MET-minutes/week	NA	NA	NA	NA
Total transport-related physical activity, MET-minutes/week	4.7 $\pm$ 9.8	0.633	0.9 $\pm$ 11	0.935
Total domestic and gardening physical activity, MET-minutes/week	39.5 $\pm$ 20.1	0.052	53.2 $\pm$ 23.8	0.028
Total leisure-time physical activity, MET-minutes/week	9.3 $\pm$ 11.4	0.419	10.3 $\pm$ 13.9	0.459
Total walking, MET-minutes/week	11.5 $\pm$ 12.7	0.368	9.5 $\pm$ 14.2	0.504
Total moderate-intensity activities, MET-minutes/week	42.0 $\pm$ 23.0	0.070	54.9 $\pm$ 27.4	0.048
Total vigorous-intensity activities, MET-minutes/week	NA	NA	NA	NA
Total physical activity, MET-minutes/week	53.5 $\pm$ 29.6	0.073	64.4 $\pm$ 34.9	0.068
Total physical activity, MET-kcal/week	76.5 $\pm$ 37.9	0.046	83.0 $\pm$ 44.9	0.067
The average time spent sitting (without time spent on HD session and on transportation), minutes/day	-2.7 $\pm$ 4.3	0.521	-6.2 $\pm$ 5.0	0.212
Total physical activity level scores	0.006 $\pm$ 0.016	0.699	0.01 $\pm$ 0.02	0.542
Quality of life by QLI-D				
Health and functioning subscale	0.06 $\pm$ 0.08	0.494	0.07 $\pm$ 0.10	0.497
Social and economic subscale	0.01 $\pm$ 0.10	0.953	-0.04 $\pm$ 0.11	0.754
Psychological/spiritual subscale	0.07 $\pm$ 0.12	0.585	0.09 $\pm$ 0.14	0.542
Family subscale	-0.06 $\pm$ 0.11	0.585	-0.06 $\pm$ 0.13	0.682
Overall quality of life score	0.07 $\pm$ 0.08	0.367	0.05 $\pm$ 0.09	0.580
Psychiatric functioning by GHQ-28				
Somatic symptoms	0.06 $\pm$ 0.09	0.492	0.16 $\pm$ 0.20	0.447
Anxiety/insomnia	-0.07 $\pm$ 0.08	0.397	0.01 $\pm$ 0.17	0.947
Social dysfunction	0.10 $\pm$ 0.06	0.135	0.08 $\pm$ 0.14	0.561
Severe depression	-0.08 $\pm$ 0.08	0.339	-0.02 $\pm$ 0.15	0.909
Total score	0.01 $\pm$ 0.24	0.976	0.23 $\pm$ 0.49	0.639
Affects by PANAS				
Positive affect	0.15 $\pm$ 0.27	0.585	-0.01 $\pm$ 0.32	0.983
Negative affect	-0.43 $\pm$ 0.23	0.061	-0.11 $\pm$ 0.27	0.683

^a β coefficient and SE values can be interpreted as: for a 1 ng/mL in 25(OH)D concentration, the predicted psychological variable would change by $\beta \pm SE$; ^b adjustment for the GG genotype of *GC* rs7041, female sex, treatment with HF-HD, as well as additionally for age and chronic glomerulonephritis as a cause of ESRD in self-reported physical activity by IPAQ-L, for age and type 2 diabetic nephropathy as a cause of ESRD by QLI-D, for type 2 diabetic nephropathy as a cause of ESRD, serum PTH concentration, and serum albumin concentration in psychiatric functioning by GHQ-28, and for age and type 2 diabetic nephropathy as a cause of ESRD in affects by PANAS; Significant differences are indicated using bold font

the minor allele of *GC* rs7041, a substitution of aspartic acid to glutamic acid at amino acid position 432 (Asp432Glu) of vitamin D binding protein attributed to the functional properties of the *GC* rs7041 variant seems to be an important contributor to decreased plasma 25(OH)D levels, possible by inducing a lower affinity of 25(OH)D to vitamin D binding protein. A negative correlation between 25(OH)D concentrations and CC genotype in *GC* rs1155563 was borderline in the present study, however also in the general trend with the previous findings [38, 40].

Female gender was associated with the negative impact on 25(OH)D, like in previous studies [14, 16, 38].

Carrying out this study in autumn, we followed the International Physical Activity Prevalence Study protocol [36], and we avoided differences in the impact of sunlight exposure on vitamin D level between patients who used to sunbathe in the summer time and those who did not. Additionally, during autumn in Poland the temperature is already low enough to discourage people from exposing their body to the sunlight and at the same time the number of sunny days is highly limited. Moreover, a habit of sunbathe was declared only by 4.5% of patients, and sun exposure was restricted to face and hands.

HD modality of higher efficiency (in the current study HF-HD compared with LF-HD) was associated with better preserved plasma 25(OH)D concentrations [16, 17]. As

Table 5. Demographic, genetic, clinical, and laboratory data of HD patients in relation to tertiles of 25(OH)D concentration

Characteristics	25(OH)D concentration, ng/ml			P value	P value for difference between tertiles
	T1 <12.4 n = 37	T2 ≥12.4 - ≤16.6 n = 38	T3 >16.6 n = 37		
Age, years	68 (29 - 91.5)	68.5 (29.5 - 86.4)	68 (34.3 - 90.1)	0.935	
Female sex, n, % of all	24 (64.9)	19 (50)	9 (24.3)	0.002	T1-T2 0.193 T1-T3 0.0004 T2-T3 0.021
College education or more, n, % of all	9 (24.3)	10 (26.3)	11 (29.7)	0.869	
RRT vintage, years	5.2 (2 - 17.9)	4.9 (2 - 21)	4.6 (2.1 - 16.7)	0.517	
GG genotype of GC rs7041, n, % of all	10 (27.0)	11 (28.9)	19 (51.4)	0.030	T1-T2 0.853 T1-T3 0.018 T2-T3 0.027
CC genotype of GC rs1155563, n, % of all	6 (16.2)	8 (21.1)	2 (5.4)	0.123	
HF-HD, n, % of all	15 (40.6)	24 (63.2)	26 (70.3)	0.025	T1-T2 0.049 T1-T3 0.010 T2-T3 0.514
Dry body mass, kg	71 (43 - 135)	73.3 (46 - 113)	80 (55 - 118)	0.025	T1-T2 0.164 T1-T3 0.006 T2-T3 0.226
BMI, kg/m ²	25 (16.3 - 47.4)	26.7 (18.3 - 39)	28 (20 - 38.8)	0.111	
Type 2 diabetic nephropathy, n, % of all	11 (29.7)	10 (26.3)	13 (35.1)	0.705	
Chronic glomerulonephritis, n, % of all	8 (21.6)	9 (23.7)	4 (10.8)	0.285	
Chronic tubulointerstitial nephritis, n, % of all	1 (2.7)	3 (7.9)	4 (10.8)	0.349	
Hypertensive nephropathy, n, % of all	8 (21.6)	7 (18.4)	8 (21.6)	0.923	
Coronary artery disease, n, % of all	8 (21.6)	9 (23.7)	16 (43.2)	0.084	
Myocardial infarction, n, % of all	3 (8.1)	4 (10.5)	7 (18.9)	0.349	
Total calcium, mg/dl	8.8 (6.7 - 10)	8.8 (6.8 - 12.8)	8.8 (7.3 - 10.2)	0.610	
Phosphorus, mg/dl	4.4 (2.6 - 8.5)	4.8 (2.7 - 8.7)	4.7 (3.2 - 8.3)	0.753	
Parathyroid hormone, pg/ml	493.3 (30 - 1603.3)	407.8 (92.2 - 1762.5)	413 (32.5 - 2397.7)	0.901	
Albumin, g/dl	3.8 (2.8 - 4.4)	3.9 (2.8 - 4.7)	3.9 (3.1 - 4.6)	0.779	

Significant differences (after the Bonferroni correction, $P < 0.017$, for specific tertiles) are indicated using bold font. Conversion factors to SI units are as follows: for albumin, 10.0; for calcium, 0.2495; for parathyroid hormone, 0.1061; and for phosphorus, 0.3229

Table 6. Physical activity, quality of life, and psychiatric functioning of HD patients in relation to tertiles of 25(OH)D concentration

Parameter	25(OH)D concentration, ng/ml			P value
	T1 <12.4 n = 37	T2 ≥12.4 - ≤16.6 n = 38	T3 >16.6 n = 37	
Self-reported physical activity by IPAQ-L				
Total work-related physical activity, MET-minutes/week	NA	NA	NA	NA
Total transport-related physical activity, MET-minutes/week	0 (0 - 1134)	0 (0 - 2079)	0 (0 - 2772)	0.889
Total domestic and gardening physical activity, MET-minutes/week	0 (0 - 3120)	0 (0 - 525)	0 (0 - 6930)	0.171
Total leisure-time physical activity, MET-minutes/week	0 (0 - 1416.4)	0 (0 - 1188)	0 (0 - 4200)	0.483
Total walking, MET-minutes/week	0 (0 - 1419)	0 (0 - 2079)	0 (0 - 4158)	0.953
Total moderate-intensity activities, MET-minutes/week	0 (0 - 3100)	0 (0 - 765)	0 (0 - 6930)	0.144
Total vigorous-intensity activities, MET-minutes/week	NA	NA	NA	NA
Total physical activity, MET-minutes/week	247.5 (0 - 3100)	144 (0 - 2079)	160 (0 - 7969.5)	0.668
Total physical activity, MET-kcal/week	318.1 (0 - 3790.2)	142.1 (0 - 2494.8)	221.4 (0 - 10318.1)	0.674
The average time spent sitting (without time spent on HD session and on transportation), minutes/day	300 (51.4 - 720)	300 (120 - 720)	300 (51.4 - 720)	0.831
Total physical activity level scores	1 (1 - 3)	1 (1 - 3)	1 (1 - 3)	0.834
Quality of life by QLI-D				
Health and functioning subscale	17.6 (7.9 - 23.6)	17.1 (4.5 - 22.6)	17.1 (11 - 24)	0.926
Social and economic subscale	19.4 ± 4.3	20.2 ± 4.7	19.9 (13.7 - 27.3)	0.673
Psychological/spiritual subscale	22.8 (5 - 30)	23 (8.1 - 30)	22.8 (13.7 - 29)	0.887
Family subscale	25.5 (9.9 - 30)	26 (12 - 30)	26.4 (15 - 30)	0.730
Overall quality of life score	20.3 (11.4 - 24.7)	20 (11.8 - 25.4)	19.9 (13.2 - 30)	0.918
Psychiatric functioning by GHQ-28				
Somatic symptoms	5 (3 - 21)	6 (3 - 17)	7 (3 - 17)	0.276
Anxiety/insomnia	3 (0 - 19)	3 (0 - 13)	3 (0 - 19)	0.994
Social dysfunction	7 (2 - 15)	7 (7 - 21)	7 (7 - 16)	0.170
Severe depression	0 (0 - 12)	0 (0 - 15)	0 (0 - 18)	0.651
Total score	15 (8 - 56)	17 (10 - 51)	18 (11 - 65)	0.603
Affects by PANAS				
Positive affect	31 (15 - 55)	30 (15 - 67)	30 (15 - 58)	0.950
Negative affect	16 (15 - 65)	15 (15 - 51)	15 (15 - 42)	0.535

HF-HD was used in 58% of our patients, it might result in less pronounced prevalence of 25(OH)D deficiency in the present study (15.2% subjects with vitamin D below 10 ng/mL) than in prior reports on HD subjects (42% patients with vitamin D below 10 ng/mL [16]) or HD/peritoneal dialysis patients (65% with vitamin D below 15 ng/mL [14]).

We have not found the association between circulating 25(OH)D concentrations and BMI in the entire group of HD patients, confirming the results shown by Jean et al. [16], but not those reported as inverse by Anand et al. [14]. Moreover, plasma 25(OH)D and dry body mass were positive correlates in unadjusted analysis and patients showing 25(OH)D in the third tertile has significantly higher dry body mass than those showing 25(OH)D in the first tertile. This finding may reflect a phenomenon of reverse epidemiology of obesity in HD patients [42]. In our study, BMI, serum albumin, and age, were not correlates of circulating vitamin D what is in disagreement with previous observation by Anand et al. [14]. However, lower BMI, higher serum albumin, and older age of our patients than of those previously reported makes both studied groups different, and it might be a reason for inconsistent relationships.

Searching for correlates of psychological characteristics among HD patient data aimed to understand factors possible contributing to physical activity, quality of life, and mental health of the studied group beyond vitamin D. This approach is also useful in evaluating whether the results of the studied HD group correspond with already known data in the explored field. However, we are aware of many established factors being barriers to physical activity in HD patients [43] that are not mentioned in our study.

As expected, physical activity or functional status are reported in chronic kidney disease patients as worse in older subjects compared with younger individuals [37, 44, 45], and this phenomenon was also shown in the studied HD patients examined by IPAQ-L. Together with worse physical activity, older patients revealed also less positive affect intensity. As showed by Theofilou [37], self-reported functional status is an important predictor of mental health in dialysis patients.

Patients, which have chronic glomerulonephritis as a cause of ESRD, usually present less comorbid signs and symptoms than those suffering from renal diseases secondary to systemic diseases, and they are usually younger (in the present study 60.1, 29.5 - 76.0 years in the glomerulonephritis group vs. 70.6, 29.0 - 91.5 years in the remaining patients, $P = 0.000001$, Mann-Whitney U test). These facts may explain higher physical activity in glomerulonephritic patients compared with those without glomerulonephritis as a cause of ESRD. Inversely, patients, who were dialyzed due to type 2 diabetic nephropathy, showed worse quality of life in health and functioning subscale and in psychological/spiritual subscale as well as higher scores in anxiety/insomnia and negative affect intensity. This finding is not a surprise. Diabetic patients show shorter life expectancy among HD subjects [46], and diabetes is an established predictor of mortality in HD patients [25]. Therefore, HD subjects with type 2 diabetic nephropathy may present worse satisfaction with various aspects of life, worse mood and more fear.

HD patients with higher serum PTH concentration revealed worse psychiatric functioning (depression) by GHQ-28. Secondary hyperparathyroidism was already related to depression [47].

In HD patients, serum albumin concentration is a positive marker of protein nutrition [48] and a negative marker of inflammation [49]. It was also associated with higher plasma 25(OH)D in dialysis patients [14]. In this study, "severe depression" item correlated negatively with serum albumin levels. Depression and serum albumin were already linked in dialysis patients [50].

Although dialyzed women show lower vitamin D levels compared with men [14, 15, 38], and it was also present in this study, female gender was associated with less negative affect score by PANAS. Differences in age or educational level might be an explanation for different intensity of negative affects [35, 51], but such differences did not reach statistical significance in studied gender groups, see online supplemental material, Table S22).

When the independent correlates of plasma 25(OH)D levels and appropriate variables correlating with psychological characteristics beyond possible influence of vitamin D were used for adjustment in analyses exploring vitamin D associations with psychological characteristics, significant associations were revealed for total domestic and gardening physical activity as well as for total moderate-intensity activities.

An association of 25(OH)D with physical activity may be explained by relationship of low vitamin levels with uremic myopathy [1, 3]. Vitamin D deficiency-related myopathy is manifesting with muscle weakness, easy tiring, difficulty in climbing stairs and arising from a squatting or kneeling position, and poorer physical performance [52]. Plasma 25(OH)D concentrations below 15 ng/ml were associated with musculoskeletal pain the European Male Ageing Study [53]. These all symptoms may discourage from undertaking physical activity. In the studied group, none of the HD patients was performing vigorous-intensity activities, and physical activity was mainly related to walking.

Effects of vitamin D supplementation may confirm its role in muscular function. In vitamin D-depleted chicks, a diminution of muscular force was reversed upon administration of vitamin D [54]. Active vitamin D treatment diminished muscle weakness in dialysis patients [2], increased muscle mass in HD men (not in HD women) [55], and was possibly associated with slower deterioration of physical functioning [55]. On the other hand, muscle function as determined using surface electromyography and the Chair Stand Test was not associated with 25(OH)D in chronic kidney disease patients including peritoneal dialysis group [56]. Combined treatment with cinacalcet and low-dose vitamin D sterols also did not improve the physical composite scores in HD patients [23]. In the light of numerous influences on plasma vitamin D concentration, including non-modifiable genetic factors [38, 40], and, similarly, numerous determinants of physical activity, it seems that only large scale randomized, prospective studies might clarify whether and to which extend vitamin D has a causative impact on physical activity in HD patients.

Our study did not show significant associations between circulating vitamin D and quality of life or mental health of HD subjects. In the earlier study by Anand et al. [14], such associations were observed. As we have already mentioned, our study group was different in many crucial aspects from that of Anand et al. [14]. Particularly, our patients were on RRT for median 4.82 years, whereas Anand et al. [14] studied subjects who were new on dialysis. Self-reported domains may change over time. This phenomenon was evidently shown by Rustøen et al. [51] on patients with newly diagnosed cancer who were studied for 9 months. Self-reported quality of life changed also in dialysis patients after one year on dialysis [57]. These changes could be hardly related to plasma vitamin D concentration, because low vitamin D levels are reported in non-supplemented HD patients independently of HD vintage [15, 18], and circulating 25(OH)D was not correlated with RRT vintage in the present study.

Strengths of the study

In our study, the well-characterized prevalent dialysis population underwent complex examination which included physical activity, quality of life, and related psychological features. Tested psychological characteristics of the studied group were analyzed in connection with numerous demographic, clinical, and laboratory data, and the GC polymorphism.

Only Polish versions of well known, broadly used, valid and reliable instruments to assess physical activity, quality of life and psychological status were used. Each method was administered in a face-to-face contact with an experienced surveyor. This procedure allowed to ensure that there was no misunderstanding of questions by patients.

Limitations of the study

The implementation of self-report assessment methods forced us to exclude patients who – with high probability – might have difficulties with understating questions and providing adequate answers that could be used in the analysis. However, since the group of these patients was diversified (diagnosis of dementia, intellectual disability or other

conditions like vision or hearing loss) one might expect that they were not a homogenous group in terms of the plasma levels of 25(OH)D. Hence, exclusion of this patients should not introduce any significant bias on the results of the research. Moreover, all these patients were also uremic and treated with regular HD, therefore they were predisposed to vitamin D deficiency like majority of such patients. However we are aware of the fact that verification of this assumption would need further research that would involve more objective measurement methods that do not depend on individual's cognitive skills.

Even though the instruments were validated measures of physical activity, quality of life, and related psychological features, as self-report methods they depend on subjective perceptions of the participants and their qualities like the level of self-reflection. Therefore study findings may have been strengthened with addition of more objective measurement methods.

The results may be biased by the limited variation in plasma 25(OH)D concentrations. All our results are conclusive for HD patients showing suboptimal concentrations of circulating 25(OH)D.

Presented conclusions were drawn from a cross-sectional study. Casual relations between tested parameters should be established under supplementation of vitamin D in prospective studies. In the work by Hewitt et al. [20], vitamin D supplementation in HD patients did not change muscle strength, functional capacity, and health-related quality of life, although at baseline 25(OH)D concentrations correlated with the distance covered in a 6-minute walk. Basing on our results, we postulate evaluations of vitamin D effects on more uniform HD populations, like categorized according to gender, HD modality, or the *GC* polymorphism.

Conclusions

1. Plasma 25(OH)D concentrations are suboptimal in prevalent HD patients not receiving vitamin D supplements.
2. Higher circulating 25(OH)D concentrations are associated with the *GC* rs7041 and treatment with HF-HD, while lower levels occur in female patients.
3. Type 2 diabetic nephropathy as a cause of ESRD negatively correlates with quality of life, psychiatric functioning, and affect intensity.
4. Circulating 25(OH)D is a meaningful positive correlate of self-reported physical activity.
5. Quality of life and mental health do not seem to be associated with circulating 25(OH)D under condition of its suboptimal levels.

Abbreviations

ALT - alanine aminotransferase, AST - aspartate aminotransferase, BMI - body mass index, GC - the group-specific component gene, GHQ - the General Health Questionnaire, HBsAg - surface antigen of hepatitis B virus, HCV - hepatitis C virus, HD - hemodialysis, HF-HD - high flux hemodialysis, IPAQ-L - long version of the International Physical Activity Questionnaire, LF-HD - low flux hemodialysis, NA - not applicable, PANAS - the Positive and Negative Affect Schedule, QLI-D - Dialysis Version III of the Ferrans & Powers' Quality of Life Index, RNA - ribonucleic acid, RRT - renal replacement therapy.

Disclosure Statement

None declared.

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