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(RESEARCH ARTICLE)

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Bone mineralization disorder in patients on chronic hemodialysis and the effect on the occurrence of muscle hypotrophy

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Abstract

Bone mineralization disorders in patients undercoating chronic hemodialysis commonly arise due to secondary hyperparathyroidism, a condition characterized by disrupted parathyroid hormone (PTH) regulation. PTH increases bone resorption and affects calcium and phosphorus levels in the body, enhances calcium reabsorption in the kidneys and intestines, and elevates phosphorus excretion through the kidneys. Chronic kidney disease leads to dysregulation of PTH secretion, resulting in secondary hyperparathyroidism.

The aims of this study were to assess muscle weakness in osteoporotic extremities, investigate the role of rehabilitation exercises in hemodialysis patients to prevent lower extremity muscle atrophy, and highlight the significance of calcimimetics and vitamin D analogs.

Study results indicate

- High correlation between bone mineralization disorders and P and Ca disorders in patients on a chronic hemodialysis program
- High correlation between mineralization disorders and muscular hypotrophy.
- Moderate positive correlations among P values and urate, T and Z scores, pulse rate, respiratory rate, and systolic blood pressure

In our study, initial physical functioning was poor, but after physiotherapy, almost all patients in both groups reported improvement, evident from analysis of the 6-minute walk test (6MWT) and manual muscle test (MMT). There was an increase in bone mineral density, strengthening of leg and back muscles, and improvement in patient mobility and stability.

It is crucial to emphasize that complete recovery is not achievable without rehabilitation. Post-fracture rehabilitation plays a significant role in patient recovery and returns to daily activities. Physical medicine, including electrotherapy, cryotherapy, and kinesiotherapy, contributes to faster recovery. Therefore, the importance of physical therapy, both post-surgical and non-surgical fracture treatments, cannot be overstated.

Key words: Bone Mineralization Disorder; Rehabilitation; Dialysis, Muscular hypotrophy

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1. Introduction

Bone mineralization disorder in patients on a chronic hemodialysis program is most often due to a disorder of parathyroid hormone (PTH) (secondary hyperparathyroidism occurs). PTH in the body works by increasing bone breakdown and calcium and phosphorus levels in the body, increasing calcium resorption in the kidneys and intestines, and increasing phosphorus excretion via the kidneys. In patients with chronic renal insufficiency, PTH secretion is impaired, which is characterized as secondary hyperparathyroidism (1).

The first change that indicates an emerging problem with parathyroid gland function is hyperphosphatemia. The kidneys that have reduced function cannot sufficiently, efficiently and quickly enough to get rid of the excess phosphate in the blood that occurs after eating. Transient, first postprandial episodes of hyperphosphatemia in the blood lead to a drop in blood calcium, both overall and ionized. As a result of a decrease in calcium in the blood, increased synthesis and secretion of PTH occurs. The body actually tries to compensate for the reduced levels of calcium by engaging it from the place where it is most abundant, which is the bones. Elevated PTH secretion is initially an adaptable mechanism that attempts to restore Ca levels to normal values (2). Calcium and phosphorus are important minerals that need to be balanced in the body. When the kidneys are deficient, the body does not take calcium enough or eliminate phosphorus completely. The body tries to correct this situation by taking calcium from the bone (3).

Maintaining the balance of calcium, phosphorus and vitamin D is the primary therapeutic goal. This is very difficult to achieve because of their closely related mutual regulation and interdependence. The concentration of phosphorus in the blood depends primarily on the intake of food and on the drugs that the disorder is trying to control. If the increase in phosphorus is not corrected to a sufficient extent, there is a decrease in the concentration of calcium. The magnitude of the calcium drop depends on the ability of the parathyroid glands to compensate for the missing calcium from storage of bone tissues (4).

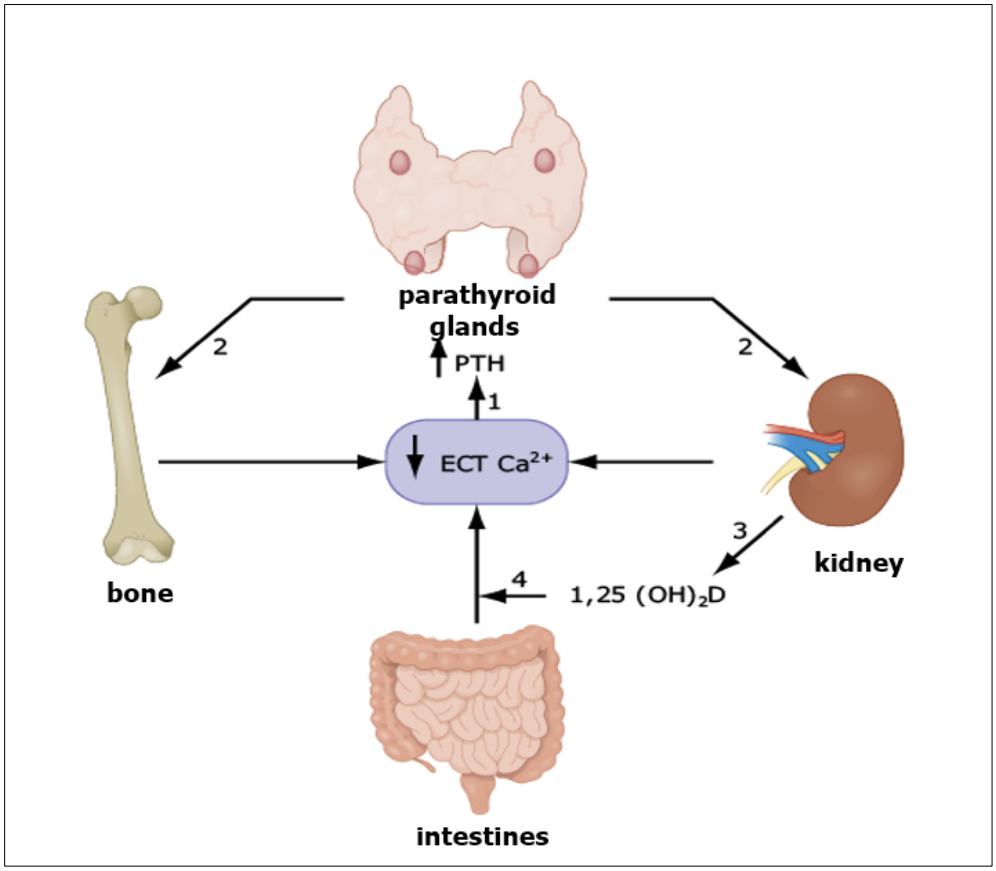

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Figure 1 Effects of parathyroid gland on bone

1.1. Complications of secondary hypeparathyroidism

Vascular complications affect the blood vessels, heart and soft tissues and manifest themselves earlier than skeletal and orthopedic problems. Predisposing factors for the occurrence of extraskeletal calcifications are: the age of the patient, the duration of dialysis, the degree of disturbances in the level of calcium and phosphate in the plasma, high parathormone values and expressed acidosis. The presence of local tissue damage is an additional contributing factor. Extra skeletal calcifications do not occur in all patients equally pronounced; although they have equal factors for occurrence, individuals do not develop complications. The reasons for this are unclear. Constant care for early detection of changes is required for most patients. Periarticular calcifications occur due to high concentrations of Ca and P in the serum and can occur with high doses of vitamin D, CA preparations, dialysate with high Ca concentration with simultaneous presence of hyperphosphatasemia and can be lost by phosphate restriction. PTH can increase the buildup of Ca in soft tissues, these periarticular calcifications result in acute arthritis and periarthritis, and periarticular masses can limit movement[28]. In all patients that are on chronic hemodialysis, over time, secondary hyperparathyroidism (SHPT) occurs, which has a direct impact on Ca and P metabolism. Disruption of CA and P metabolism alters bone metabolism according to type of mineralization disorder and decrease in bone density. As a result, bone mineralization diseases occur, i.e. osteopenia and osteoporosis, which result in frequent fractures due to minor injuries, as well as the appearance of pathological fractures. Rehabilitation in the form of static exercises and actively assisted exercises is a measure of fracture prevention and Prevention of muscular hypotrophy (5).

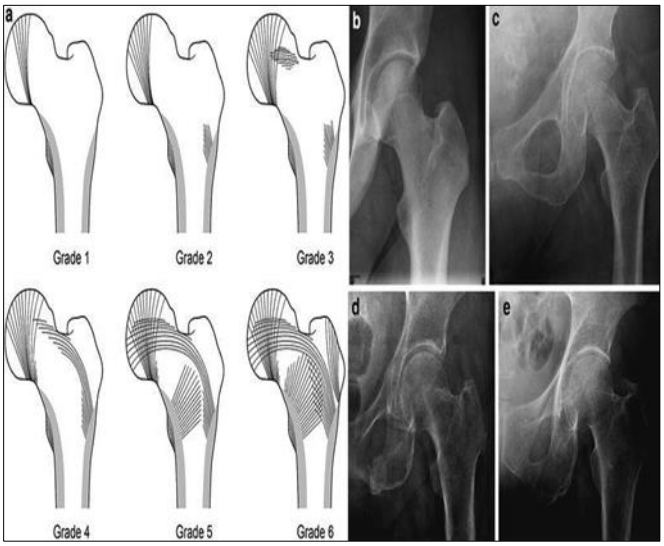


Figure 2 X-ray grades (degrees) of osteoporotic changes on the hip - Töönis classifiers

1.2. Treatment of mineralization disorders

Phosphate binders are a group of drugs that help maintain adequate serum phosphorus values. Their action is based on the binding of phosphates from food in the lumen of the intestine, thus reducing reabsorption. Phosphate binders are divided into calcium and non-calcium. Calcium carbonate is the most commonly used calcium phosphorus binder. Calcium acetate is also used. Active forms of vitamin D3 and vitamin D analogues (paricalcitol, deoxy calciferol) can successfully keep hyperparathyroidism under control. The daily dose of calcitriol ranges from 0.25 to as much as 1.5 µg/day. Its downside is that it can cause hypercalcemia. It is available on our market in oral form, which may further affect patient cooperation. Among other available preparations from this group is paricalcitol in parenteral form. An indicator of the success of therapy is a decrease in serum PTH, i.e. the maintenance of PTH in optimal values (6). Vitamin D exists in several forms in the body, as a provitamin and as active vitamin D. Vitamin D activation is carried out in the liver and kidneys. It is clear that if there is kidney disease, the activation of vitamin D will be reduced, which inevitably leads to a lack of the active form of vitamin D. The deficiency must be compensated by supplementation, by taking an additional amount of vitamin D. Vitamin D can be supplemented in two forms; as a drug that must be activated in the body to be effective, or as a pharmacologically active form of the drug that is already active and does not require additional changes in the body to have an effect. Active vitamin D is called calcitriol and it has a physiological role to promote the resorption of calcium and phosphorus from the intestine and thus reduce the excessive secretion of PTH. In this way, already existing excessive secretion of PTH can also be prevented or treated. Therapeutic, dosage width; that is, the minimum and maximum dose of vitamin D that gives an optimal response is very narrow. This means that vitamin D can be given too little or overdosed very easily and quickly. This requires careful administration with a gradual and patient change of the dose, both its reduction and increase (7).

1.3. Oste muscular complications and physical rehabilitation

Bones have a basic supporting role in the locomotion of the organism, their development and density depends both on the substances deposited in them and on physical activity. Dialysis patients have considerably less physical activity, and if secondary parathyroidism is added to that, it is clear that osteopenia and osteoporosis can also be causes of muscle hypotrophy. Muscle strength largely depends on their activity. Bone consists of osteocyte cells and an intercellular substance (matrix) that is calcified in the Matrix. The basic substance is collagen which is permeated with lime salts. Bones contain 25% water, 35% protein and 45% minerals. Bone chemicals include calcium, phosphorus, potassium, magnesium, iodine, iron, and chlorine. As part of electrotherapy, we use interference currents and magnetotherapy in the case when no metal is implanted in the surgical treatment of fractures. Electrotherapy in non-operative treatment of fractures, apart from the mentioned therapies, includes diadynamics, electropherosis of drugs, laser, ultrasound. In kinesitherapy, we use an active movement performed by the patient himself. At the initial stage of rehabilitation, the application of ice for swelling and static contractions without movement. We use actively assisted exercises that are performed with the help of a physiotherapist in order to increase the volume of movements. Rehabilitation when mobility is achieved includes muscle strengthening (8).

The goal of rehabilitation is to train the patient and return him to normal life activities. It is important to point out that without rehabilitation, there is no real and complete cure. Rehabilitation after bone fractures plays a major role in the patient's recovery process and return to daily activities. Physical medicine and within its electrotherapy, cryotherapy, and kinesitherapy contribute to faster recovery. Therefore, it is necessary to emphasize the great importance of physical therapy, both after operative and non-operative treatment of fractures (9).

It is clear that physical therapy alone cannot provide stable segment restitution, especially if the underlying kinematic mechanism is damaged.

Therefore, the main goals of rehabilitation are:

- Pain reduction;
- An increase in muscle strength;
- Increased movement (10).

1.4. The objectives of the paper are:

- Determine whether there is a change in Ca and P in patients on a chronic hemodialysis program.
- Determine the state of bone density in patients on the chronic HD program.
- Determine the strength of the muscles in the extremities affected by osteoporosis.
- Investigate the effect of rehabilitation exercises in hemodialysis patients related to the prevention of muscle hypotrophy

2. Material and Methods

A retrospective-prospective study was conducted at the Hemodialysis Center in Živinica on 55 hemodialysis (HD) patients, in the period from October 1, 2023 to March 31, 2024. The study included both genders over the age of 18. During the study, there were a total of 58 patients at the Center for hemodialysis, three patients were immobile and were not included in the study. All patients are on a chronic hemodialysis program for at least 6 months, with no previous history of bone mineralization disorders. The first measurement of PTH and laboratory findings was carried out to the patients on 1 October 2023, and the control measurement after therapy was done after 6 months. Data were collected from the history of the disease, monitoring of PTH, Ca, P, Na, K, CRP, SE, urati, fibrin and rheumatic factor in patients treated at the clinic, densitometry (T-and Z scor) was performed. Since the densitometry apparatus of the UKC Tuzla was not in operation during the study period, ultrasound screening of the bone density of the heel bone was performed. An analysis of age, gender, occupation and place of residence was carried out, the cause of kidney failure, which could be related to the occurrence of bone mineralization disorders. A 6-minute walk test (6 MWD), a manual muscle test (MMT), Ta, SpO2, respiration of all patients was performed before inclusion in rehabilitation treatment and after completion of rehabilitation treatment. In addition, at the beginning of the study, patients were asked an oral question of subjective feeling of general condition, and the same question was asked at the end of the study.

The patients are divided into three groups; each group has three subgroups according to the municipalities from which the patients are:

The group has 5 patients who have PTH values up to 180 pg and do not use vitamin D analogues or calcimimetics, the patients are divided into three subgroups according to the municipality from which they come.

The group has 28 patients who have PTH values from 180 to 400 pg and use calcitriol (an analogue of vitamin D), the patients are divided into three subgroups according to the municipality from which they come.

The group has 22 patients who have PTH values from 401 to 1100 pg and use paricalcitol (active form of vitamin D) or cinacalcet (calcimimetic), the patients are divided into three subgroups according to the municipality from which they come.

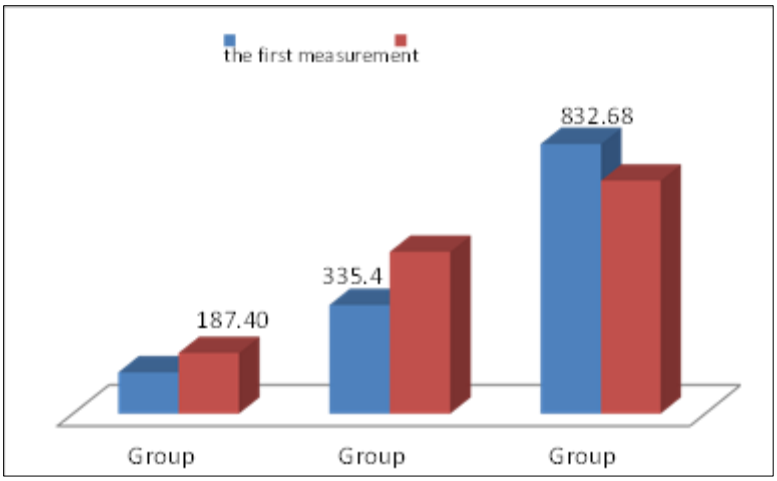
Statistical processing of the collected primary data was carried out using techniques and methods of inferential and descriptive statistics, whereby appropriate software support in the form of programs was used for the processing and analysis of the collected data. *Microsoft Excel* the statistical data processing program *IBM SPSS Statistics*. Descriptive statistical analysis included the calculation of measures of central tendency and dispersion of the collected data, presented through appropriate Tabular overviews and graphical representations.

3. Results

Given that indicators of calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) levels were monitored for each patient, it was considered expedient to determine the difference in these indicators before and after therapy. In order to answer this question, the values of the descriptive statistical indicators were calculated in terms of the number of respondents (N), minimum and maximum values, average or mean values and standard deviation of these indicators individually. These are calculated at the level of the entire sample, as well as at the level of individual groups of patients, as seen in Table 1.

Table 1 Descriptive statistical indicators of calcium, phosphorus and parathyroid hormone before and after treatment

		Before therapy	**Before therapy**	**Before therapy**	**Before therapy**	**After therapy**	**After therapy**	**After therapy**	**After therapy**
	N	Min.	Max.	Average	St.deviation	Min.	Max.	Average	St.deviation
PTH	55	98,00	1,04	515,42	293,84	100,00	3130,00	559,22	460,80
Ca	55	1,282,81	2,81	2,26	0,47	0,87	2,86	2,3	0,41
P	55	0,83	4,90	1,55	0,56	0,70	2,65	1,48	0,37
PTH	5	98,00	163,00	127,4	25,19	100,00	276,00	187,40	81,09
Ca	5	2,06	2,71	2,52	0,27	1,35	2,55	1,82	0,56
P	5	0,85	2,65	1,47	0,68	0,90	1,51	1,31	0,23
PTH	28	196,00	400,00	335,43	62,36	112,00	3130,00	499,68	569,55
Ca	28	1,33	2,80	2,22	0,48	0,87	2,86	2,31	0,46
P	28	0,83	1,74	1,44	0,28	0,70	2,65	1,45	0,40
PTH	22	419,00	1045,00	832,68	180,04	291,00	1047,00	719,50	251,26
Ca	22	1,28	2,81	2,25	0,48	1,45	2,83	2,39	0,29
P	22	1,10	4,90	1,70	0,77	0,93	2,35	1,55	0,34



Legend: Group 1 – hemodialysis patients who have a PTH value of up to 180 pg and do not use vitamin D analogues or calcimimetics, group 2-hemodialysis patients who have a PTH value in the interval between 180 and 400 pg and use calcitrol, group 3-hemodialysis patients who have a PTH value in the interval between 401 and 1100 pg and use paricalcitrol or cinacalcet

Figure 3 Portion of the results related to changes in the average parathyroid hormone

Based on the graph, it can be concluded that in the group of hemodialysis patients who did not use vitamin D analogues or calcimimetics (Group 1) there was an increase in the mean PTH level by 60 pg, in the group of patients who used calcitriol (Group 2) there was an increase in this indicator by 164.25 pg, while in the group of patients who used paricalcitol or cinacalcet (Group 3) there was a decrease in its mean value by 113.18 pg.

According to the manual muscle test, scores for muscle strength are shown in the interval from 0 to 5, with the following meanings

- no muscle activity,
- a muscle contraction appears in the trace, which can be palpated or visualized, and 15% of muscle strength is preserved,
- the muscle is capable of overcoming the full range of motion in the joint when the force of earth's gravity is turned off (in suspension, on an inclined plane, in water) and 25% of the muscle strength is preserved,
- muscle contraction is possible to master the full range of motion without excluding the gravity and 50% of muscle strength is preserved,
- muscle contraction is possible to overcome the full range of movement against the force of the gravity and mild resistance, while preserving 75% of muscle strength,
- shows that the muscle can master the full range of movement with maximum resistance provided by the therapist manually, which means that the muscle possesses 100% of the strength.

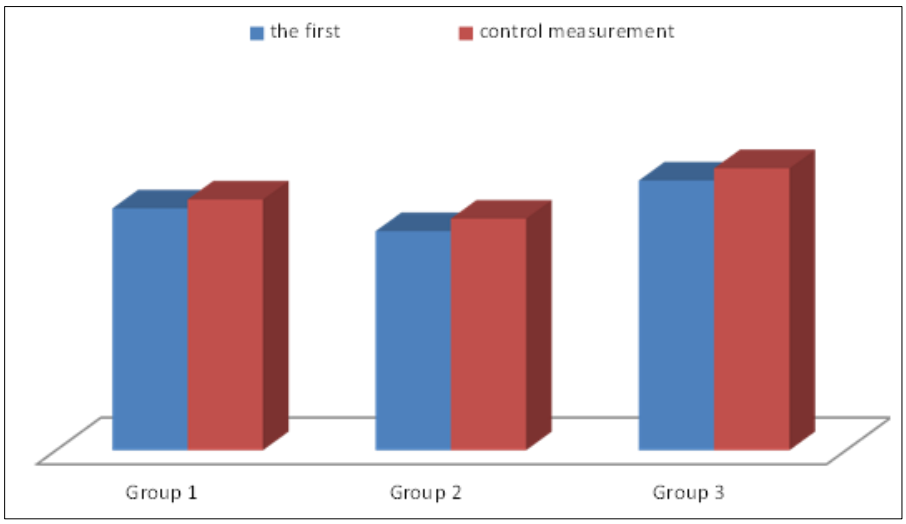
Considering that in the process of collecting data on the patients included in the research, among other things, the data on the distance traveled by the patients during the 6-minute walk test, as well as the manual muscle test scores at the first and control measurements were collected, it was considered expedient to test whether and in which direction there was a change in these indicators between these two moments in time. For this purpose, at the level of the entire patient sample, as well as at the level of groups of patients, the values of descriptive statistical indicators of these indicators measured at the first and control measurements were calculated.

The obtained results are shown in Table 2.

Table 2 First and control measurements for 6MWD and MMT

		Before therapy	**Before therapy**	**Before therapy**	**Before therapy**	**After therapy**	**After therapy**	**After therapy**	**After therapy**	**Difference average**
	N	Min.	Max.	Average	St.deviation	Min.	Max.	Average	St.deviation	
6MWT	55	150	405	259,51	69,89	155,00	420	272,47	71,254	12,96

MMT	55	3,00	5,00	3,84	0,57	3,00	5,00	4,13	0,64	0,29
6MWT	5	180,00	300,00	260,00	50,49	183,00	320,00	269,00	54,75	9,60
MMT	5	3,00	4,00	3,80	0,44	4,00	5,00	4,20	0,44	0,40
6MWT	28	150,00	310,00	235,00	56,70	155,00	325,00	248,93	56,88	13,46
MMT	28	3,00	4,00	3,71	0,46	3,00	5,00	3,96	0,636	0,25
6MWT	22	150,00	405,00	290,00	78,72	155,00	420,00	303,09	81,24	13,09
MMT	22	3,00	5,00	4,00	0,69	3,00	5,00	4,32	0,64	0,32



Legend: Group 1 – hemodialysis patients who have a PTH value of up to 180 pg and do not use vitamin D analogues or calcimimetics, group 2-hemodialysis patients who have a PTH value in the interval between 180 and 400 pg and use calcitrol, group 3-hemodialysis patients who have a PTH value in the interval between 401 and 1100 pg and use paricalcitrol or cinacalcet

Figure 4 Average distance values at the first and control measurement per group of patients

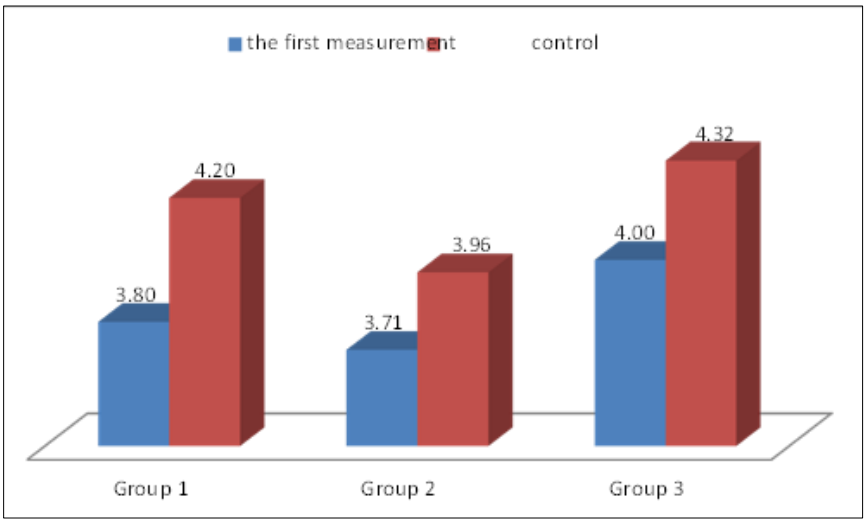


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Figure 5 Average values of the manual muscle test at the first and control measurements by groups of patients

In order to visualize the direction of the changes that have occurred over time when it comes to these two indicators, the average values of the same on the first and control measurement are presented graphically. In Graph 7. the results of the average distance values are presented by the groups of patients. As you can see, in all three groups of patients, there was an increase in distance. In doing so, the highest average growth of this parameter, in the value of 13.46 meters, was recorded in hemodialysis patients using calcitriol (Group 2).

For the purpose of target testing, regression analysis was used, with secondary hyperparathyroidism as an independent variable operationalized through parathyroid hormone levels, while the dependent variable was operationalized through at score value. In doing so, the operationalization of both of these variables was carried out through the value of the above indicators on the control measurement. The key part of the regression analysis results is shown in Tables 3, 4. and 5.

Table 3 Evaluating the impact model secondary hyperparathyroidism to changes in bone density

model summary[b]				
model	**R**	**coefficient of determination**	**corrected coefficient of determination**	**standard estimation error**
1	0,335[a]	0.113	0.096	1.0521

a. Predictors: (const.), secondary hyperparathyroidism
b. Dependent variable: change in bone density

Table 4 Analysis of Variance (ANOVA)

	sum of squares	**df**	**average of squares**	**F**	**sig.**
Regression section	7.436	1	7.436	6.719	0.012
Residual part	58.661	53	1.107		
Total	66.097	54			

Table 5 Coefficients of regression analysis of the model of the influence of secondary hyperparathyroidism on changes in bone density

model		**non-standardized coefficients**		**standardized coefficients**	**t**	**Sig.**
		B.	**st. error**	**beta**		
1	(Constant)	-0.219	0.224		-0.975	0.334
	secondary hyperparathyroidism	-0.001	0.000	-0.335	-2.592	0.012

The coefficient of determination presents how much of the variance of the dependent variable is explained by the model. In our case, the model explains 11.3% of the variance of the change in bone density. The statistical significance of this indicator is shown in the ANOVA table (Sig.=0.012) and presents that the analyzed model reaches statistical significance.

4. Discussion

Patients on a chronic hemodialysis program are often exposed to diseases and complications other than kidney failure. Understanding bone mineralization and the resulting disorders in the process can greatly prevent complications such as osteoporosis and fractures. This research reflects the current state of a dialysis center, but it could be a pilot project for larger research on the importance of early rehabilitation of hemodialysis patients, as a form of prevention of disorders of bone mineralization and fracture formation.

Evidence from previous studies suggests that the prevalence of osteoporosis in patients on a chronic hemodialysis program is 31. %59. Based on this fact, this paper should contribute to a better understanding of the importance of preventing bone mineralization disorders in patients on chronic hemodialysis program60. Early rehabilitation will also reduce the immobility of the patient after the fracture, and regular static exercises will contribute to the non-development of muscle hypotrophy due to pain in the extremities, which results in lower mobility of certain extremities.

Epidemiological studies have shown an association of hyperphosphataemia and accelerated deterioration of renal function, and it is also indisputable that phosphorus retention is one of the most important factors in the pathogenesis of SHPT, i.e. renal osteodystrophy (11).

A study by Kwalkarf et al concluded that dialyzed patients with phosphorus > 6.5 mg/dL compared to those with 2.4 – 6.5 mg/dL increased the relative risk of sudden death by 20 %. Also, the relative risk of death due to unknown causes was 25% higher in patients with serum phosphorus > 6.5 mg/dL compared to the Reference Group (12) in the same study.

Although no statistically significant relationship between PTH and phosphate levels was found in our study, the presence of hyperphosphataemia in the SHPT positive group was seen in 68% of patients. Phosphorus correction can be achieved by taking a phosphorus binder and a suitable diet, which largely depends on the education and discipline of the patient.

The results showed that patients who did not use vitamin D analogues or calcimimetics had an average decrease in Ca levels by 0.70 mmol/L, while the other two groups of patients had an increase in its mean value. More precisely, in the group of patients who used calcitriol, this indicator increased by 0.09 mmol/L, while in the group of patients who used paricalcitol or cinacalcet, it increased by 0.14 mmol/L.

Ganesh showed in his study that women who regularly consumed dairy products in recommended amounts during childhood had fewer bone fractures, both before and after puberty. A healthy and balanced diet with an intake of additional amounts of calcium, vitamin D, which are essential elements that determine bone mass and other nutrients that are necessary for the normal functioning of the body, is key for healthy and solid bones (13).

In their research, Melton and colleagues point out that lifestyle factors such as adequate nutrition are very important for bone health (14).

Research by Hans showed that thinner girls in their early twenties, who have an inadequate diet and who are likely to be on a frequent diet, have lower bone mineral density. A lower femoral fracture rate compared to rural populations was found, which was associated with the difference in intake of calcium-rich foods as well as increased physical activity (15).

In our study, the average reduction in phosphorus was almost identical in non-calcimimetic subjects and cinacalcet subjects. We conclude that patients treated with vitamin D or calcimemetics experienced a slight decrease in blood phosophores.

The results of this study showed that the self-assessed sense of health of the patients after physical therapy improved in all parameters related to physical and emotional health, given that the study included patients of both sexes, different ages, and different socioeconomic status.

There are a number of unchanging and variable risk factors that can increase or decrease the risk of developing bone mineralization disorders and bone fractures. The influence of some factors on the occurrence of mineralization disorders is known and confirmed by appropriate tests, however for some of the factor's data are insufficient or contradictory. Komenda and colleagues in the study came to the conclusion that significant risk factors for fractures are disruption of bone mineralization of negative values of T and Z score (16). In our research by objectively measuring bone mineral density in patients on the chronic hemodialysis program, we give insight into the importance of physical manual exercises in reducing the occurrence of osteoporosis.

The key factor in the prevention and treatment of bone mineral disorders in patients with HBB is the maintenance of serum calcium and phosphate within normal limits, i.e. the maintenance of PTH at optimal values for patients with HBB, for which there are several ways. Diet is one of the basic measures for maintaining adequate serum calcium and phosphate levels. Healthy people consume 1.0 – 1.3 g of phosphorus per day. Dialysis patients should take a daily dose

of 400 to 800 mg to prevent hyperphosphataemia. The downside of a low-phosphorus diet is that it is also associated with reduced protein intake and increases the possibility of developing malnutrition.

The best effect on the monitored parameters was shown by combinations of exercises that included musculature strengthening exercises, aerobics, weight exercises and high-intensity exercises.

The key to the success of rehabilitation is the early start of treatment, motivation of the patient, continuity of treatment after recovery, and early prevention and treatment of the resulting complications with an adequate selection of kinesiotherapy procedures and other physical-therapeutic procedures. There are aggravating circumstancesWhen all this is applied to patients who are on a chronic hemodialysis program, First of all, care must be taken not to cause a violation of the vascular access (central venous catheter or arterio-venous fistula).

5. Conclusion

Based on the results of this paper, we can conclude the following

- The study showed that the onset of osteoporosis, not the occurrence of fractures, reduces the health costs resulting from the disability of patients.
- Rehabilitation in the course of impaired bone mineralization and existing muscular hypotrophy plays a large role in the patient's recovery process and return to daily activities.
- Patients on hemodialysis need daily exercises that should be carried out with a physiotherapist while the patient is on hemodialysis, and independent exercise in home conditions. First of all, patients need to be educated about the importance of kinesitherapy as well as the way of independent exercise.
- The use of exercises in patients who are on a chronic hemodialysis program is aggravating circumstances. First of all, care must be taken not to cause a violation of the vascular access (central venous catheter or arterio-venous fistula).

Compliance with ethical standards

Disclosure of conflict of interest

All authors of the manuscript have no conflict of interests to declare.

Statement of informed consent

No information about any individuals.

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