Medical University – Varna

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Motor activity in hemodialysis patients and opportunities for its optimization

Abstract

of dissertation work

for awarding an educational and scientific degree

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The dissertation is illustrated with 17 tables, 33 figures and one appendix. The bibliography includes 356 literature sources, of which 13 are in Cyrillic and 343 in Latin.

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The materials for the defense are available at the Scientific Department of the Medical University - Varna. They are published on the website of the Medical University - Varna.

Contents

ABBREVIATIONS USED

Cyrillic abbreviations

AP – Alkaline phosphatase
SHP - Secondary hyperparathyroidism
GF – Glomerular Filtration
EchoCG – Echocardiography
BMD-CKD – Bone mineral disorders in chronic kidney disease
CPT – Cardio Pulmonary Testing
CT – Computed Tomography
GFR – Glomerular Filtration Rate
WHO – World Health Organization
VC – Vascular calcification
CVC – Cardiovascular changes
CKD – Chronic Kidney Disease
CKF – Chronic Kidney Failure
HD – Hemodialysis

Latin abbreviations

ANOVA – Analysis of Variances
AR – Acute Kidney Injury/Acute rejection
Ca – Calcium
CPET – Cardiopulmonary exercise symptoms
CaSR – Calcium Sensing Receptor
CV – Cardiac vascularizations
DASI – Duke Activity Status Index
EDTA – Ethylenediaminetetraacetic acid
ELISA – A plate-based enzyme-linked immunosorbent assay designed to detect specific biomolecules in biological samples
ESRD – End-stage renal disease
FGF-23 – Fibroblast Growth Factor-23
HD – Hemodialysis
HDF – Hemodiafiltration
HRQoL Health-related quality of life
KDIGO – Kidney Disease Improving Global Outcomes
KDQoL-SF – Quality of Life in Kidney Disease
LV – Left ventricle
MBD – Mineral and Bone Disorders
MBD- CKD- Mineral and Bone Disorders-Chronic Kidney Disease
OPG – Osteoprotegerin OPG
P – Phosphorus
PTH – Parathyroid hormone
QOL – Quality of Life
RANKL – Receptor activator of NF-κB ligand
ROD – Renal osteodystrophy
VO2 peak – Peak oxygen consumption
USRDS – United States Renal Data System

I. INTRODUCTION

Chronic kidney disease (CKD) is a clinical and laboratory symptom complex associated with a progressive decrease in renal function as a result of irreversible nephrosclerosis. This leads to the loss of the main renal functions - excretory, regulatory and endocrine, and to disturbances in the functioning of all organs and systems in the body.

In recent years, the term chronic kidney disease (CKD) has been increasingly used, reflecting the continuity and progression of kidney damage. The average global incidence of CKD is about 10–12%, with a tendency to increase. Data indicate that each year approximately 300–400 patients per 1,000,000 population reach the terminal stage of CKD, requiring the initiation of hemodialysis treatment. In Bulgaria, the incidence of CKD is about 26%, and an increasing trend is also observed.

CKD is a serious global health problem associated with reduced life expectancy. In patients with end-stage CKD (ESCKD) undergoing hemodialysis (HD), survival is about 75% lower than that of their peers. There is also a significantly reduced physical functional capacity - about 70% of that of clinically healthy individuals, and after the initiation of HD the values decrease to approximately 50%. Patients on hemodialysis often also suffer from a high degree of disability, resulting from the complications of CKD and an immobilized lifestyle, which further limits their ability to perform daily activities.

The clinical manifestation of CKD includes various manifestations and complications, among which bone mineral disorders (BMD) occupy a leading place. Renal bone disease develops, characterized by bone pain and pathological fractures.

As a result of the disturbed homeostasis, phosphorus retention, hypocalcemia, increased levels of fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH), bone fragility and vascular calcification are observed. These changes lead to pathological changes in bone metabolism and the formation of vascular and soft tissue calcifications. This has a significant impact on the quality of life and is a leading factor for permanent disability of patients.

All these processes constitute the syndrome of bone mineral disorders in CKD (BMD-CKD)**.** The syndrome develops secondary to progressive loss of nephrons and decreased renal function. The ability of the kidneys to eliminate P and synthesize calcitriol is gradually impaired, and disorders in calcium homeostasis also occur. The sequence of pathological changes includes:

Hyperphosphatemia → Secondary hyperparathyroidism → Bone disorders

CKD leads to serious complications that often cause disability in patients. This highlights the need for actions aimed at improving their quality of life. In recent years, increasing attention has been paid to the role of physical activity and renal rehabilitation in overcoming motor disorders associated with CKD.

Motivating patients and their psycho-emotional resilience play a key role in their effective participation in rehabilitation programs. It is necessary to overcome fear and resistance, stimulate positive thinking and engagement in exercises aimed at improving motor function and coping with the consequences of CKD. This necessitates teamwork between nephrologists and specialists in physical and rehabilitation medicine, with a focus on the development and implementation of innovative methods for dealing with BMD in CKD.

Of utmost importance for patients at different stages of CKD is their physical activity. BMD lead to a negative impact on the functional and physical capacity of patients and to a deteriorated quality of life. An appropriate method for positively influencing the low motor activity in patients with ESCKD is the introduction of intradialysis exercises in hospitals through a bicycle specially mounted to the patient's bed. Intradialysis exercises demonstrate great continuity on the part of patients. Even with the first intradialysis training session, overcoming the fears and concerns of patients related to performing physical activities is supported. Aerobic exercises with a specially mounted bicycle improve blood circulation, muscle tone and physical endurance, reduce fatigue and muscle spasms (cramps) that appear at the end of the dialysis procedure. They contribute to the prevention of muscle mass loss and malnutrition, thus affecting the quality of life and mental state of HD patients.

In order to overcome the described changes and complications in recent years, intradialysis exercises are considered a suitable choice for dialysis patients. Their implementation during HD is recommended.

Renal rehabilitation has received little attention over the years. It is a coordinated, multifaceted intervention designed to optimize the physical, psychological, and social functioning of the patient. Renal rehabilitation is an effective, feasible, and safe strategy for secondary prevention of BMD-CKD. Future efforts should focus on the effects of rehabilitation and exercise programs, as these topics and types of exercise have not been adequately studied, as have cardiovascular and pulmonary rehabilitation. The new rehabilitation concept is to add life to years and years to the lives of patients with CKD.

In foreign literature, there are studies on the implementation of renal rehabilitation in chronic dialysis patients, which show good results in terms of biochemical indicators and the functional state of the lower extremities [Bae et. al., 2015, Chigira et., al., 2017, Blaine et. al. 2015, Clarcson et. al.,2019, Elshinnawy et. al. 2021, Hargrove et. al., 2021, Bernier et. al., 2022, Konsuki M., 2024]. In our country, there are no studies in this field.

II. GOAL AND OBJECTIVES

Purpose of the study

The aim of this dissertation is to prove that the use of specialized intradialysis kinesitherapy improves motor activity, social rehabilitation and quality of life in patients with end-stage kidney disease (ESKD).

Research objectives

To achieve this goal, we set ourselves the following tasks:

1. Study of the motor activity of two groups (experimental and control) of patients with CKD on dialysis treatment by means of:

- Duke Activity Status Index (DASI) – a patient-reported assessment of functional capacity, maximal oxygen consumption (VO2 max), and maximal metabolic equivalents of tasks (METs). Maximal oxygen consumption (VO_{2max}) is a proven predictor of mortality in hemodialysis patients;
- A 6-minute walk test (6MWT) – clinical assessment of gait disorders and static and dynamic balance;
- Sit to stand test (STS60) – clinical assessment of functional strength of the lower extremities.

2. Study of the impact of chronic dialysis treatment in both groups of patients with ESKD on their motor activity and individual quality of life using an adapted version of a standardized questionnaire for quality of life in patients with kidney disease (KDQOL-SF).
3. Evaluation of the impact of specialized cardio-cycling exercises on the clinical status of chronic dialysis patients, objectified by examining laboratory indicators of bone-mineral disorders.
4. Creation and implementation of an innovative specialized questionnaire to identify the main causes of deterioration in motor activity of patients with ESKD and stratification of risk factors.
5. Creation of an original algorithm for performing intradialysis exercises with the aim of optimizing routine clinical practice, preventing complications of the underlying disease, improving disease management, rehabilitation and quality of life of patients with ESKD.

HYPOTHESIS

- Motor activity in patients with CKD G 5 is severely impaired.
- Cardio-cycling exercises have the potential to improve bone mineral status, as objectified by Ca/P metabolism indicators.
- Dosed physical activity improves the quality of life in chronic dialysis patients.
- The awareness of patients with CKD is increasing as a result of specialized health education by medical professionals.

IV. MATERIALS AND METHODS

To achieve the goal and tasks of the dissertation, we conducted an experimental study with a parallel design, following the previously developed detailed protocol, approved by the Research Ethics Committee (REC) at the Medical University of Varna with decision N 129/ 06. 04. of 2023.

Materials

The study was conducted in the period May 2023 - November 2024 at the Clinic of Nephrology and Dialysis, dialysis treatment activity of the University Hospital "St. Marina" Varna. It is a leading center among all 4 dialysis centers in the city and offers diagnostic and therapeutic procedures to patients in need of hemodialysis from Northeastern Bulgaria.

The general population is all patients with CKD G5 stage of chronic hemodialysis. The selection of the studied individuals was made from the patients with CKD who underwent treatment in 2023-2024 at the dialysis center at the University Hospital "St. Marina" Varna - the largest in the city and Northeastern Bulgaria. Of these, 81 individuals were included in the sample, representing 45% of those who underwent hemodialysis treatment for the period from May 2023 to November 2024.

Criteria for inclusion of individuals:

- Persons 31-74 years old;
- Individuals who signed informed consent;
- Persons with proven CKD G 5 undergoing dialysis treatment;
- Patients with vascular access AV fistula or indwelling vascular catheter.

Criteria for excluding individuals:

- Persons under 18 years of age;
    - Individuals who have not signed informed consent;
    - Clinical condition that does not allow physical exercise, such as people with autoimmune, oncological diseases, with amputated limbs, with heart disease (unstable angina pectoris, rhythm disorders, frequent hypotension during dialysis, dyspnea at rest).

An invitation to participate in the study was sent to 119 patients. Of these, 39 patients did not meet the criteria. 5 patients refused to sign informed consent.

According to the protocol and the sample size estimate, it was planned to reach 80 participants, which would guarantee a power of 80% to detect a difference in size $\delta > 1$ and a statistical significance

of 5% in two-sided statistical tests. The selection was carried out until it reached 81 participants in the study. Of these, 47 were men and 34 were women with ESKD. The participants were randomly assigned, following the simple randomization method, to two parallel groups. The study group included 42 patients, and the control group – 39 patients.

Table 1. Description of the surveyed individuals: by gender, age, education.

		Number	%
Gender	Men	47	58.0
	Women	34	42.0
Age	Up to 54	30	37.0
	55-69	35	43.2
	70+	16	19.8
Average age	Environment and SD	59.3	11.9
Education	Mainly	17	20.9
	Average	50	61.7
	Higher	14	17.3
Total		81	100

Table 2. Description of the subjects studied, divided into two groups: control and experimental.

Characteristics		Total	Experimental	Control	p value
Gender	Men	47(58.0)	24 (57.1)	23 (59.0)	0.867
	Women	34 (42.0)	18 (42.9)	16 (41.0)	
Age	up to 54	30 (37.0)	16 (38.1)	14 (35.9)	0.975
	55-69	35 (43.2)	18 (42.9)	17 (43.6)	
	70+	16 (19.8)	8 (19.0)	8 (20.5)	
Average age	mean (SD)	59.3 (11.9)	58.6 (11.94)	59.9 (12.1)	0.613
Education	Mainly	17 (20.9)	13 (31.0)	4 (10.2)	0.02
	Average	50 (61.7)	25 (59.5)	25 (64.1)	
	Higher	14 (17.3)	4 (9.5)	10 (25.6)	
Total		81 (100.0)	42 (100.0)	39 (100.0)	

When comparing the statistical analysis between the control and experimental groups of patients, significance was found in terms of education ($p = 0.02$).

Methods

The following tests were planned and carried out for all participants:

- Detailed medical history;
- Physical status;

It includes measurement of arterial pressure under standard conditions. Arterial blood pressure is measured after a period of rest (10 minutes), at the level of the underarm, in a sitting/lying position before the hemodialysis procedure, during and after intradialysis cardio-cycling training and at the end of the dialysis procedure.

Laboratory tests:

Parathyroid hormone (PTH): Serum concentrations of modified intact iPTH were quantified by a two-step automated chemiluminescent immunoassay (CLIA) using two polyclonal antibodies as used in LIAISON/DIASORIN;

Calcium (Ca): Serum calcium concentrations were quantified using the automated Arsenazo III photometric method;

Serum (P): Serum inorganic phosphorus concentrations were quantified using the automated phosphomolybdate/UV method, adapted to a fully automatic biochemical analyzer ADVIA 1800, Siemens;

CRP in mg/l: immuno-turbidimetric assay; biochemical analyzer ADVIA chemistry 1800, Siemens. Linearity of the method: 0.12 – 164 mg/l. Reference limits: 0.5 mg/l. Lower detectable value (LOD): 0.04 mg/l.

Functional status studies:

- Duke activity status index (DASI), calculated using a standardized formula;
- Maximum oxygen consumption (VO2 max), calculated using a standardized formula;

- Maximum metabolic equivalent of tasks by reference (METs), calculated by a standardized formula.
- 6 Minute Walk Test (6 MTWT). Assessment of gait and static and dynamic balance disorders. The 6-minute walk test assesses the physical capacity of the patient. It determines the walking distance covered by the patient within 6 minutes on flat terrain and a defined route. The patient is instructed before the test by means of a standard information text that he should walk as far as possible in 6 minutes. A rest period of approximately 5 minutes should be observed before the walk test, during which neither walking nor running should be performed. Changes in pace and pauses are allowed during the walk test, with the patient determining his own speed;
- 1-minute sit-to-stand test (STS60): an assessment of functional strength of the lower extremities. The test assesses how many times in 1 minute the patient is able to stand up and sit down in a height-standardized chair.

Assessment of quality of life through:

Direct survey on the impact of chronic dialysis treatment on motor activity and quality of life using an adapted version of the standardized quality of life questionnaire for patients with kidney disease (KDQOL-SF). Direct survey to identify the main reasons for the deterioration of motor activity in patients with ESKD.;

An innovative specialized questionnaire aimed at identifying the main reasons for the deterioration of motor activity in patients with ESKD and stratifying risk factors.

The experimental group's protocol included an aerobic program of motor activity using a bicycle ergometer - cycling.

The working (experimental) group performs intradialysis exercises consisting of “cycling” at the beginning of the dialysis procedure with low load intensity. The device used for the needs of this study is a specialized bike and is a product of the Danish company LEMCO MOBILITY, which creates precisely designed, highly effective simulators for hospital beds for dialysis patients, with physical disabilities or with neurological diseases. The device offers valuable solutions for individuals at risk of losing mobility. The bike facilitates the implementation of adapted physical exercises, allowing for the improvement of the quality of life of patients. The non-pharmacological intervention

is safe and easy to implement, and the integration of exercises into dialysis regimens shows significant improvements in treatment outcomes.

The device is of good quality, durable, easy to service, and allows for quick and easy adjustments. According to health experts, exercising in the hospital bed during dialysis not only optimizes treatment, but also improves the overall health of patients.

The bike is specialized for use by people in a supine position, loading the lower limbs. The intradialysis exercises applied cover the beginning of the dialysis procedure and are characterized by low intensity of loading.

Fig. 1. Lemko Mobility for intradialysis exercises.

According to the technical specifications, the exercise bike weighs 9.3 kg, has a 1-year warranty, is powered by 1xAA battery 3.6 V, is designed for users weighing up to 120 kg. and is a certified sports device. The display shows the duration of the workout, the distance covered and the recorded speed. For maximum convenient storage, there is an optional wall hanger. Due to its low weight, the bike is easy to move and can be easily installed at the end of the hospital bed. The design of the device is tailored specifically to the needs and limitations of dialysis patients, encouraging an active lifestyle without compromising the effectiveness of the treatment.

The simulators developed by the company include proprietary technology – BEAT – Body Energy Accumulating Technology. This innovation enables people with physical disabilities to perform healthy exercises using the power of their own muscles.

Regular exercise affects the many side effects associated with lack of movement: it reduces cramps during movement, maintains good blood circulation, increases the patient's energy level

between dialysis sessions, and significantly reduces depressive episodes and cognitive impairments observed in some patients.

The control group of patients were examined in terms of biochemical parameters, questionnaires and survey methods. They did not perform intradialysis exercises, which gives grounds to compare them with the patients from the experimental group.

Statistical methods

The statistical methods used are tailored to the specifics of the tasks set, the type of variables studied, and the scales for their measurement.

The following methods were applied in the statistical processing of the data:

-Descriptive analysis:

Analysis of variance – to summarize the quantitative data, arithmetic mean ± standard deviation (mean±SD) was used in the case of normal distribution; median and interquartile range in the case of deviation from the normal distribution;

Alternative analysis – to summarize qualitatively measurable data such as those that are part of the studied demographic and clinical characteristics, an estimate of the relative share in (%) was used;

The normality of the data distribution was checked graphically and quantitatively. For the graphical assessment, histograms with normal distribution curves and quantile graphs (Q-Q plots) were created. For the quantitative assessment, the Kolmogorov-Smirnov test was applied.

To test hypotheses, the following were applied:

- Parametric methods – for normally distributed quantitative variables:

1. Student's t-test when testing hypotheses for the presence of a significant difference between two independent samples (e.g. for comparisons by gender);
2. t-test for dependent (related) samples when comparing the mean values of quantitative indicators before and after the intervention;
3. Analysis of variance (one-way Anova) when testing hypotheses for the presence of a statistically significant difference between the mean values of more than two quantitative normally distributed variables;
4. Pearson correlation analysis to assess the presence of a linear relationship between quantitative variables with a normal distribution.
5. Nonparametric methods – for testing hypotheses for variables deviating from the normal distribution and qualitative variables:

- $\chi 2$ – Pearson's test for multiple tables, and Fisher's test for comparison of proportions;
- Mann-Whitney U test for two independent samples;
- Spearman's test, when searching for correlation between quantitative variables that deviate from a normal distribution;
- Kruskal-Wallis test when comparing more than two independent samples.

The significance level of the null hypothesis was set at $\alpha = 0.05$.

All statistical tests are two-sided.

Tabular and graphical methods for visualizing the results obtained:

The results are presented in a summarized form in tables and are illustrated with appropriate graphs: box plot, bar graphs, etc.

Data processing and analysis were performed with the statistical package IBM SPSS ver. 21, and graphs were constructed in Microsoft Excel for Windows.

V. RESULTS AND DISCUSSION

Task 1.

Study of the motor activity of two groups of patients with CKD on dialysis treatment by:

Duke Activity Status Index (DASI): a patient-reported assessment of functional capacity, maximal oxygen uptake (VO2 max) and maximal metabolic equivalents of tasks (METs). Maximal oxygen uptake (VO2 max) is a proven predictor of mortality in hemodialysis patients. This method was applied to patients in both groups using a specific calculator, comparing their functional capacity. Positive responses were summed to obtain a total score that ranged from 0-58.2. Higher scores indicate higher functional capacity.

Execution of the first task aims to assess functional capacity at the beginning and end of the study, as well as the influence of motor activity on it. Functional capacity was assessed subjectively by the study participants using the DASI tool. It provides information on predicted and actual VO2 max and METs.

Table 3. Comparative analysis between the two groups of patients (experimental and control) at the beginning and at the 6th month of the study

Indicator	Experimental group			Control group		
	Start	End	p-value	Start	End	p-value
DASI	25.1 (12.2)	30.7 (11.5)	<0.001	16.7 (9.3)	17.2 (10.2)	,057
Predicted VO2	19.5 (6.0)	21.2 (6.3)	<0.001	17.8 (1.1)	17.8 (1.1)	,480
Real VO2	19.5 (6.0)	22.5 (6.3)	<0.001	18.6 (1.1)	18.6 (1.1)	1
Predicted Mets	5.9 (1.6)	6.5 (1.5)	<0.001	5.5 (0.3)	5.6 (0.3)	,168
Real METS	5.9 (1.6)	7.6 (1.8)	<0.001	5.5 (0.3)	5.5 (0.3)	,797

Table 4. Results of studies in both groups of patients (experimental and control)

Indicator	Groups	Number	Medium	SD	P
DASI	**Control**	39	15.4	8.48	<0.001
	Experimental	42	25.5	11.60	
Expected VO2	**Control**	39	16.6	6.84	0.028
	Experimental	42	19.8	5.73	
Actual VO2max	**Control**	39	18.1	6.46	0.191
	Experimental	42	19.9	5.71	
Expected METs	**Control**	39	5.2	1.72	0.077
	Experimental	42	5.8	1.49	
Real METs	**Control**	39	5.2	1.73	0.049

	Experimental	42	5.9	1.51	

The results of the analysis show that patients from the experimental group achieved significance in all indicators, while the control group did not. The capacity of physical activity in patients on chronic dialysis G5 is increased by conducting intradialysis exercises.

In the comparative analysis by gender (men and women), statistically significant differences between the experimental and control groups were found for the DASI indicator. For the other indicators, due to the reduction in the number of participants in the groups, no statistically significant differences were achieved.

Table 5. Results of studies in men for both groups of patients

Groups		Number	Mean	SD	p value
DASI	Control	23	16.2	9.05	0.000
	Experimental	24	28.8	12.74	0.000
Expected VO2	Control	23	17.1	7.56	0.087
	Experimental	24	20.7	6.73	0.088
Actual VO2max	Control room	23	17.9	5.84	0.104
	Experimental	24	20.9	6.62	0.103
Expected METs	Control	23	5.6	1.93	0.214
	Experimental	24	6.3	1.63	0.216
Real METs	Control	23	5.6	1.94	0.185
	Experimental	24	6.3	1.67	0.187

Table 6. Results of studies in women for both groups of patients

Groups	Number	Average	SD	p-value	
DASI	Control room	16	14.4	7.74	0.019
	Experimental	18	21.2	8.33	0.019
Expected VO2	Control room	16	15.9	5.83	0.146
	Experimental	18	18.5	3.85	0.158
Actual VO2max	Control room	16	18.4	7.45	0.960
	Experimental	18	18.5	3.95	0.961
Expected METs	Control	16	4.6	1.20	0.104
	Experimental	18	5.3	1.09	0.106
Real METs	Control	16	4.7	1.21	0.063
	Experimental	18	5.5	1.12	0.064

The results obtained in the experimental group revealed a statistically significant difference between predicted VO2 for both men and women, while no such correlation was found in the control group. These tests prove that intradialysis exercises improve the physical endurance and functional status of the patient.

A group of HD patients underwent 6-month cyclical training during dialysis sessions. The following data were analyzed: 6MWT and STS60.

The evaluation of both tests was done between the two groups and within each group before and after the start of the study.

Table 7. Results of the two tests in the control group at the beginning and at the 6th month of the study

		Average	Number	Standard deviation	P-value
Couple 1	MWT6_start	228.08	39	71.3	0.156
	MWT6_6month	253.97	39	84.9	0.065
Couple 2	STRS60_strat	18.05	39	7.9	0.112
	STS60_6m	22.69	39	11.2	0.089

Analysis of the two tests conducted in the control group:

In the tests conducted: 6MWT and STS60 of the control group, no statistical significance was found between the initial period and after 6 months.

Table 8. Results of the two tests in the experimental group at the beginning and at the 6th month of the study

		Average	Number	Standard deviation	p-value
Couple 1	MWT6_start	236.90	42	34.1	0.001
	MWT6_6month	253.10	42	40.4	0.001
Couple 2	STRS60_strat	18.57	42	15.38	0.001
	STS60_6m	21.24	42	18.63	0.001

Analysis of the two tests conducted in the experimental group

The statistical analysis conducted in the experimental group demonstrated a correlation in the initial period and after 6 months in our study regarding 6MWT and STS60 (p value = 0.001).

Table 9. Summary comparative analysis between the two groups of patients in the tests performed.

Group		Number	Mean	Standard deviation	p value
MWT6_start	control	39	228.1	71.32	0.156
	experimental	42	236.9	54.10	0.001
MWT6_6month	control	39	254.0	84.92	0.065
	experimental	42	253.1	60.35	0.001
STRS60_strat	control	39	18.1	8.00	0.112
	experimental	42	18.6	10.32	0.001
STS60_6m	control	39	22.69	11.19	0.089
	experimental	42	21.24	13.63	0.001

In the experimental group, participants achieved better results at the 6-month follow-up for both the 6MWT and the STS60 test. The differences before and after assessed by a paired samples t-test were statistically significant.

A difference was found in the experimental group between the beginning of the experiment and 6 months after intradialysis exercises. In the control group, no such difference was reported. The results coincide with studies conducted in this area by other authors [Broers et. al. 2017, Brito, et. al. 2022].

Our study demonstrates the role of the above-mentioned tests in improving the functional status of the lower extremities. The data are also confirmed by other studies [Assawasaksakul et.al.2021, Bernier et., al. 2022, Bennet et., al., 2022], which showed that in 6MWT the increase in walking speed was 4% (3.56 km/h before and 3.73 km/h after training with cycling exercises ($p < 0.01$). These studies demonstrated that at an angular velocity (AV) of 60°/s, the peak extension torque in the knee joint increased by 7% and at an AV of 300°/s by 4% ($p = 0.04$). The peak flexion torque at an AV of 180°/s increased by 13% ($p = 0.0005$). The program did not affect nutritional or inflammatory parameters. No complications directly related to the exercises were observed.

Cyclic exercises during dialysis is safe even in older HD patients with multiple comorbidities. This is also confirmed by other studies [Martins et., al., 2021, Bishop et., al., 2023]. This leads to a significant increase in the patient's overall walking ability and an increase in lower limb muscle strength. The values increase up to 6 months for both tests, both in the experimental and control groups (the differences are statistically significant). It is observed that in the experimental group the increase is smaller (as an absolute value) compared to the control group.

The results obtained showed that patients performing intradialysis exercises had significantly higher capacity than patients in the control group. When performing the 6MWT and STS60 tests, over 80% of patients in the experimental group reported relatively significant higher results. These results of ours are consistent with other studies in this direction [Painter et., a., 2013, Chiriga et., al., 2017, Manfredini et., al, 2017]. They show the significance of the tests performed for improving the functional activity of the lower extremities in patients with ESRD.

Task 2.

Study of the assessment of the impact of chronic dialysis treatment in the two groups of patients with ESKD on their motor activity and their individual quality of life using an adapted version of a standardized questionnaire for quality of life in patients with kidney disease (KDQOL-SF).

A comparative analysis was conducted in the Nephrology Clinic, dialysis treatment activity of St. Marina University Hospital - Varna to study the factors influencing health-related quality of life (HRQoL) and motor activity in patients on dialysis treatment.

We used a questionnaire for research and assessment KDQoL-SF-36 after modification by Prof. Sv. Staykova. This instrument has a number of advantages – validated in Bulgarian, easy to interpret, possibility to calculate two summarized indicators for physical and mental health, comparison of the obtained data with other populations, etc.

The questionnaire includes 8 scales assessing different aspects of health:

1. physical activity;
2. physical endurance;
3. emotional stability;
4. social activity;
5. mental health;
6. body pain;
7. vitality (energy/fatigue);
8. perception on overall health.

Answers include yes/no/can't decide.

The questionnaire is completed independently, which takes 5-10 minutes. Once completed, the SF-36 questions are scored using developed criteria to calculate the significance of individual responses, using a point system.

In the group in which the intervention was carried out, a significant improvement in the condition of the patients was found for the period before and at the end of the experiment on the following issues:

Self-rated health improved significantly in the experimental group:

- Before the experiment: 31% of participants self-rated their health as good;
- After the experiment: 57% rated their health as better than at the beginning (p= 0.002).

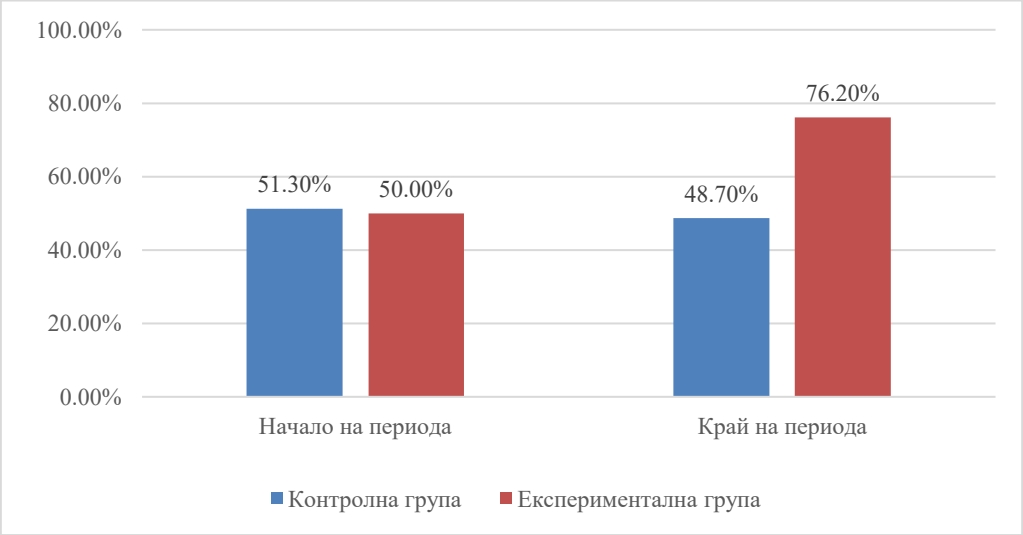
In the control group that did not exercise:

- The proportion of participants who rated their health as good remained stable (28.2% felt good at the beginning of the period and 30.8% at the end of the period (p= 1.0).

Table 10. Impact of the intervention on the self-assessment of health of the study participants. (Answer to the question "How do you assess your health?" was given before the intervention /start of the period/ and a year after the intervention – /end of the period/).

Studied group	My health is better now.		
	Start of the period	End of period	p
Control group	28.20%	30.80%	1.00
Experimental group	31.00%	57.10%	0.002
Total	29.60%	44.40%	0.001

Improvement in the experimental group, but not in the control group, was found in the ability to climb stairs. The proportion of participants who reported climbing stairs without problems increased from 50% to 76.2% at the end of the intervention period (p=0.001).



Start of the period **End of the period**

Control group Experimental group

Fig. 2. Proportion of participants climbing stairs without a problem at the beginning and end of the intervention for experimental and control groups

The proportion of patients in the experimental group experiencing intolerable pain decreased over the follow-up period from 41.4% to 20.7% (p= 0.029). The proportion of patients in the control group with intolerable pain increased over the same period of the experiment.

Table 11. Relative share of participants experiencing unbearable pain before the intervention /start of the period/ and one year after the intervention – (end of the period)

Study group	Experiencing unbearable pain		
	Start of the period	End of period	p
Control group	34.60%	46.20%	0.41
Experimental group	41.40%	20.70%	0.029
Total	38.20%	32.70%	0.176

In the experimental group, the proportion of people who limited their professional work and other activities decreased statistically significantly from 78.6% to 71.4% (p= 0.046), while in the control group, the proportion of these people remained the same (p=0.223).

An impressive difference between the control and experimental groups was found when answering the question "Did you feel happy?" In the control group, the proportion of those who answered positively was 1/3, while for those in the experimental group their proportion increased from 54.8% to 76.2% (p= 0.002).

Table 12. Relative share of participants who said they felt happy before the intervention /start of the period/ and a year after the intervention – /end of the period/

Study group	They feel happy.		
	Start of the period	End of period	p
Control group	35.20%	64.10%	0.001
Experimental group	54.80%	76.20%	0.002
Total	45.70%	70.40%	0.001

We found a systematic improvement in clinical symptoms for the experimental group, with the proportion of insensible muscle pain increasing from 19 to 33% (p= 0.02). There was no similar statistically significant difference in the control group.

Table 13. Changes in clinical symptoms before and after the intervention for the experimental and control groups

Indicator	Experimental		p	Control group		p
	Home	End		Home	End	
They don't have muscle pain.	19.00%	33.30%	0.02	17.90%	33.30%	0.05
They do not have pain or heaviness in the chest.	35.70%	73.80%	<0.001	76.90%	59.00%	0.08
They don't have muscle cramps.	11.90%	26.20%	0.03	12.80%	25.60%	0.04
They have no shortness of breath.	50.00%	69.00%	0.005	51.30%	59.00%	0.13
They do not have itchy skin.	19.00%	54.80%	0.001	46.20%	48.70%	0.14
They don't have seizures.	38.00%	52.40%	0.014	25.60%	35.90%	0.05
They don't have nausea.	52.40%	66.70%	0.03	33.30%	41.00%	0.08

The proportion of people who did not experience chest pain or heaviness increased from 35.7 to 73.8% ($p< 0.001$). There was no similar difference in the control group.

The positive result for muscle cramps was similar in the proportion of patients in the experimental group. Their proportion increased from 11.9 to 26.2% ($p= 0.03$).

The condition regarding shortness of breath improved. The proportion of patients without shortness of breath in the experimental group increased from 50 to 69% ($p= 0.005$).

Itching of the skin, an indicator of high nitrogen retention, improved significantly in the experimental group ($p < 0.001$). The proportion of patients without itching increased from 19 to 54.8%. No improvement was reported in the control group.

The condition also improved in terms of seizure symptoms. The proportion of patients without such symptoms increased in the experimental group from 38 to 52.4% ($p= 0.014$).

The status of gastrointestinal symptoms improved, again related to the intervention. The proportion of participants without nausea and vomiting increased from 52.4 to 66.7% ($p= 0.03$). Similar changes were not observed in the control group.

The subjective assessment of the participants in the experimental group about the effect of kidney disease on their daily lives was not as positive at the end of the observation period. The study shows that the participants in the experimental group have adapted to the need to drink less fluid and

the proportion of those who indicate their limited intake as a problem decreased from 83.3% to 60% (p= 0.006).

A positive effect was reported in the experimental group regarding sleep duration. The proportion of participants who reported getting enough sleep increased from 39% to 54% (p= 0.031).

Questions related to limited travel opportunities, limited dietary variety, emotional stress, and sexual life did not show improvement over the observed period in either group.

Due to abnormalities in serum calcium, phosphorus, and iPTH, we further divided the patients into three groups:

- according to serum Ca values (Ca <2.2 mmol/l; Ca 2.2-2.55 mmol/l and Ca >2.55 mmol/l);
- according to serum P concentrations (P <1.2 mmol/l; P 1.2-1.8 mmol/l and P> 1.8 mmol/l)
- according to PTH values (iPTH 150-300pg/ml; iPTH – 300 – 600 pg/ml and iPTH above 600 pg/ml).

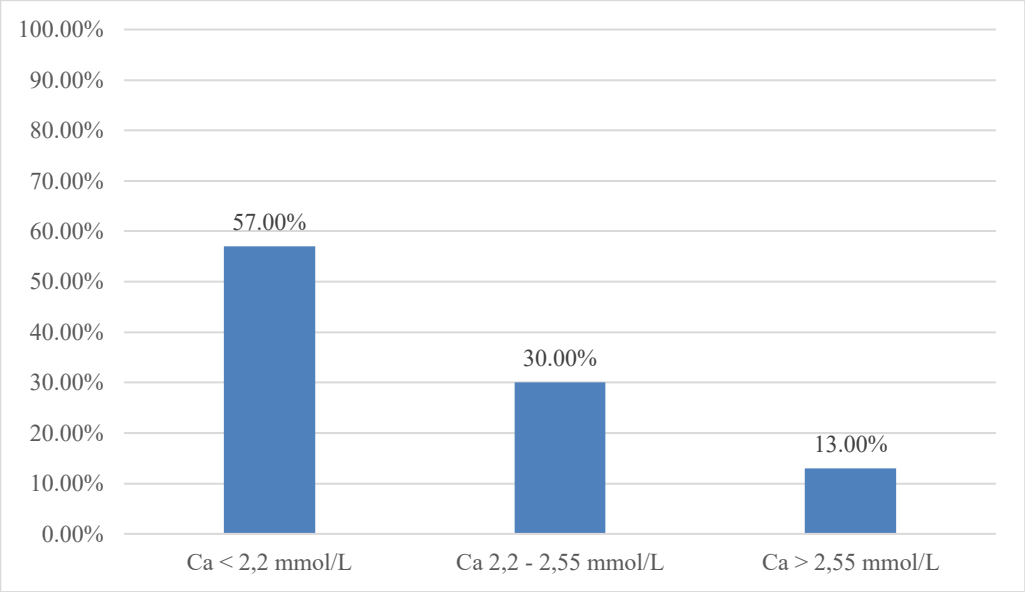


Fig. 3. Distribution of patients according to serum calcium values

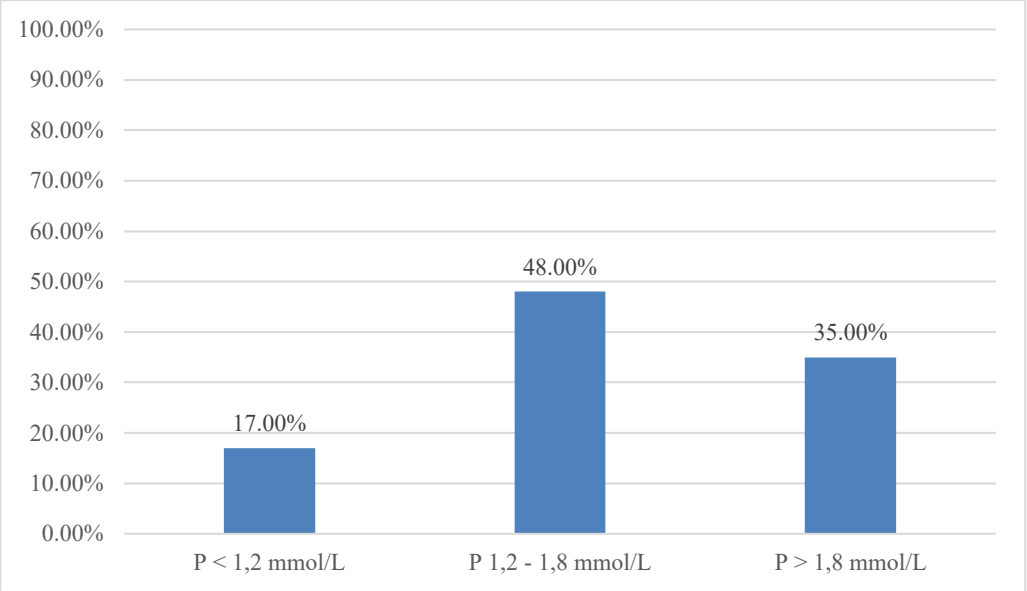


Fig. 4. Distribution of patients according to serum phosphorus values

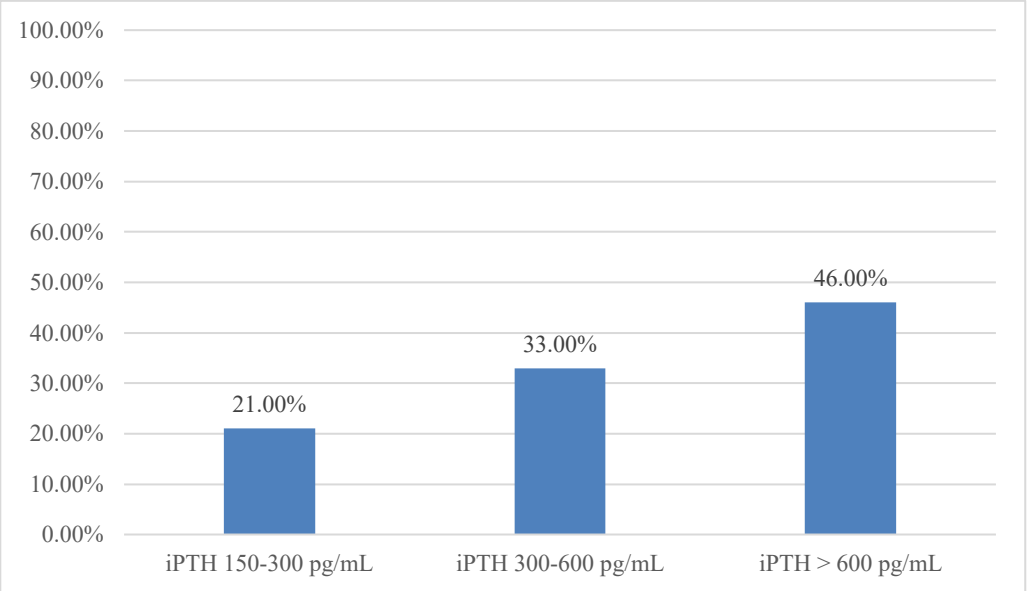
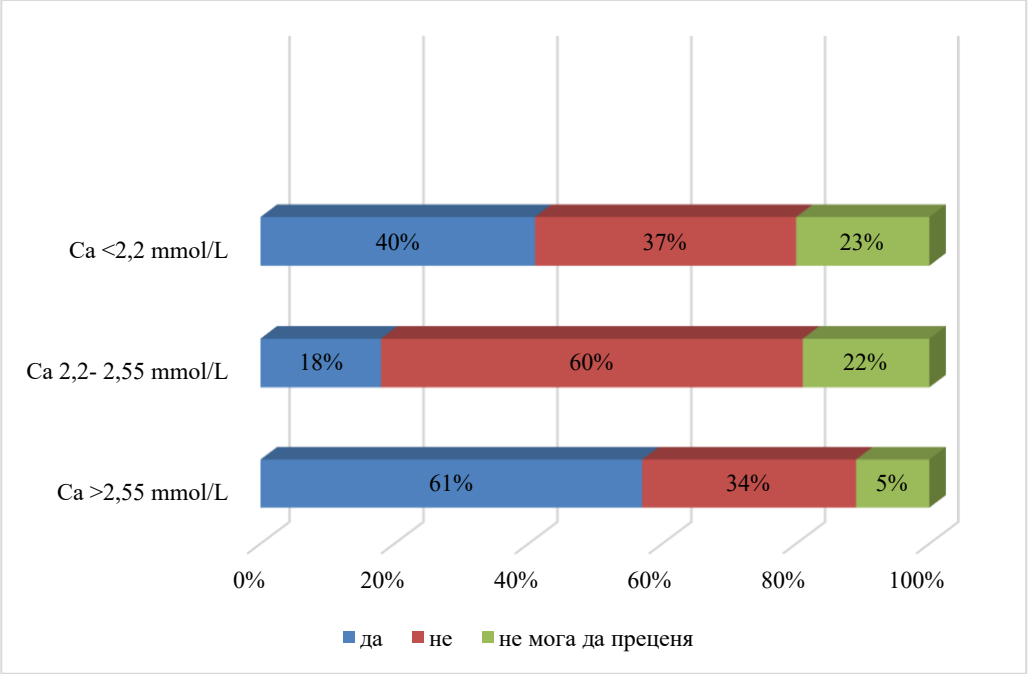


Fig. 5. Distribution of patients according to iPTH values

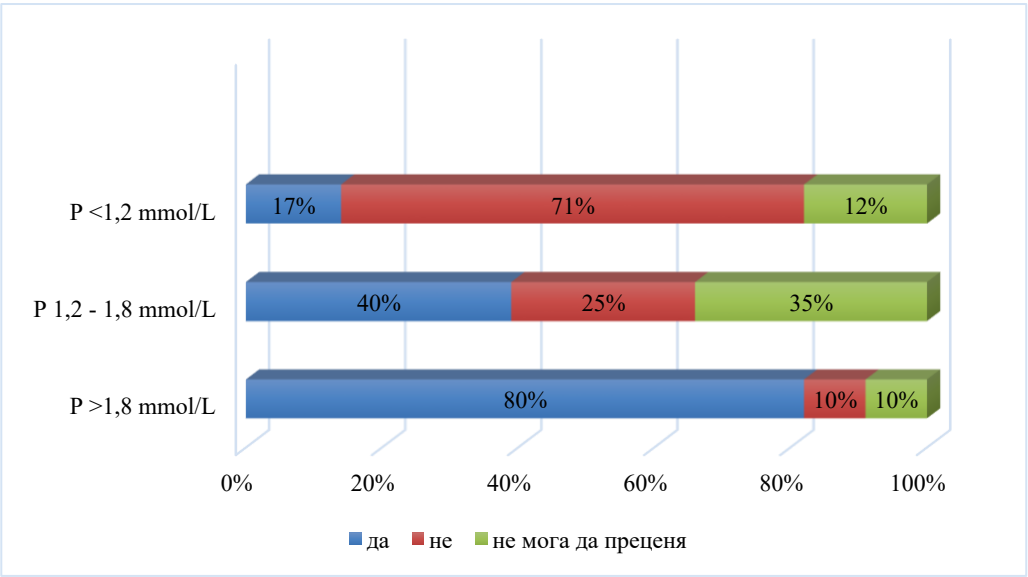
The following figures demonstrate the distributions of the patients' specific answers to the survey questions.



Yes No Not sure

Fig. 6. Assessment of the impact of hemodialysis on physical activity and endurance according to serum calcium values

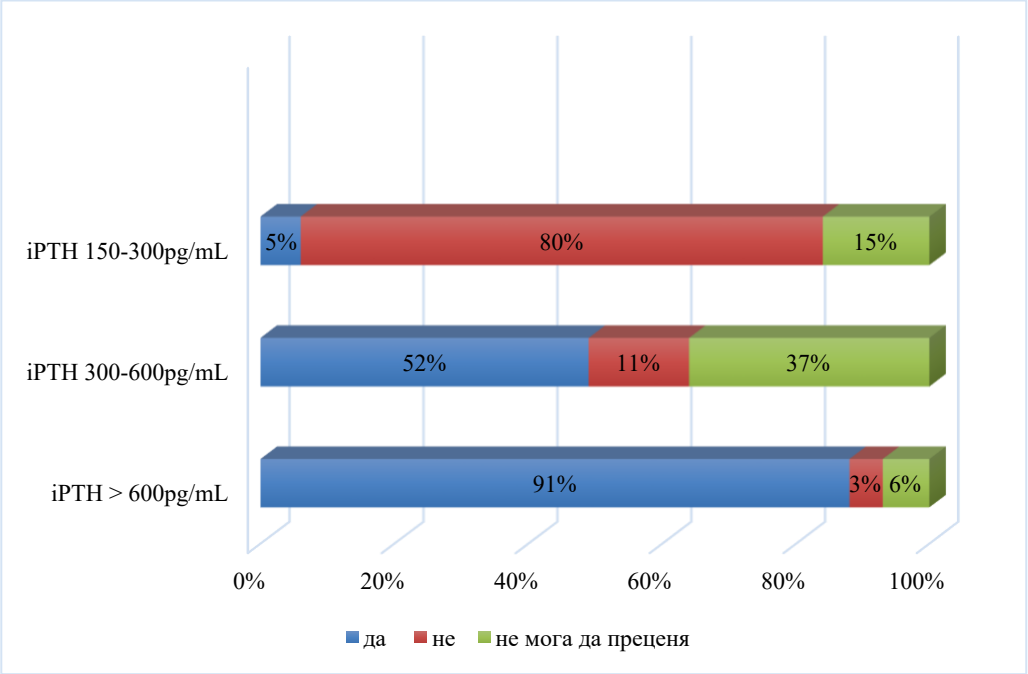
A statistically significant value (p=0.039) was reported in HD patients with serum Ca concentration above 2.55 mmol/l.



Yes No Not sure

Fig. 7. Assessment of the impact of hemodialysis on physical activity and endurance according to serum phosphorus values

The impact is significantly more pronounced in HD patients with serum phosphorus values above 1.8 mmol/l.

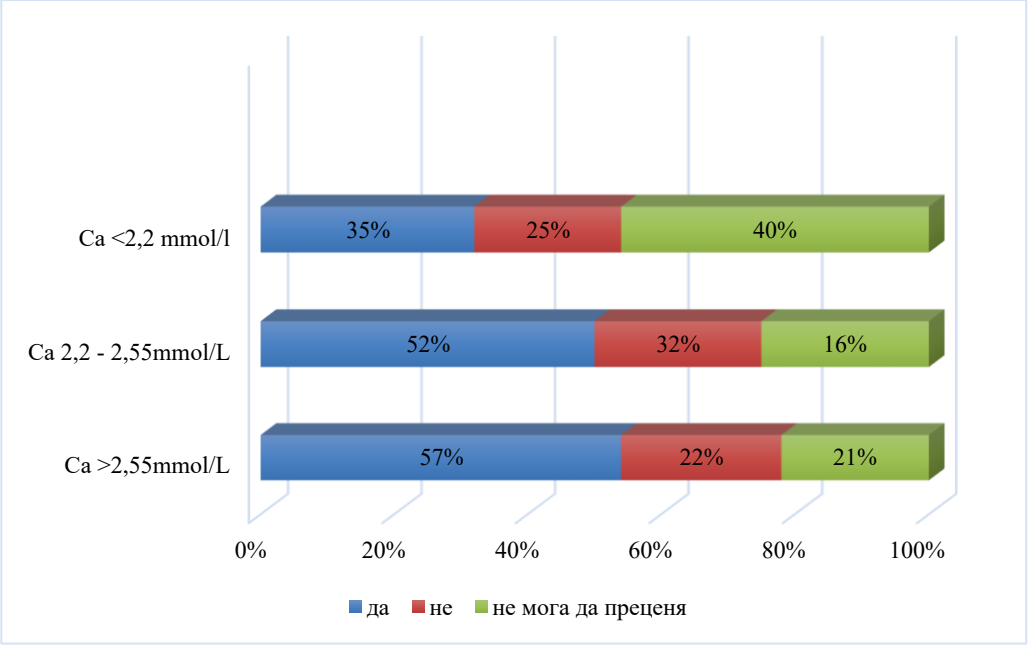


Yes No Not sure

Fig. 8. Assessment of the impact of hemodialysis on physical activity and endurance according to iPTH values

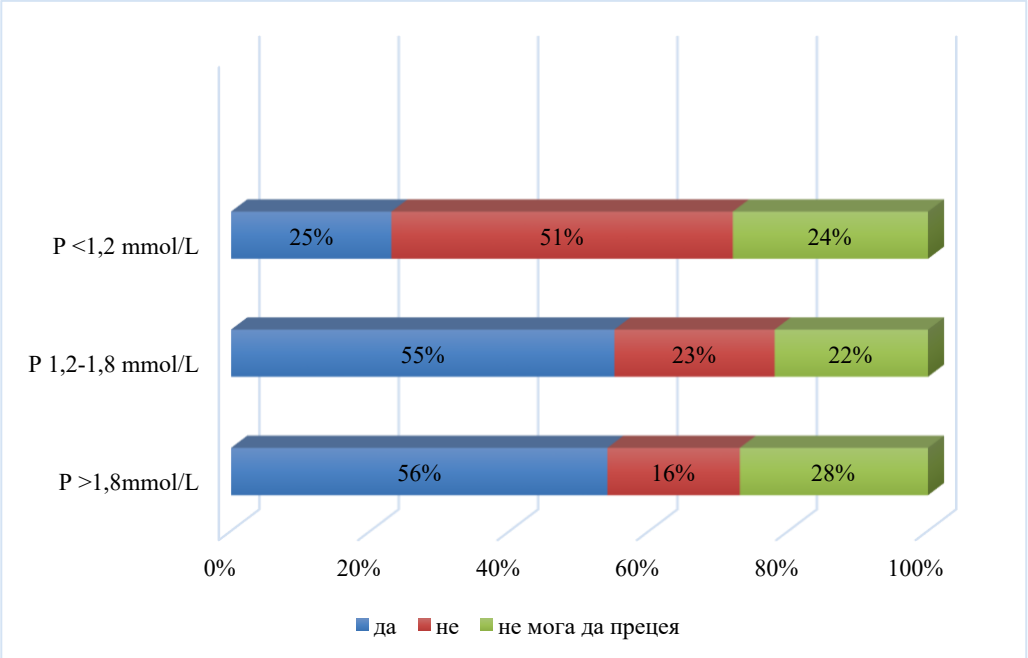
In more than half of patients with PTH values > 600 pg/ml, HD affects physical activity and endurance, which affects their quality of life (p=0.022).

The impact of pain on the work environment and quality of life in dialysis patients was monitored according to Ca, P and iPTH values.



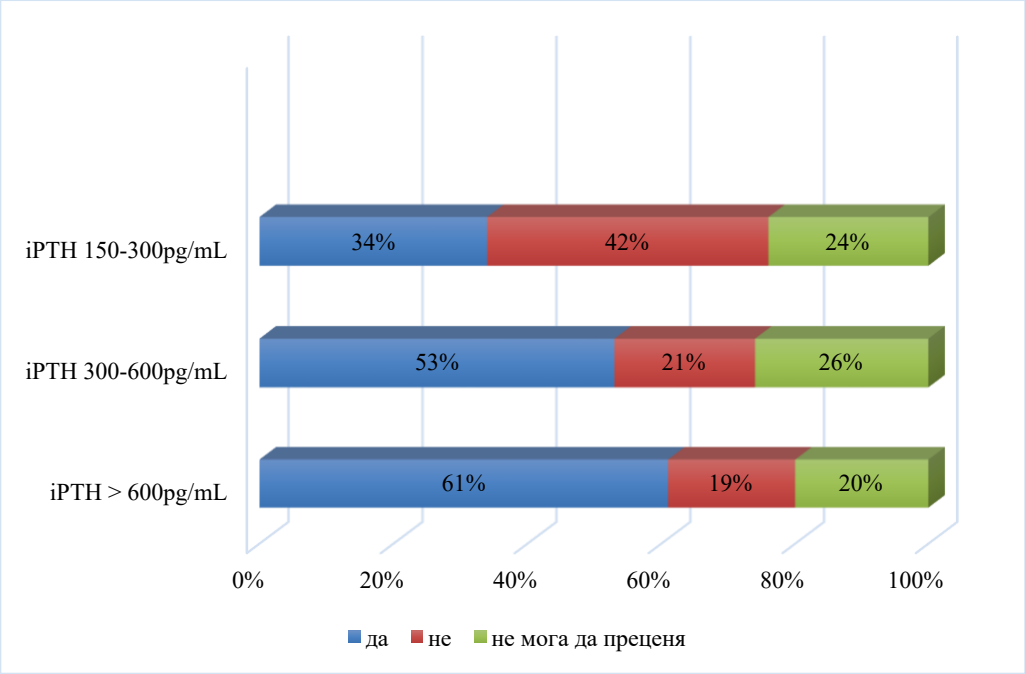
Yes No Not sure

Fig. 9. Assessment of the impact of pain on the work environment and quality of life according to serum calcium values



Yes No Not sure

Fig. 10. Assessment of the impact of pain on the work environment and quality of life according to serum phosphorus values

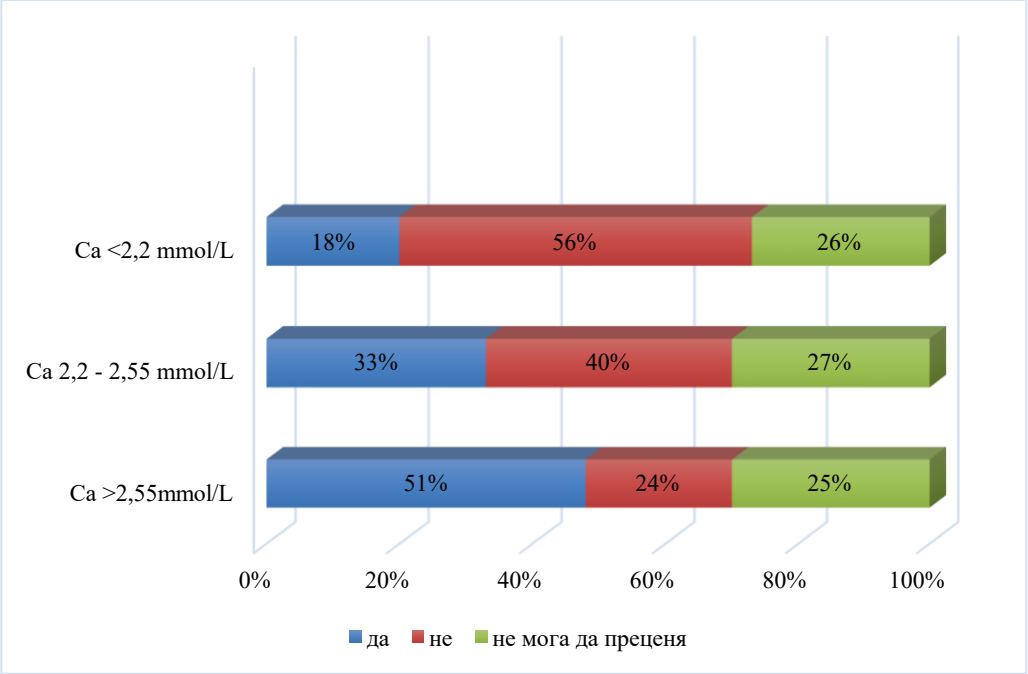


Yes No Not sure

Fig. 11. Assessment of the impact of pain on the work environment and quality of life according to iPTH values.

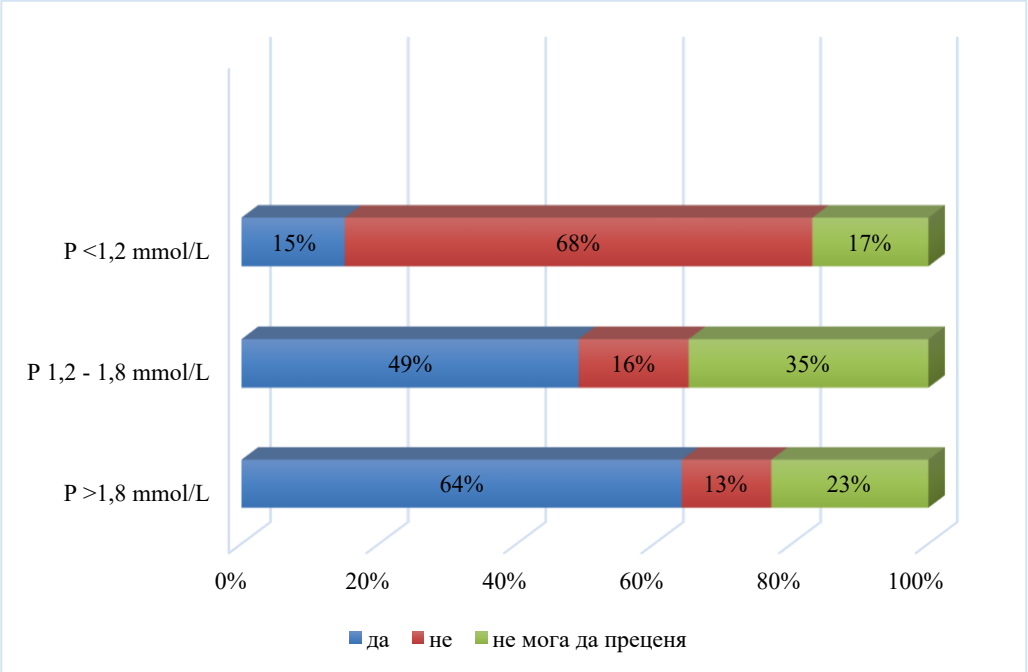
It was found that in more than 50% of patients with hypercalcemia, hyperphosphatemia and high iPTH values, the pain syndrome affected the work environment. Statistical significance was found in terms of their quality of life (p=0.025).

The results of the comparative analysis of patients' responses regarding their assessment of the impact of HD on their perception of general health according to Ca, P and iPTH values are illustrated in figures: 12, 13, 14.



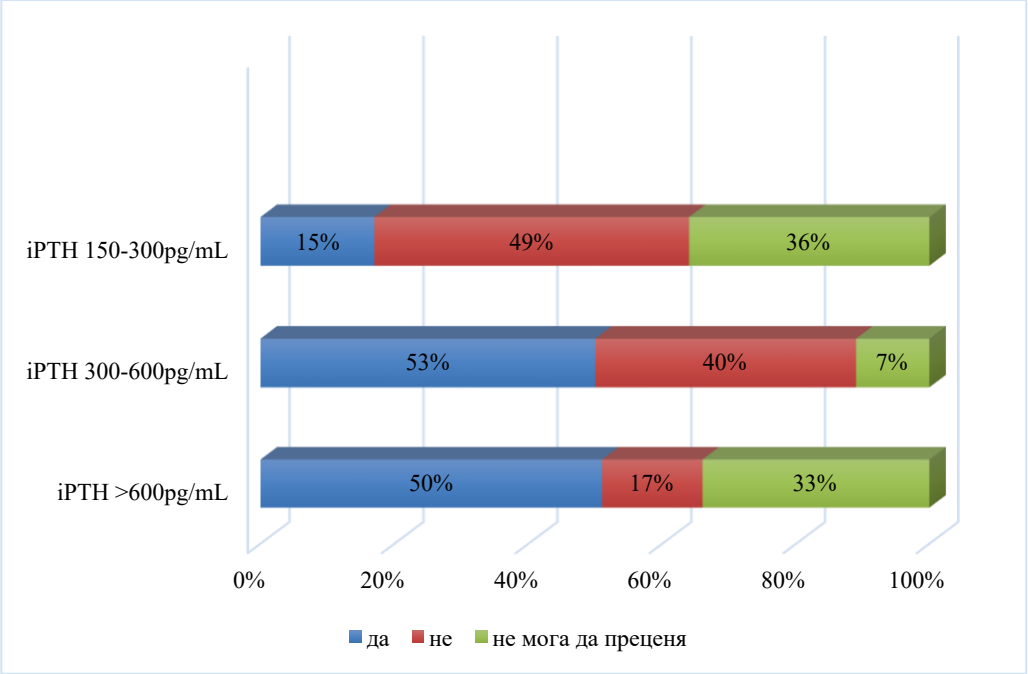
Yes No Not sure

Fig. 12. Assessment of the impact of HD on the perception of general health according to serum calcium values



Yes No Not sure

Fig. 13. Assessment of the impact of HD on the perception of general health according to serum phosphorus values



Yes No Not sure

Fig. 14. Assessment of the impact of HD on the perception of general health according to iPTH values.

A significant proportion of patients from the groups with high iPTH, Ca and P values shared that HD and its complications have an impact on their perception of general health (p=0.003).

The highest HRQoL was reported in patients with PTH concentration 150 to 300pg/ml, Ca 2.10-2.55 mmol/l and serum P concentration <1.2mmol/l.

HD most often has a moderate impact on patients' physical activity, as well as their perception of general health.

When studying the quality of life in chronic diseases, the subjective feeling of one's own condition is of primary importance, regardless of the objective results and the opinion of medical specialists.

The concept of quality of life expands the traditional notion of health, and this makes it possible for the specific physical and mental health needs of these patients to be met by services in the health and social care systems.

Quality of life reflects the patient's subjective opinion about the impact of their illness on their daily life.

Bone mineral disorders affect the well-being and quality of life of chronic dialysis patients. Common symptoms include joint pain and stiffness, muscle pain, dry skin, and pruritus.

A recent study demonstrated reduced physical function and increased pain in dialysis patients with elevated PTH levels. A separate and important contributor to the overall reduced quality of life in dialysis patients is the high incidence of clinical events with a significant impact on patient well-being. SHP-related events, including fractures and CV events, have short- and long-term negative consequences for quality of life. Health-related quality of life (HRQoL) in this model is measured by utility values that evaluate human life and yield health outcome QALYs. The utility values used in the analysis model were taken from the published EVOLVE analysis. In this analysis, HRQoL was assessed with the EuroQoL (EQ)-5D instrument, which measures general health and health status across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) using a 3-point scale (no problem, some problem, and extreme problem). The EQ-5D instrument was administered after a study-specified clinical event and at a pre-specified, scheduled trial visit. The analysis set included patients who had a baseline EQ-5D measurement and at least one post-baseline measurement. All events showed results in the expected direction (events associated with reduced HRQoL), with most of the coefficients being large in magnitude and significant, emphasizing the impact of the events on HRQoL. The only exception was the long-term impact of parathyroidectomy, where the coefficient was relatively small and insignificant.

According to latest studies, poor physical activity in patients with CKD is associated with mortality, morbidity, muscle atrophy, impaired quality of life, cardiovascular complications, and depression [B. Afsar et al., 2018]. The effect of implementing various physical exercise programs has been proven to improve the objective condition of patients and increase their quality of life.

Bone mineral disorders are a complication of chronic kidney disease (CKD). The prognosis is poor, increasing the risk of complications and fatal outcome in these patients. These disorders are considered an important factor affecting HRQoL. Based on studies of patients undergoing hemodialysis, it has been shown that serum phosphorus (P) and intact parathyroid hormone (iPTH) values that are too high or too low are associated with poor HRQoL. However, previous studies conducted on this topic have mainly focused on the effects of individual biochemical markers of BMD-CKD on HRQoL, but these studies have not considered the combination of serum phosphorus, serum calcium and iPTH values in assessing their correlation with HRQoL. There is a close relationship and interaction among these three factors.

We conducted an analysis to investigate factors affecting health-related quality of life (HRQoL) in patients with BMD-CKD on hemodialysis and their motor activity. This analysis aimed to observe the relationships between different combinations of serum Ca, P, and iPTH levels and HRQoL in patients on extracorporeal therapy and to investigate the associated factors affecting HRQoL in these patients.

We found that BMD significantly affect HRQoL. Correction of abnormal values of serum phosphorus, serum calcium and iPTH is of great importance for improving the quality of life in BMD-CKD patients on dialysis treatment, as well as their physical activity.

The widespread use of this questionnaire is related not only to its universal applicability to various diseases, but also to the general understanding of individual aspects of health as a whole - physical, mental, and social.

Hyperphosphatemia has been shown to be strongly associated with mortality in dialysis patients. A number of studies have been conducted in this direction. Data were collected from 7970 patients undergoing HD treatment at Fresenius hemodialysis centers in Europe. The results showed correlations among iPTH, serum Ca, and serum P levels with the relative risk of mortality, revealing that baseline serum phosphorus levels increased the risk of mortality, except for the group with levels from 1.13 to 1.78 mmol/L. The correlation between serum phosphorus levels and mortality risk was analyzed over time. The risk of mortality showed a significant increase when the serum P level was >2.25 mmol/L. Fouque et al. investigated the correlations among iPTH, serum Ca and P levels with the relative risk of mortality among 8377 HD patients, and a significantly increased risk of mortality was observed among patients with serum $p < 0.71$ mmol/L or $p > 1.98$ mmol/L. Based on the pathophysiology, it has been shown that the increase in serum phosphorus levels in HD patients within a certain range is a compensatory mechanism of the disease.

Task 3.

Creation of an innovative specialized questionnaire to identify the main causes of deterioration in motor activity of patients with ESKD and stratification of risk factors.

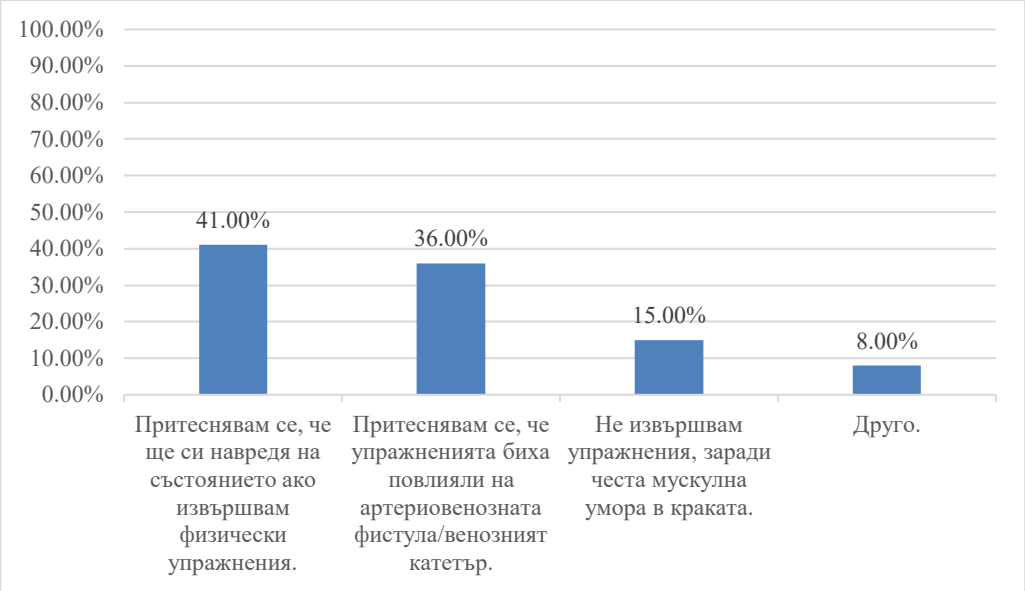
In a nephrology clinic, dialysis treatment activity at the University Hospital "St. Marina" Varna, direct surveys were conducted among both groups of patients, using the innovative questionnaire created, in order to identify the main reasons for the deterioration of motor activity of patients with ESKD and stratification of risk factors.

Our study used recent medical literature regarding the attitude of hemodialysis patients towards physical activity in developing a specialized questionnaire using a four-point Likert scale.

The questionnaire was approved by the Research Ethics Committee of the Medical University of Varna for use in the study. This questionnaire assesses the importance of 33 statements related to potential motivating and demotivating factors for increasing physical activity and exercises. The questionnaire was completed by patients undergoing routine hemodialysis at the University Hospital "St. Marina". The questionnaire was distributed during routine dialysis sessions to all patients, after being familiarized with the study and giving consent to participate in it.

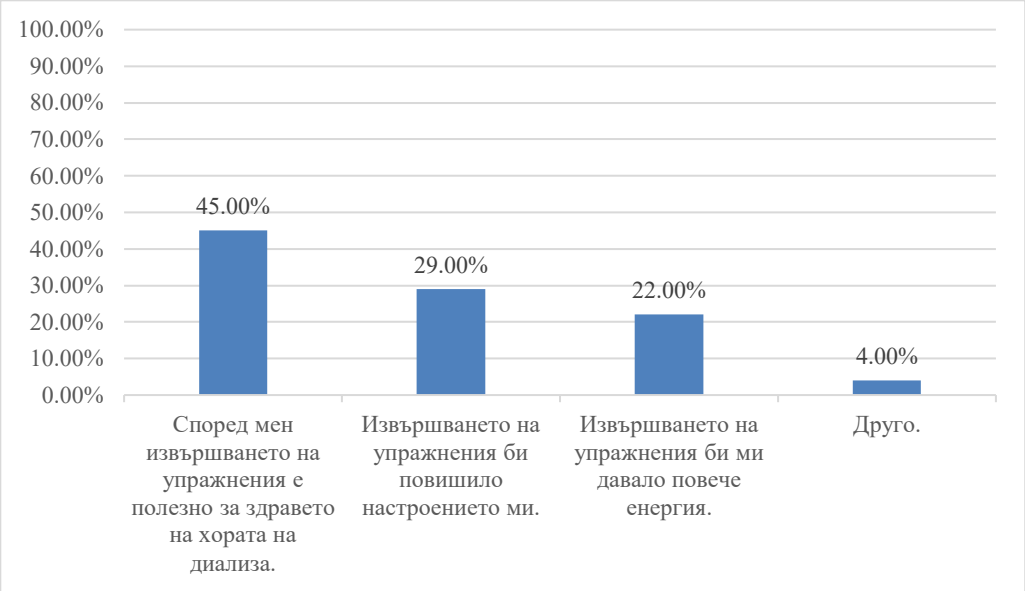
Physical exercise therapy during dialysis is currently recommended by some authors because it is easy for patients to follow and results in high participation rates. In multiple studies, exercise for patients with kidney disease or those requiring dialysis has been shown to improve exercise tolerance without negatively affecting their kidney function, thereby increasing the effectiveness of dialysis.

From the analyzed data, we find that in the control group, refusal and anxiety about performing physical exercises prevail, while in our experimental group of patients (performing intradialysis physical exercises) a positive attitude towards their general and physical health, namely, performing physical exercises, dominates.



I am concerned that I will harm myself if doing physical exercises	I am concerned that exercises would affect the arterial-venous fistula/venous catheter	I am not doing exercises because of the frequent muscular fatigue in the legs	Other

Fig. 15. Summarized results of the control group of patients from the questionnaire Appendix A.



I think doing physical exercises is useful for human health in dyalisis people	Doing physical exercises would increase my mood	Doing physical exercises would give me more energy	Other

Fig. 16. Summary results of the experimental group of patients from a questionnaire. Appendix A.

The questionnaire is innovative and demonstrates the attitude of both groups towards their perception of performing physical exercises. A positive attitude is observed in the experimental group when performing these exercises.

A large proportion of patients diagnosed with end-stage kidney disease require renal replacement therapy – maintenance hemodialysis. Although hemodialysis treatment prolongs the life of patients with CKD, it does not in itself guarantee preservation of quality of life (QOL). Patients undergoing hemodialysis usually suffer from a significant deterioration in QOL compared to their healthy peers or those with a successful kidney transplant.

Patients affected by end-stage kidney disease show much lower physical activity and motor capacity compared to healthy people, and lack of activity is associated with multiple additional disabilities and higher mortality.

Muscle strength and aerobic capacity are extremely limited in hemodialysis (HD) patients. Uremic intoxication, anemia, mineral and metabolic abnormalities, and cardiovascular comorbidities may explain the low physical performance in patients with CKD.

Furthermore, a sedentary lifestyle is favored by the lack of specific advice on implementing physical exercise in healthcare settings.

Planned physical exercise, including aerobic and resistance training, is well known in the scientific literature as a therapeutic intervention that has been shown to alleviate some of the complaints accompanying their treatment (e.g., easy fatigue), improve physical fitness and health, reduce mental stress, and improve quality of life (QoL).

The benefits of increasing physical activity in patients with end-stage kidney disease undergoing hemodialysis are well established in the global scientific community. Physical exercise is recommended in a number of current manuals and guidelines, but patient understanding and perceptions are essential for the implementation of these recommendations.

Intradialysis exercises usually combine aerobic (for endurance) and resistance training and are performed under the supervision of physical medicine and rehabilitation physicians or physiotherapists while patients go through their routine hemodialysis session.

Many authors [Kouidi et., al., 2004, Kraus et. al., 2016, Mallamaci et., a., 2020, Martinis et., al. 2020, Moenzadeh et., al., 2022] report that these programs are well tolerated by participants, with no patient safety issues observed.

Although physical exercise in dialysis settings is usually limited to the lower extremities, exercise therapy during dialysis allows patients to safely exercise while receiving treatment 3 times a week.

Our study demonstrates the need for multidisciplinary collaboration to influence patients' understanding of physical activity through better awareness. It confirms the need for consultation with physical medicine and rehabilitation specialists regarding which exercises are most beneficial and how to perform them most correctly and effectively. By working together, multidisciplinary teams can develop a comprehensive, patient-centered approach to changing misconceptions and overall behavior towards physical exercise, allowing patients to achieve a better quality of life by increasing their physical activity.

Task 4.

Assessing the impact of specialized cardio-cycling exercises on the clinical status of chronic dialysis patients, objectified by examining laboratory indicators of bone-mineral disorders.

In the nephrology clinic, dialysis treatment activity of the University Hospital "St. Marina" - Varna, we assessed the impact of cardio-cycling exercises on the clinical status of hemodialysis patients, objectified by examining laboratory indicators - serum phosphorus, serum calcium, iPTH and CRP.

We studied a total of 69 patients – divided into two groups – control (n=32) and experimental (n=37). Serum phosphorus, calcium and CRP values were examined in both groups at baseline, 3rd and 6th months, and iPTH values at baseline and at the 6th month.

Table 13. Distribution of patients by groups: control and experimental

			Number
Group	0	Control	32
	1	Experimental	37

Table 14. Comparison of P values in the two groups of patients

	Total	Experimental group	Control group	p value
	n = 69	n = 37	n = 32	
Initial measurement	1.78 (0.460)	1.85(0.427)	1.71(0.491)	0.569
Value at the 3th m.	1.61(0.447)	1.54(0.358)	1.69(0.524)	0.161
Value at the 6th m.	1.45(0.343)	1.38(0.225)	1.55(0.425)	0.633

A statistically significant difference was found in both groups regarding P values at baseline, as well as at 3rd and 6th months.

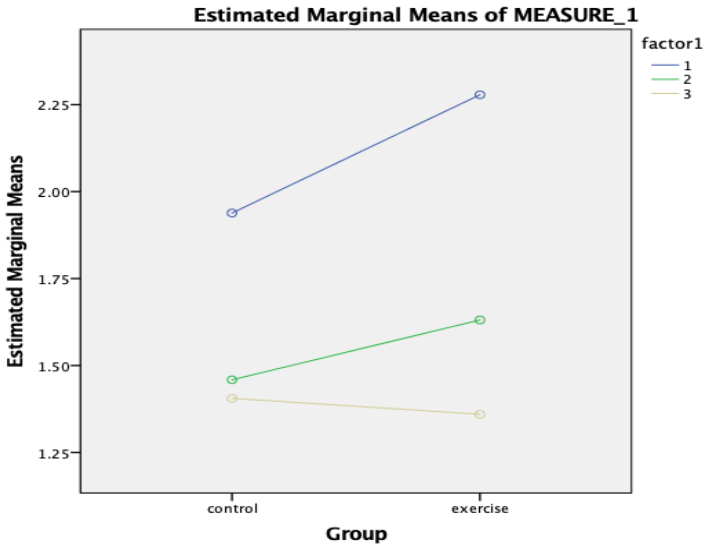


Fig. 17. P values in both groups at the beginning of the study

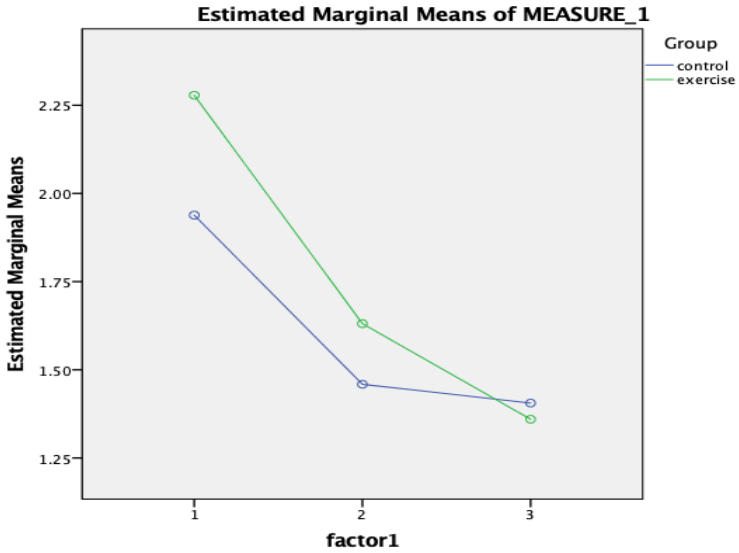


Fig. 18. P values at month 6 of the study

The comparative analysis of CRP values between the two groups did not report a significant difference, but there was statistical significance when compared at month 3.

Table 15. Comparison of CRP values

	Total	Experimental group	Control group	p value
	n = 69	n = 37	n = 32	
Initial measurement mean (SD)	17.4 (26.28)	17.1 (18.26)	17.7 (28.89)	0.001
Value at month 3 mean (SD)	13.6 (26.25)	12.4 (27.27)	15.1 (26.28)	0.001
Value of month 6 mean (SD)	7.3 (9.10)	6.8 (8.59)	7.9 (9.77)	0.001

We performed a comparative analysis regarding iPTH values, both between the two groups of patients and over a period of 6 months; no statistical significance was found in the subjects studied in either group.

Table 16. Comparison of iPTH values

	Total	Experimental group	Control group	p value
	n=69	n=37	n=32	
Initial measurement mean (SD)	347.9 (535.16)	423.4 (625.20)	260.5 (399.52)	0.21
Value at month 6 mean (SD)	340.7 (560.95)	407.1(616.37)	263.9 (487.55)	0.294

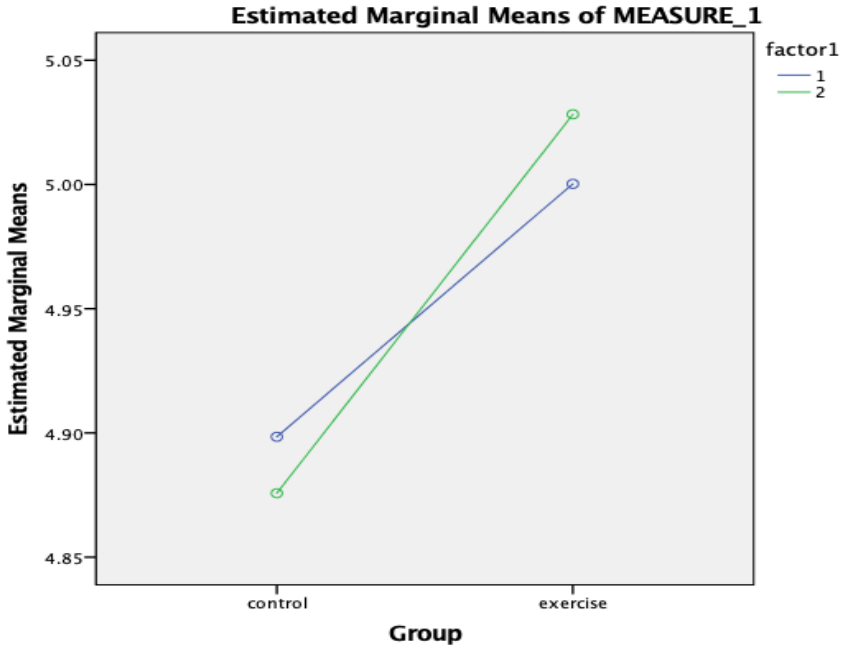


Fig. 19. iPTH values in both groups of patients at the beginning of the study

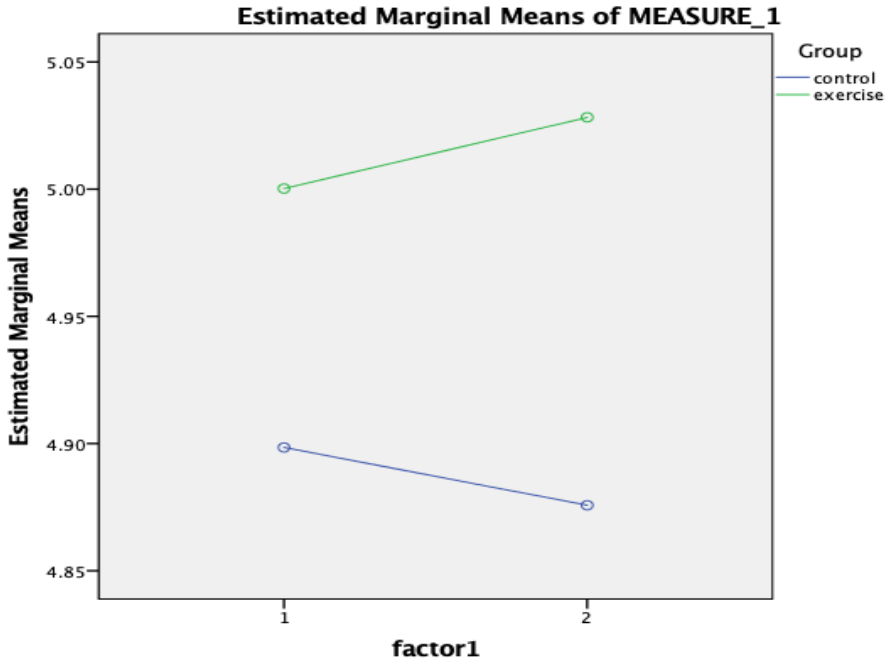


Fig. 20. iPTH values in both groups of patients at month 6 of the study

We compared serum calcium values at baseline, at months 3 and 6 in both groups of patients.

Table 17. Comparison of serum calcium values

	Total	Experimental group	Control group	p value
	n=69	n=37	n=32	
Initial measurement mean (SD)	2.1 (0.104)	2.1(0.100)	2.1 (0.109)	0.916
Value of 3 months mean (SD)	2.2 (0.167)	2.3(0.119)	2.1 (0.149)	0.680
Value of 6 m mean (SD)	2.2 (0.237)	2.4(0.089)	2.0(0.244)	0.633

From the results obtained, we establish significance in our experimental group of patients, and in the control group - no significance is reported. The statistical reliability in the experimental group is proven already in the 3rd month of conducting the cardio-cycling physical exercises.

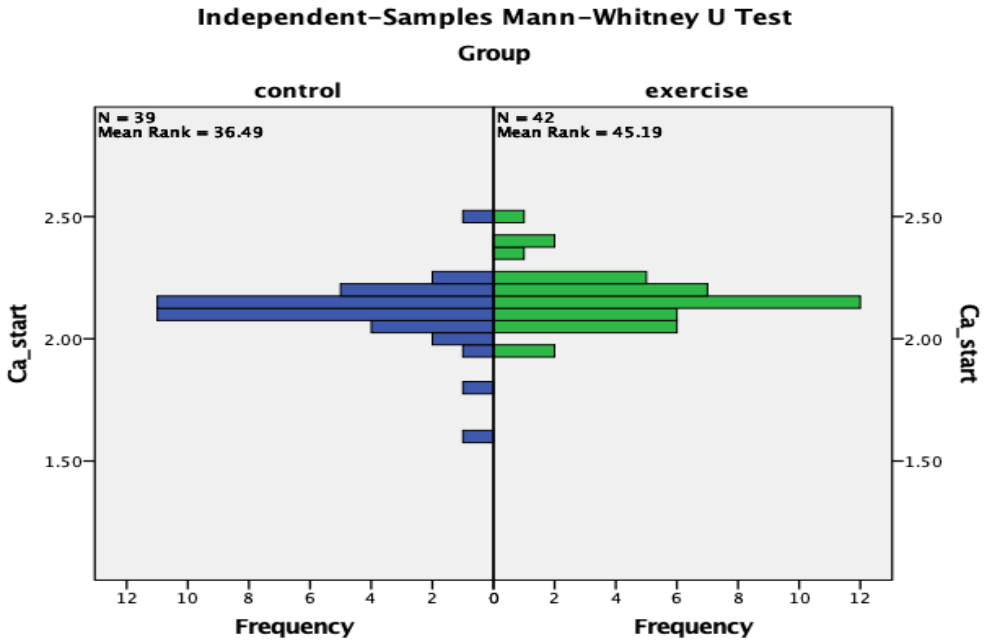


Fig. 21. Analysis of Ca in both groups of patients at the beginning of the study using a statistical method – Mann-Whitney U Test

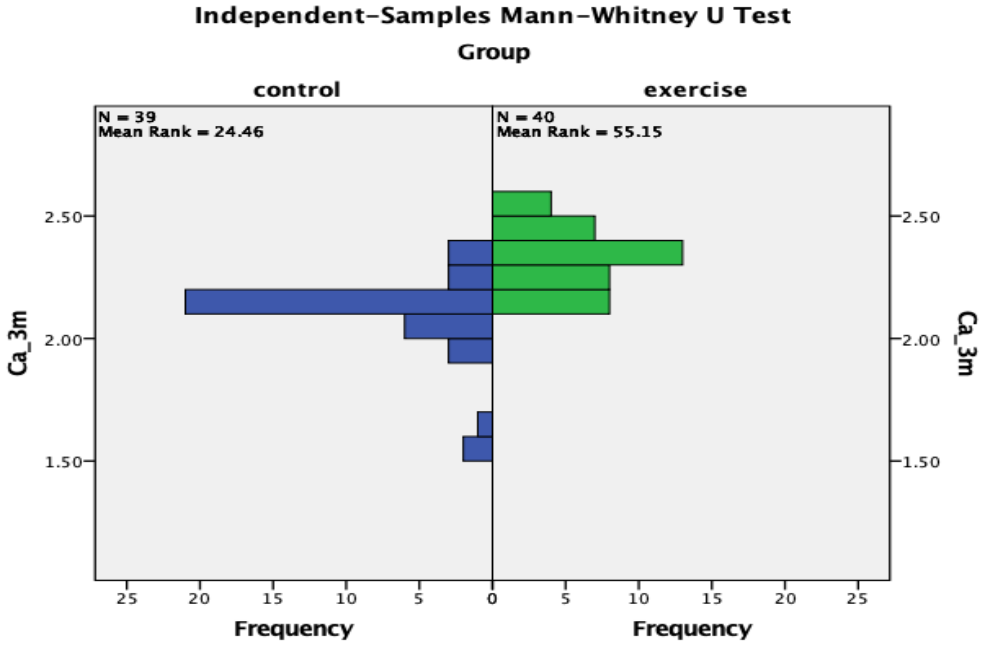


Fig. 22. Analysis of Ca in both groups at the 3rd month of the study using a statistical method – Mann-Whitney U Test

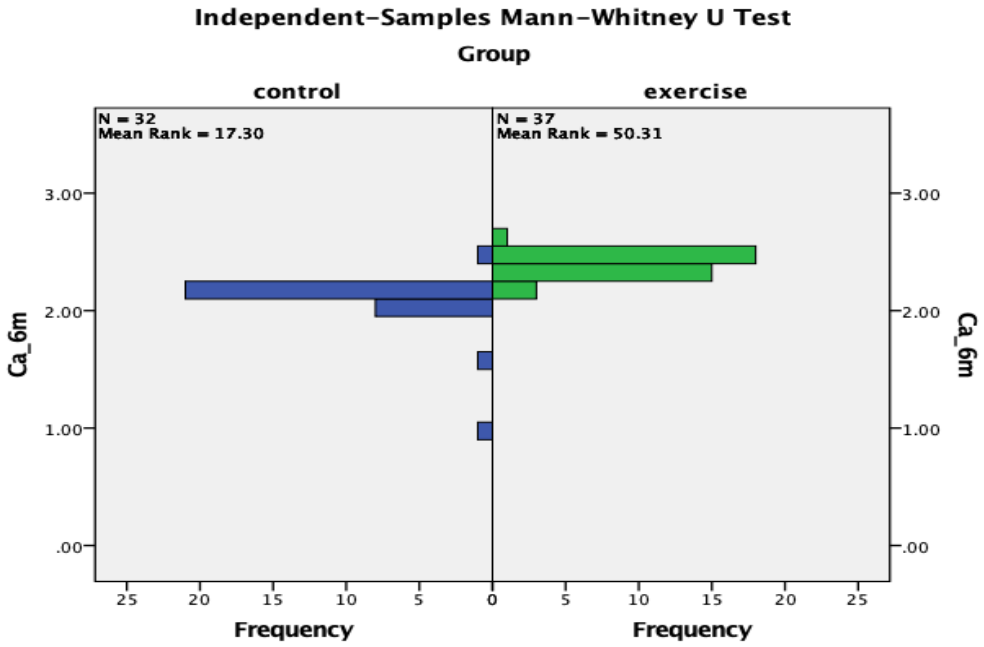


Fig. 23. Analysis of Ca in both groups at the 6th month of the study using a statistical method – Mann-Whitney U Test

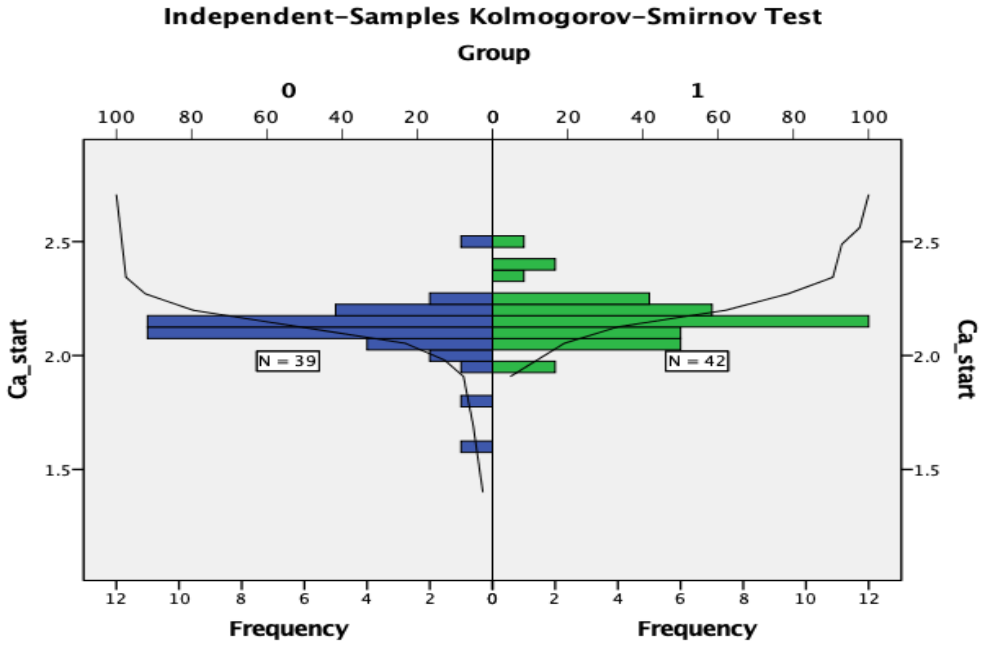


Fig. 24. Analysis of Ca in both groups at the beginning of the study using a statistical method – Kolmogorov – Smirnov Test

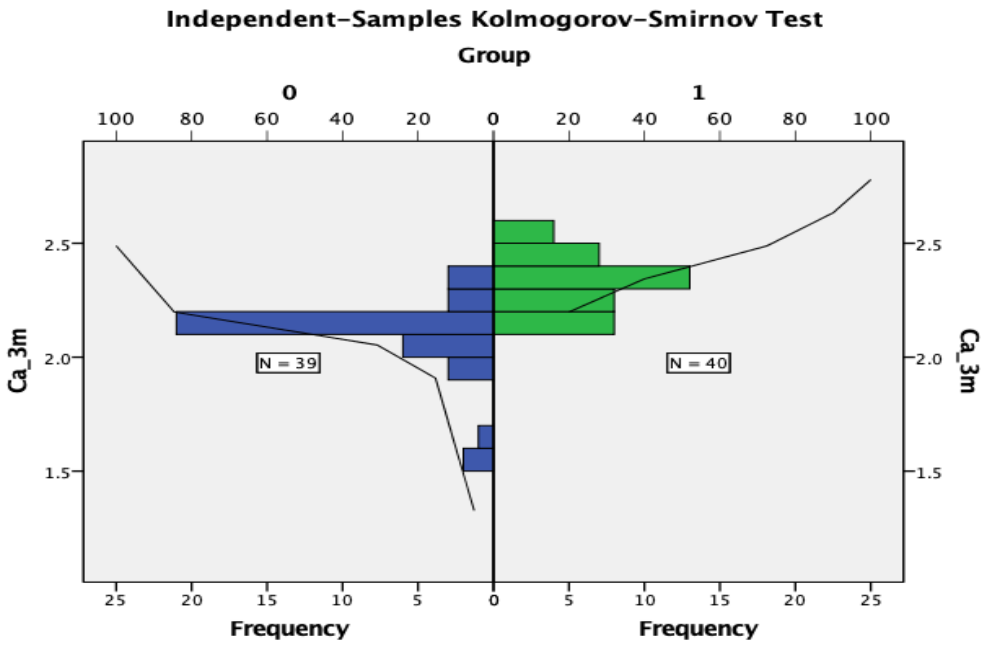


Fig. 25 Analysis of Ca in both groups at month 3 of the study using a statistical method – Kolmogorov – Smirnov Test

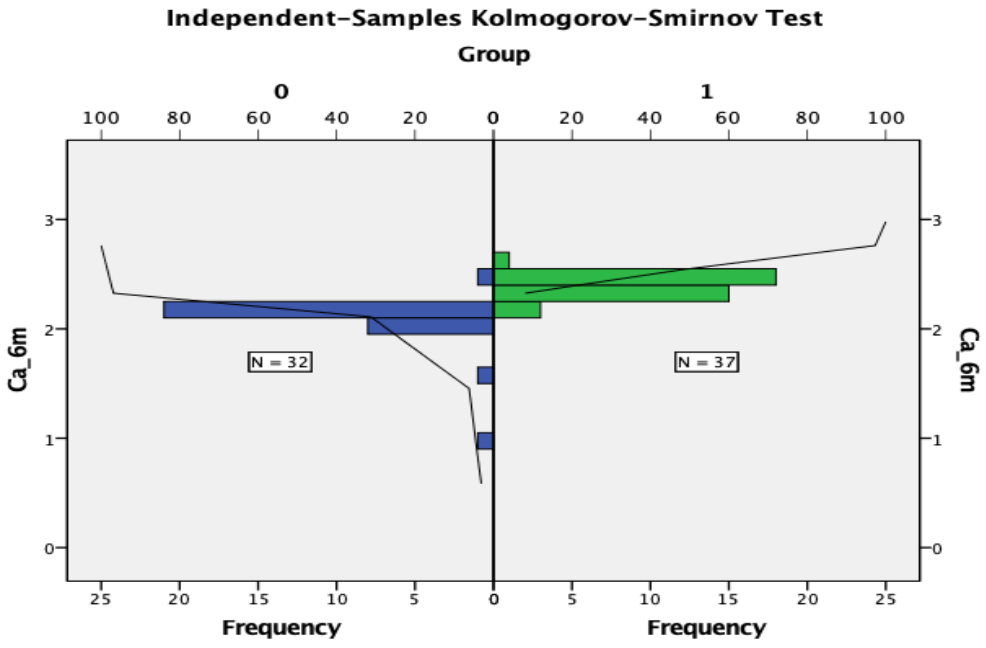


Fig. 26. Analysis of Ca in both groups at month 6 of the study using a statistical method – Kolmogorov – Smirnov Test

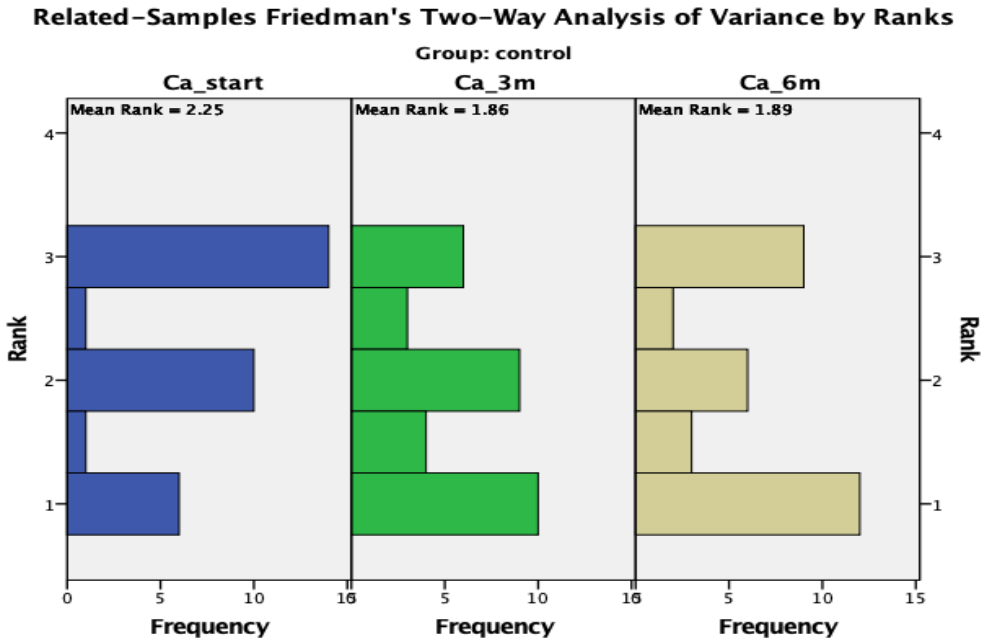


Fig. 27 Analysis of Ca levels in the control group

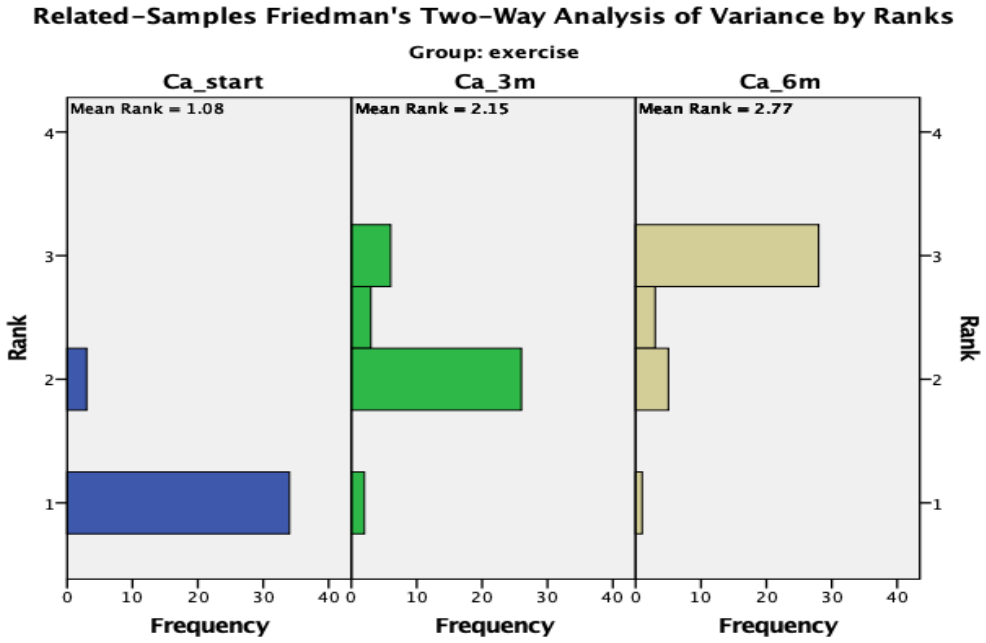


Fig. 28. Analysis of Ca levels in the experimental group

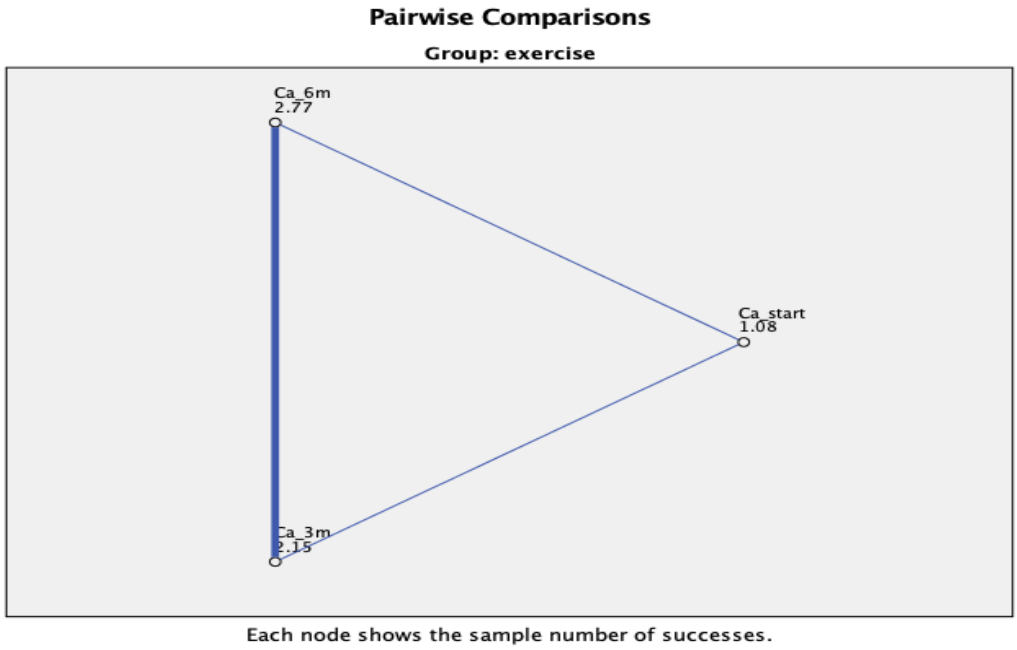


Fig. 29. Pairwise analysis for Ca levels for the experimental group

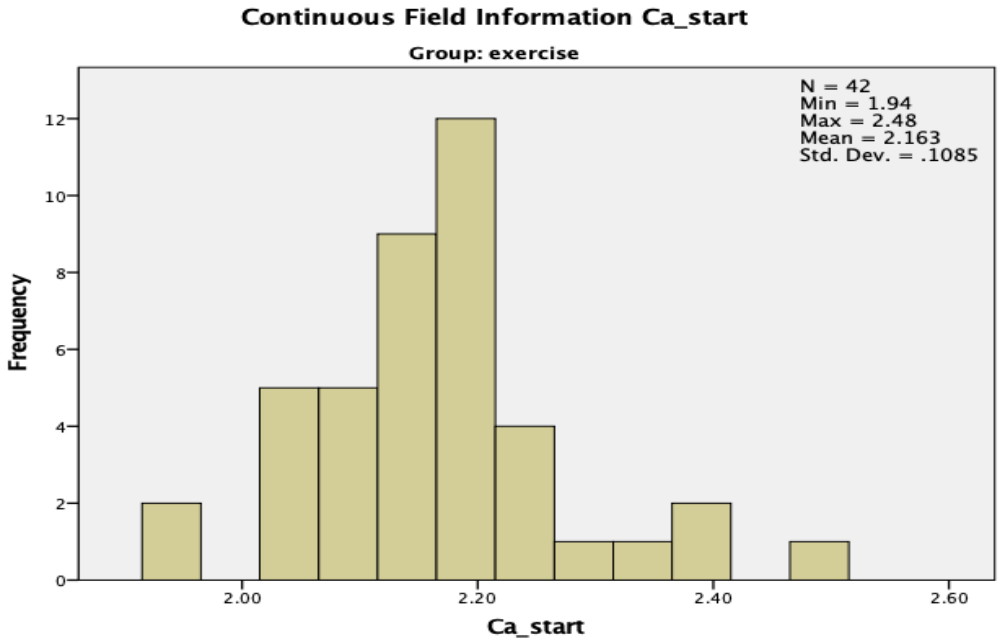


Fig. 30. Continuous Field analysis for Ca levels for the experimental group at the beginning of the study

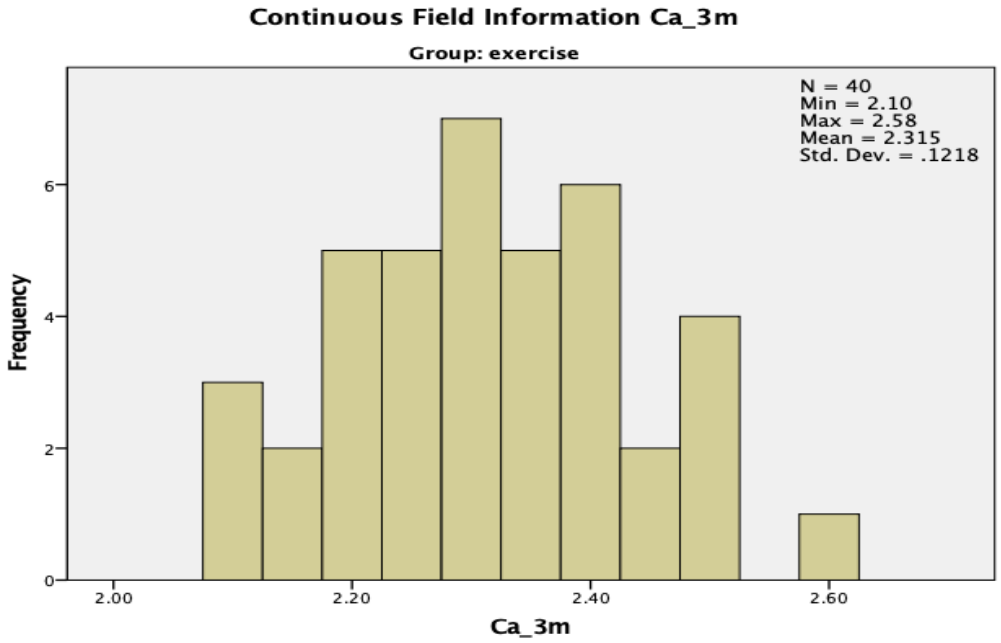


Fig. 31. Continuous Field analysis of Ca levels for the experimental group at month 3 of the study

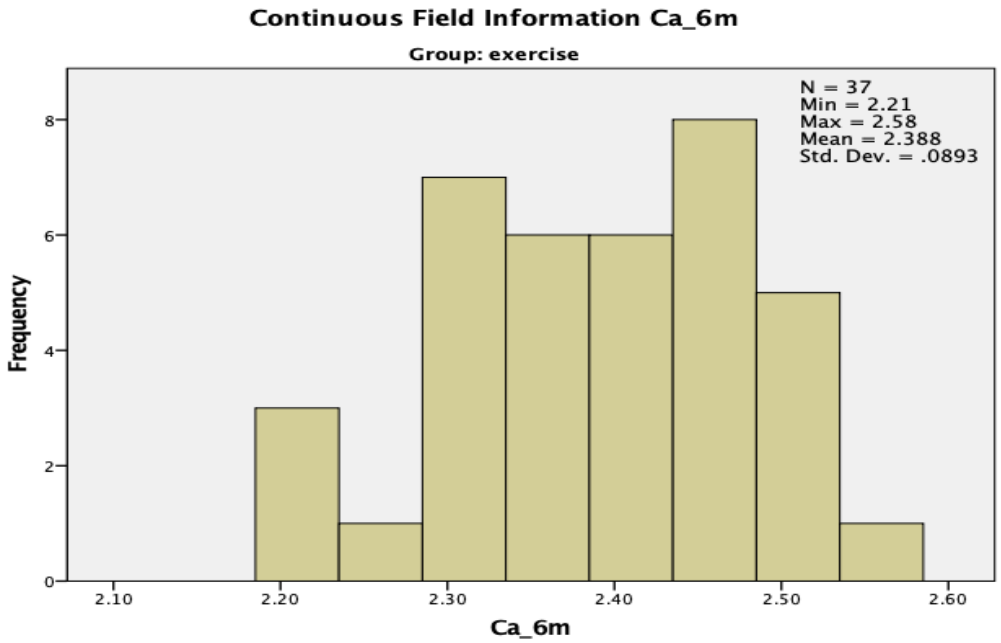


Fig. 32. Continuous Field analysis of Ca levels for the experimental group at month 6 of the study

The analyzed data show that in HD patients performing intradialysis exercises, bone mineral indices improve in terms of Ca and P, but not those for PTH. The highest correlation is found for serum Ca.

Task 5.

Creation of an original algorithm for performing intradialysis exercises and its implementation in routine clinical practice with a view to preventing complications of the underlying disease, improved disease management, rehabilitation and quality of life of patients with ESKD.

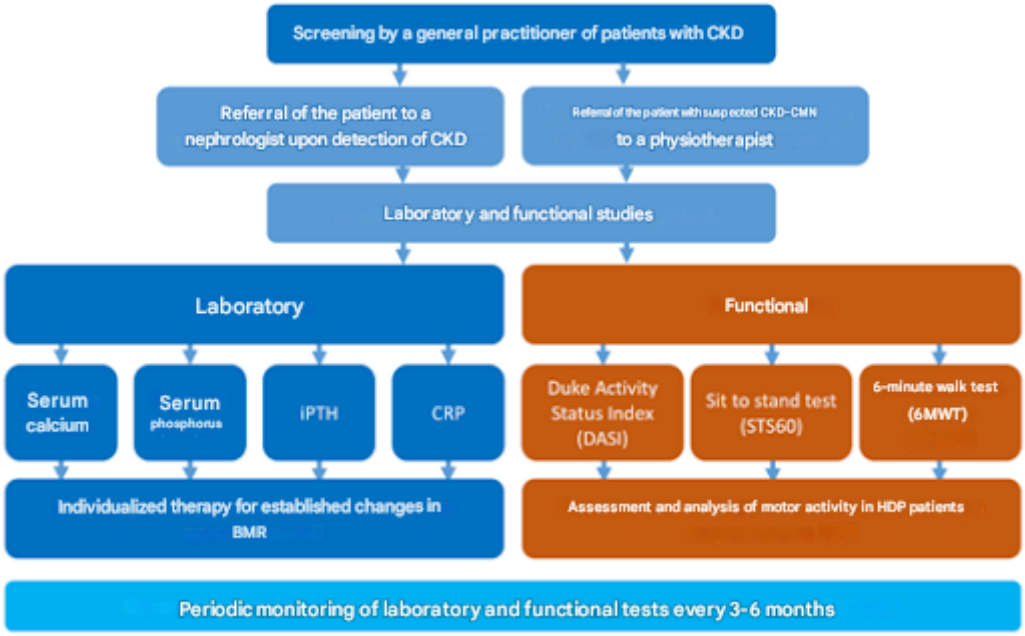


Fig. 33. Algorithm for performing intradialysis exercises and implementing them in routine clinical practice

The developed algorithm emphasizes the role of the general practitioner, who should refer the patient to a nephrologist when CKD is detected. In the case of BMD-CKD, the patient is referred to a physiotherapist. The necessary laboratory and functional tests are described, through which the extent of the disease can be proven. The role of the specialists is distinguished and individualized: nephrologist and physiotherapist. The nephrologist individualizes the therapy in the case of detected changes in BMD, and the specialist physiotherapist evaluates and analyzes the motor activity in patients with CKD. Teamwork shows very good results and requires periodic monitoring of laboratory and functional tests every 3-6 months.

The innovative algorithm we describe was developed for the first time in Bulgaria and aims to improve the quality of life, physical activity and endurance of patients with BMD-CKD.

Chronic kidney disease is a global health problem affecting 5-10% of the world's population, with the majority of these patients being exposed to an increased risk of developing bone and mineral metabolism disorders. Affected patients manifest symptoms such as: bone pain, muscle-tendon rupture and high fracture rate. According to Foley et., al., 2003, Burton et., al., 2009, Bover tt., al., 2021, Hsu et., al., 2021, observation and follow-up of these patients shows that they are also predisposed to cardiovascular calcification, which determines the high rate of morbidity and mortality. In clinical practice, bone biopsy is used less frequently. It is an invasive procedure and requires precision in interpreting tissue samples by highly qualified personnel. Therefore, leading in the treatment of bone mineral disorders are the levels of serum phosphate, calcium, alkaline phosphatase, PTH as markers of bone density [Blayney et., al., 2008, Bellido et., al., 2013, Blaine et., al., 2015, Bover et., al., 2018, Yonova 2018, Staykova 2018, Atanasova 2022].

BMD as a clinical complication of CKD continues to be investigated to improve its detailing and management. Various biomarkers are being used, allowing serial measurements of calcium, phosphate, and PTH. In addition, some clinical trials have emerged since the 2009 Kidney Disease Improvement global (KDIGO) guidelines, which led to the updated KDIGO recommendations in 2017.

Patients with ESKD have reduced renal function, which alters the metabolism of calcium, phosphorus, and vitamin D. These changes often lead to SHPT, which is characterized by elevated PTH levels and is often associated with parathyroid glands hyperplasia. This chronic and progressive disease develops early in the course of CKD, worsens with decreasing renal function, and affects most patients with advanced CKD. SHPT may occur as early as CKD G3, when the glomerular filtration rate (GFR) falls below 60 mL/min/1.73 m2. ESKD (CKD G5) is defined as the need for kidney replacement therapy (dialysis or kidney transplantation) in which residual renal function is absent or found to be too low (GFR < 15 mL/min/1.73 m2) . In patients with CKD and SHPT, the concomitant metabolic disturbances in calcium and phosphorus homeostasis can lead to pathological changes in bone tissue and vessels, which may increase the risk of bone fractures and cardiovascular events [Bonewald et., al., 2011, Carillo et., al., 2021]. High levels of PTH, calcium, and phosphorus are associated with increased mortality rates in SHPT patients on dialysis.

Hyperphosphatemia in CKD is the result of several major factors: reduced phosphorus clearance, bone turnover status, use of vitamin D analogues, inadequate use of binders, and excessive phosphorus intake. Hyperphosphatemia is among the factors contributing to the development of secondary hyperparathyroidism (SHPT) in patients with CKD and is associated with morbidity and

mortality in these patients, mainly from cardiovascular events. The mechanisms by which phosphorus retention increases the risk of cardiovascular events and mortality are not yet fully understood. These mechanisms include phenotypic transformation of arterial vascular smooth muscle cells induced by phosphorus or indirectly by the effects of hyperphosphatemia on PTH, triggering SHPT and vascular calcification. The rationale for preventing phosphorus retention or treating established hyperphosphatemia lies in its known role in the development of SHPT. In addition, other unproven benefits would be a reduced risk of vascular and soft tissue calcification, prevention of cardiovascular events, and CKD progression.

SHPT can lead to hyperparathyroid bone disease, which is a common cause of bone and joint pain in dialysis patients, reduced bone mass, and a correspondingly increased risk of bone fractures. The risk of hip fractures is approximately 3 to 4 times higher in the ESKD population than in the general mixed case population. Evidence suggests that severe uncontrolled SHPT contributes to a higher risk of fractures in ESKD patients: in the DOPPS study, PTH levels > 900 pg/mL were associated with a 72% higher risk of fractures compared with PTH in the controlled range of 150 to 300 pg/mL. The disturbances in calcium and phosphorus metabolism in SHPT are also thought to contribute to soft tissue and vascular calcification, with a 50% to 80% prevalence of calcification in dialysis patients. The association of high PTH, calcium, and phosphate levels with mortality has been reported. Analysis of DOPPS data demonstrated an increased risk of all-cause mortality and mortality: CV-related events, hospitalizations most commonly related to cardiovascular events, and elevated PTH levels.

In addition, the COSMOS (Current management Of Secondary hyperparathyroidism: A Multicentre Observational Study) demonstrated that changes in biochemical parameters to control SHPT were associated with improved survival. Simultaneous monitoring of PTH, calcium, and phosphate was associated with improved survival compared with separate monitoring of one or two of these parameters. Similarly, long-term, consistent monitoring of these biomarkers was associated with improved survival compared with episodic monitoring. Results from a recent large observational study stratifying patients into phenotypes based on PTH, calcium, and phosphate levels demonstrated that phenotypes with elevated PTH and phosphate levels and phenotypes with elevated PTH and calcium levels were at higher risk of death or cardiovascular-related hospitalization compared with phenotypes in which all three parameters were within target values.

It is believed that some factors secreted by osteocytes play an important role in the pathophysiology of the complex disease – chronic kidney disease and impaired bone-mineral

metabolism. The bone expression of some proteins was studied in patients with chronic kidney disease in stages G2-3, as well as G4 and G5 on dialysis treatment, and in healthy subjects, and the levels of various markers of bone remodeling were analyzed in a comparative manner in specific bone biopsy findings. As chronic kidney disease progresses, there is a decrease in serum calcium concentration and an increase in phosphorus, alkaline phosphatase, fibroblast growth factor-23, parathyroid hormone, and osteoprotegerin levels [Yonova 2015, Bergman et., al., 2017, El Baz et., al., 2017, Atanasova 2018, Staykova 2018, Bover et., al., 2018, Leifheit et., al., 2021, Manou et., al., 2020]. There is a gradual increase in bone tissue resorption, associated with reduced bone matrix formation and impaired bone mineralization. Bone expression of sclerostin and parathyroid hormone receptor-1 increases during the early stages, and that of phosphorus, alkaline phosphatase, fibroblast and phosphorylated β-catenin levels increases during the late stages of chronic kidney disease [Frost et., al., 2003, Garnero et., al., 2013, Figurek et., al., 2020].

Disorders of bone and mineral metabolism in patients with chronic kidney disease, as well as in patients on hemodialysis treatment and after kidney transplantation, are described in detail. [Yonova 2018, Staykova 2018, Atanasova 2022]. The novelties in calcium and phosphorus metabolism and its disorders in chronic kidney disease are systematized. Some main metabolic disorders in patients with chronic kidney disease are presented [Rouf et., al., 2018]. New data on parathyroid hormone, C-reactive protein and the appearance of vascular calcifications in patients with chronic kidney disease undergoing dialysis treatment are discussed [Robeva 2018, Yonova 2018, Staykova 2018, Roetker et., al., 2019]

Prevention of hyperphosphatemia includes dietary phosphate restriction, use of phosphate-lowering agents, and dialysis for patients with CKD of stage G5-D [Sekercioglu et., al., 2017].

Phosphate removal by extracorporeal treatment is dependent on the type of dialysis and the duration of the dialysis session.

For a dialysis session duration of 4 hours, 3 times a week, approximately 2.3–2.6 g of phosphorus is removed per week. If the session length is increased to 8 hours 3 times a week (as with nocturnal dialysis), phosphate removal increases to 3.0–3.6 g per week.

BMD-CKD are also a predisposing factor for increased cardiovascular risk. This is determined by hyperphosphatemia, vascular calcification and increased fibroblast growth factor-23) have been found within CKD-CKD in recent decades [Qunibi et., al., 2005, Russo et., al., 2011 , Rodelo-Haad et., al., 2018].

Bone mineral disorders are a complication of CKD that seriously affects the prognosis of hemodialysis patients, increasing the risks of all-cause and cardiovascular mortality in these patients. They are considered an important factor affecting HRQoL [Schwarz et., al., 2000]. Based on studies of patients undergoing hemodialysis, serum P and intact parathyroid hormone (iPTH) values that are too high or too low are associated with poor HRQoL. However, previous studies conducted on this topic have mainly focused on the effects of individual biochemical markers of BMD-CKD on HRQoL, but these studies have not considered the combination of serum P, serum Ca, and iPTH values in assessing their correlation with HRQoL. There is a close relationship and interaction among these three factors.

We conducted an analysis to investigate factors affecting health-related quality of life (HRQoL) in patients with BMD-CKD on hemodialysis. This analysis aimed to observe the relationships among different combinations of serum Ca, P, and iPTH levels and HRQoL in patients on extracorporeal dialysis and to investigate the associated factors affecting HRQoL in these patients, as well as intradialytic exercise and physical endurance.

We used a questionnaire for research and assessment after modification of the reference book [Sv. Staykova- KDQoL- SF- 36]. This instrument has a number of advantages – validated in Bulgarian, easy to interpret, the ability to calculate two summary indicators for physical and mental health, comparison of the obtained data with other populations, etc.

The questionnaire includes 8 scales assessing different aspects of health: 1) physical activity; 2) physical endurance; 3) emotional stability; 4) social activity; 5) mental health; 6) bodily pain; 7) vitality (energy/fatigue); 8) perception of general health. Responses include yes/no/cannot determine.

The questionnaire is completed independently, which takes 5-10 minutes. When the card is filled out, the SF-36 questions are evaluated using developed criteria for calculating the significance of individual answers, using a point system. The points given on the individual scale are used primarily for preliminary and indicative assessment. This assessment is carried out on the main eight aspects of the questionnaire and represents an absolute assessment of the level of quality of life, obtained by converting qualitative features into an individual assessment scale with a certain dimension.

The widespread use of this questionnaire is related not only to its universal applicability across various diseases, but also to the general understanding of individual aspects of health as a whole - physical and social.

Studies by Segura et., al., 2010, Rossa et., al., 2015, Ryota et., al., 2017, Afsar et., al., 2018, Assawasaksakui et., al., 2021, on intradialysis exercises in hemodialysis patients establish their role in improving physical activity. Bernier et., al., 2022, Brito et., al., 2022, Bogataj et., al., 2024, also study the quality of life of these patients and the results obtained speak in favor of its improvement.

Our study confirmed the role of intradialysis exercises in hemodialysis patients. We established their influence on their functional capacity and physical activity. This gives us reason to recommend these exercises in the complex of treatment procedures for chronic dialysis patients as a prevention of reduced physical activity in these patients.

VI. INFERENCE

Chronic kidney disease is a global problem. It is extremely important to prevent its development on the one hand, and on the other, to slow down its progression if it has already developed. This requires knowledge of the causes that provoke it, as well as their timely prevention. A method of treatment for CKD is replacement therapy, including chronic dialysis. The latter allows for the purification of toxins and at the same time supports the function of individual organs and systems. Patients who are on long-term dialysis develop not only the symptoms of CKD, but also its complications. One of the severe complications of CKD are disorders in bone-mineral metabolism.

Assessing quality of life in patients with CKD G5 allows for a more complete understanding of their specific needs and increasing the effectiveness of clinical management. This is a potential opportunity to improve the quality and effectiveness of healthcare provided and should be widely applied in Bulgarian medical practice, especially in assessing the quality of medical care and health management.

It is extremely important for chronic dialysis patients to receive a team approach that includes not only nephrologists, but also general practitioners and, last but not least, physical and rehabilitation medicine doctors.

Many authors [Cheema et., al., 2005, Bae et., al. 2015, Greenwood et., al., 2021, Brito et., al., 2022, Bennet et., al., 2023, Botagaj et., al., 2024] in the application of renal rehabilitation such as "Riding a bike", 6-minute walk test, sit to stand give good results. This requires convincing patients of the positivity of intradyalisis exercises in order to improve their muscle tone and physical activity.

VII. CONCLUSIONS

1. The present study on the application of aerobic intradialysis exercises with a specialized bike in chronic dialysis patients is being conducted for the first time in Bulgaria.

2. The development of an algorithm for assessing and increasing the physical activity of patients on dialysis treatment and its implementation in controlled hospital/outpatient settings represents the implementation of tertiary prevention aimed at preventing the development of complications associated with the end-stage of CKD, maintaining maximum functional capacity and improving the quality of life of these patients.

3. We found that patients who perform aerobic intradialysis exercises with a specialized bike have an impact on their functional status. This gives us reason to recommend that these exercises be used for rehabilitation.

4. The impact of chronic dialysis treatment in two groups of patients with ESKD on motor activity and their individual quality of life has been demonstrated through an adapted version of a standardized reference for assessing the quality of life in patients with kidney disease (KDOOL-SF) with regard to biochemical indicators in BMD-CKD.

5. An innovative specialized questionnaire was created to identify the main reasons for the deterioration of motor activity in patients with ESKD and stratify risk factors.

6. An original algorithm for performing intradialysis exercises has been created and implemented in routine clinical practice with a view to preventing complications of the underlying disease, improving disease management, rehabilitation and quality of life of patients with ESKD.

7. Bone mineral disorders significantly affect the quality of life in patients with CKD. The implementation of renal rehabilitation in the future is one of the factors that will improve the quality of life in patients with BMD-CKD on dialysis treatment.

VIII. CONTRIBUTIONS

Theoretical contributions:

1. It has been found that bone mineral disorders significantly affect physical activity, emotional and mental stability in patients, as well as the perception of their overall health.
2. In HD patients, there is a significant impairment in their functional status, which necessitates the discussion and application of aerobic intradialysis exercises.
3. An original algorithm for performing intradialysis exercises has been created and implemented in routine clinical practice with a view to preventing complications of the underlying disease, improving disease management, rehabilitation and quality of life of patients with ESKD.

Contributions of a practical nature:

1. For the first time in our country, aerobic intradialysis exercises with a specialized bike have been applied to chronic dialysis patients.
2. The role of intradialysis aerobic exercises in chronic dialysis patients was evaluated, as well as their impact on the emotional status and self-esteem of the patients.
3. For the first time in Bulgaria, a behavioral algorithm has been developed, including laboratory and functional tests in patients with BMD-CKD.

IX. PUBLICATIONS

Publications related to the dissertation

1. T. Zlateva, **M. Bliznakova** , D. Bliznakova, Chronic kidney disease, bone changes and physiotherapy, Current Nephrology, 2021,1, 62-66.
2. **M. Bliznakova,** Irina Momcheva, Ivelina Hristova, Eva Hristova, Zhenya Ruseva, Valentina Madzhova , Kinesitherapy in hemodialysis patients, Current Nephrology, issue 1, volume 16, 2022, 34-37.
3. **M. Bliznakova,** D. Nenova, S. Atanasova, I. Momcheva, I. Hristova, E. Hristova, Zh. Ruseva, Sv. Staykova, V. Madzhova, Perceptions of hemodialysis patients regarding physical exercise, Nephrology, Dialysis and Transplantation, volume 29, 2023, 3, 64-69.
4. **Magdalena Bliznakova,** Snezhana Atanasova; Research of the impact of chronic dialysis treatment in patients with ckd-bmd on physical activity and individual quality of life; Scripta Scientifica Medica, 2024;56(2):29-33.
5. **Magdalena Bliznakova** , Snezhana Atanasova, Valentina Madjov a; Evaluating the impact of specialized cardio-cycling exercises on the clinical status of chronic dialysis patients, objectified by examining laboratory indicators of mineral and bone disorders; Scripta Scientifi ca Medica, 2024; Online First.