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Tittle: Six-month Physical Activity versus Sclerostin and Interleukin 6 Concentration in Patients Receiving Renal Replacement Therapy by Hemodialysis – pilot study

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Abstract

Abstract: *Background and Objectives:* Chronic kidney disease and renal replacement therapy are associated with reduced physical activity, which may result in the presence of mineral-bone disorders and an increase in inflammation markers. The aim of the study was to assess the relationship between the performance of daily physical activity, expressed in the number of steps performed by patients undergoing hemodialysis and the concentration of selected biochemical parameters (SCL, IL-6). *Materials and Methods*: The study involved 33 patients aged 59.8 ± 9.8 years from the dialysis station at the Department of Nephrology, Transplantology and Internal Medicine PUM. Group C consisted of 30 people aged 54.9 (9.37), with GFR over 60 mL/min/1.73m. The study group was divided into S-N and N-S. Participants of the S-N group were assigned the task of performing the appropriate daily number of steps, and the N-S group was to perform spontaneous physical activity. The tasks were replaced after the third month of the research project. Physical activity was measured with pedometers. Anthropometric and biochemical parameters were assessed at baseline, after the third and sixth month of the study. Descriptive statistics, intergroup comparisons using Mann-Whitney U or Kruskal-Wallis tests and Spearman correlation analysis were performed. The level of significance was set at $p \leq 0.005$. *Results:* Patients from the S-N and N-S groups compared to group C performed significantly fewer steps in the 0-3 month and 4-6 month periods. In the S-N group, with an increase in steps performed in the period of 4-6 months, sclerostin levels dropped in the 6th month. In group C, the concentration of SCL and IL-6 decreased with the increase in the number of steps taken. Only in group C the waist circumference decreased with the increase of the number of steps performed. *Conclusions:* Patients receiving renal replacement therapy by hemodialysis showed significantly lower physical activity compared to people without kidney disease. Performing bigger number of steps can lower sclerostin levels in hemodialysis patients.

Key words: physical activity, hemodialysis, sclerostin, interleukin 6.

Introduction

Chronic Kidney Disease (CKD) is a major public health problem associated with reduced motor activity. This may result in the occurrence of mineral and bone disorders and an increase in the concentration of inflammation markers [1].

The key role in regulating bone mass and inhibiting anabolic processes of bone formation plays, among others sclerostin – a glycoprotein encoded within chromosome 17 (region 17q12–q21) in the proximity of the SOST gene [2,3,4]. Mechanical stress is a key regulator that controls bone formation and remodelling involving osteocytes. An increase in concentration of sclerostin (SCL) has been observed from stage 3 of CKD. In patients with end stage renal disease, it is several times higher compared to the population with normal renal function [5–10].

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The occurrence of inflammation and reduced muscle clearance is associated, among others with an increase in the concentration of interleukin 6 (IL–6) – a pleiotropic cytokine (a 26 kDa protein) encoded by a gene located on the short arm of chromosome 7 (7p15–p21) [11–13]. The increase in IL-6 concentration occurs already in the early stages of CKD, and reaches a significantly higher level in patients treated with hemodialysis [14, 15].

Deterioration of health, malaise and treatment with hemodialysis makes it difficult for patients to perform physical exertion. In addition, the group of patients treated with renal replacement therapy usually has a negative attitude towards physical exertion and cooperation with them in this aspect is extremely difficult. It is important to encourage patients undergoing hemodialysis to physical therapy and modification of their lifestyle by increasing the attractiveness of exercise, monitoring physical activity and highlighting the benefits of regular exercise [16-19].

The available literature lacks comparative studies on the relationship between regular physical activity and the value of interleukin 6 and sclerostin concentration in patients treated with hemodialysis. Therefore, it is justified to supplement these reports. The topic requires in-depth research and a comprehensive approach to the problem.

The aim of the study was to assess the effect of regular six-month physical activity measured by the number of steps on the plasma concentration of sclerostin and interleukin 6 and selected anthropometric parameters in the group of patients receiving renal replacement therapy by hemodialysis.

Materials and methods

Group characteristics

The study included 34 patients treated with renal replacement therapy by hemodialysis, with complete absence of diuresis for at least three months, and with a frequency of three hemodialysis sessions a week. The mean duration of a single hemodialysis session was 242.6 ± 25.2 min (X ± SD), and the average duration of hemodialysis treatment was 56 months.

Table 1. Basic characteristics of the study group in terms of duration and number of HD

	N-S (N=16)	**S-N (N=17)**	**B (N=34)**	***P*-value**
Duration of HD session (min)				0.6788[1]
avg. (SD)	244,1 (26,2)	241,4 (25,1)	242,6 (25,2)	

	range	180,0-275,0	180,0-275,0	180,0-275,0	
	median	250,0	250,0	250,0	
Number of HD (wk)					-
	avg. (SD)	3,0 (0,0)	3,0 (0,0)	3,0 (0,0)	
	range	3,0-3,0	3,0-3,0	3,0-3,0	
	median	3,0	3,0	3,0	
Duration of HD (mth)					0.2477[1]
	avg. (SD)	59,5 (33,3)	52,8 (40,7)	56,0 (37,0)	
	range	22,3-144,1	28,6-173,3	22,3-173,3	
	median	51,0	37,5	42,4	

[1]Mann-Whitney U test, **S-N** – study group with 0-3 intervention; **N-S** – study group with 4-6 intervention; **B** – study group; **HD** – hemodialysis; **duration of HD** – duration of complete renal replacement therapy by hemodialysis; **wk** – weekly; **mth** – months; **avg.** – arithmetic mean; **SD** – standard deviation; **range** – (minimum – maximum); **p-value** – statistical significance.

The control group was selected from the general population, reporting at follow-up visits at a family physician office. The control group was tested for renal function. A general urine test and morphology were performed, the levels of creatinine, urea and total proteins were determined and the glomerular filtration rate (GFR) was calculated. 31 people with GFR over 60 mL/min/1.73 m^2 were randomly qualified for the study.

The study group was selected based on qualification and disqualification study criteria for the study. The criteria qualifying for the research project were: written consent to participate in the study, complete absence of diuresis, inclusion in the renal replacement therapy by hemodialysis program for at least 3 months (with frequency of three times a week), age over 18 years. The criteria disqualifying for participation in the research project were: lack of consent to participate in the study, musculoskeletal disorders preventing participation in the study, cardiovascular diseases preventing participation in the study, not correctable vision disorders, poorly controlled diabetes (HbA1c levels of over 8% for 3 months), senile dementia, depression or other mental illnesses; cancer.

Patients with renal replacement therapy by hemodialysis (29 men, 14 women) were qualified for the study (Figure 1), 11 people (5 women and 6 men) did not agree to participate in the research project, justifying this decision with their reluctance to perform physical activity.

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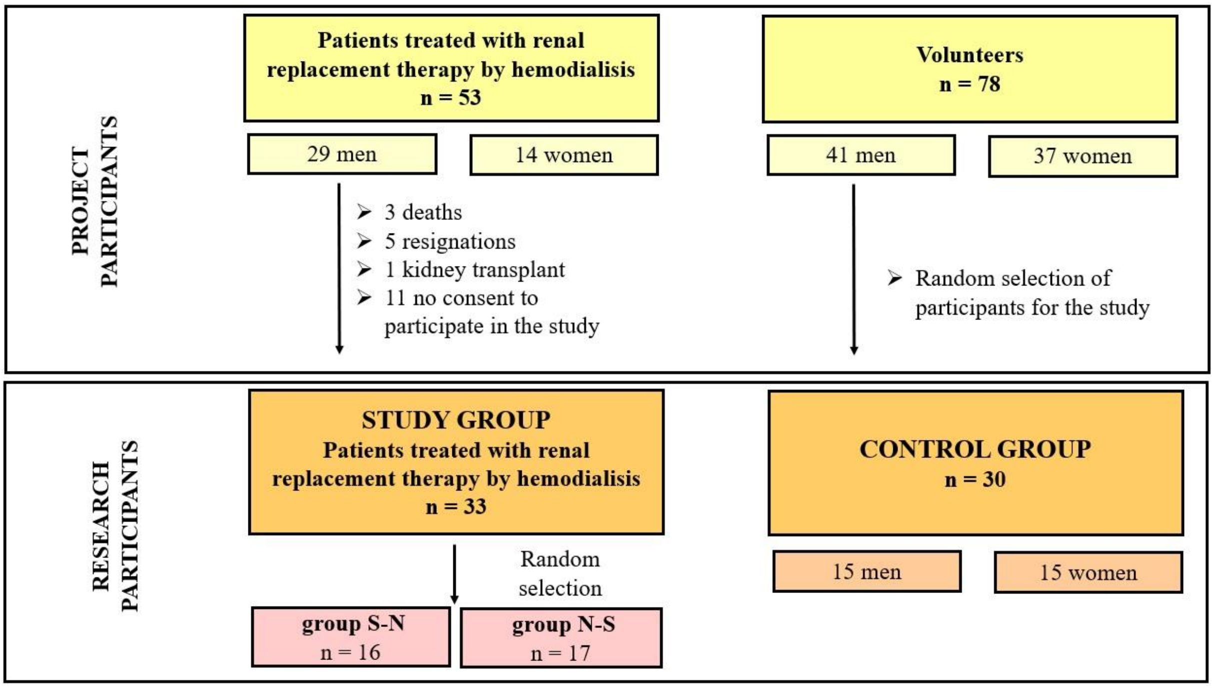
Three people (1 man, 2 women) died during the research project, one man had a kidney transplant, and 5 people (1 man, 4 women) resigned from the participation in the study. Eventually, 33 people (20 men and 13 women) completed the study. Patients were randomly divided into groups S-N (n=16) and N-S (n=17) depending on the intervention given Table 1.

The control group was also selected based on the inclusion and exclusion criteria for the research project. The inclusion criteria were: consent to participate in the study, age over eighteen, normal renal function. The exclusion criteria were the same as in the study group.

78 people (41 men, 37 women) volunteered to participate in the research project (Figure 1). Eventually, 30 people (15 men, 15 women) were randomly qualified for the study.

Figure 1. Research qualification scheme



There were no statistically significant differences in the mean values of systolic and diastolic pressure and pulse between the groups. Patients selected for the study did not declare any other chronic diseases. No statistically significant differences were observed between groups B and C in terms of gender, age, body weight, BMI and waist circumferences (Table 2). The number of hospitalizations was significantly higher in the study group than in the control group.

Table 2. Basic characteristics of the study group and the control group

Parameter	**Study group (n=33)**	**Control group (n=30)**	**P-value**

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	X (SD)	Range	Me	X (SD)	Range	Me	
Age [years]	59.4 (9.8)	29.0-78.0	60.3	54.9 (9.37)	35.0-73.0	59.5	0.1382
Body weight [kg]	74.9 (14.8)	64.5-81.5	75.6	78.2 (16.12)	65.8-91.3	79.4	0.4692
BMI [kg/m^2]	25.2(4.3)	22.1-28.8	25.1	26.2 (4.22)	24.1-29.8	30.0	0.3297
Waist circumference [cm]	96.2 (14.7)	88-105	95.9	91.3 (16.3)	83-100	89.0	0.0769
Hip circumference [cm]	101.5 (10.5)	73.0-123.0	102.1	102.5 (7.5)	91.0-120.2	103.1	0.8639
WHR	0.9 (0.1)	0.7-1.1	0.9	0.8 (0.1)	0.7-1.1	0.9	0.0105*
Hospitalizations	2.8 (2.7)	0.0-15.0	2.4	0.2 (0.5)	0.0-3.0	0.0	0.00023*

BMI – body mass index; WHR – waist hip ratio; X – arithmetic mean; SD – standard deviation; Me – median; Range – (minimum–maximum); P-value – statistical significance; * – statistically significant parameter.

The course of the study

The study subjects were given Beurer AS 50 pedometers. Data such as date, time, body weight, step length have been entered into the patient's device and sensitivity of the device was set (in the study group S-N and N-S on a day without hemodialysis).

Participants in both study and control group were asked to perform only physical activity, which can be measured with a pedometer 3 months before the start of the research project and during its duration.

The subjects belonging to the S-N, N-S and C groups were trained to use the pedometer. Participants in the research program were required to wear the device all the time in one place (on a belt, on a chain or in a pocket), throughout the whole duration of the study, excluding sleep and bath time. Depending on the assignment to a given group (N-S, S-N, K), the subjects were given an intervention (Table 3).

Table 3. Characteristics of interventions assigned to individual groups.

	Study period 0-3 months	Study period 4-6 months

Group S-N (n=18)	wearing a pedometer, performing a minimum of 3,000 steps on dialysis-free days, and the maximum number of steps possible on hemodialysis days	wearing a pedometer, not paying attention to the number of steps performed
Group N-S (n=16)	wearing a pedometer, not paying attention to the number of steps performed	wearing a pedometer, performing a minimum of 3,000 steps on dialysis-free days, and the maximum number of steps possible on hemodialysis days
Group C (n=32)	wearing a pedometer, performing normal daily physical activity	wearing a pedometer, performing normal daily physical activity

Group S-N – study group with an intervention of 0-3 months; N-S group – study group with an intervention of 4-6 months; Group C – control group.

To carry out the research project, the consent of the Bioethical Committee No. KB-0012/40/13 of 4 March 2013 was obtained. Data was collected three times: upon study inclusion (E0), after the third month (E3) and after the sixth month of the research (E6).

At the time of joining the study, patients were asked to complete an original questionnaire prepared for the purposes of the study, containing demographic questions about the participant's health and lifestyle.

Selected biochemical blood measurements (determination of sclerostin and interleukin 6 levels) and anthropometric measurements were taken at three time points (E0) – the baseline measurement at the start of the study, (E3) – after three months, (E6) – after 6 months, except for height measurement (E0). In the study group, measurements were taken 20-30 minutes after completion of hemodialysis in an examination room.

Patient height was measured. It was measured from the floor to the head vertex with a height meter attached to an electronic scale. Body weight was measured with an accuracy of 10g using the same electronic scale. Waist and hip circumferences were measured using a centimetrescale body measuring tape. Weight-height proportions were assessed using the BMI (Body Mass Index) [20,21].

The participants of the study and control groups had 2 mL of blood collected. Patients with end-stage renal disease treated with hemodialysis had blood taken from a venous line of the dialysis shunt in EDTA tubes prior to hemodialysis, at the dialysis station at the Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, on the day of periodic blood tests at E0, E3, E6 . The blood samples were centrifuged (4000 rpm for 10 minutes) at 4°C in an MPW-350R centrifuge. Plasma samples were divided into 1.0–mL aliquots, placed into two separate eppendorf tubes (1.0 mL Eppendorf Quality™ Safe-Lock tubes, colourless) and immediately frozen. Until the determination, the samples were stored at -170°C. Freshly thawed portions were used for the laboratory analysis. The assessment of concentrations of IL-6 and sclerostin in plasma was performed with the use of a commercially available ELISA kit (Quantikine High Sensitivity ELISA kit, R&D Systems Europe). The concentration of sclerostin (SCL) and interleukin 6 (IL-6) is given in picograms per millilitre [pg/mL].

Statistical Analysis

All statistical calculations were performed using the statistical package STATISTICA (data analysis software system version 12.0).

Quantitative variables were characterized by the arithmetic mean, standard deviation, median, minimum and maximum values. Qualitative variables were presented by absolute counts and percentages. Normal distribution was tested using the Shapiro Wilk test. The Mann-Whitney U test was used to assess the significance of differences between the two groups. The significance of differences between more than two groups was verified by the Kruskal-Wallis test. In the event of statistically significant differences between the groups, post hoc tests were used (Dunn's test). Correlation analysis by calculating correlation coefficients or Spearman's rank coefficients was performed to determine the relationship of strength and direction between variables. In all calculations, the level of significance was set at $p \leq 0.05$.

Results

The research involved an analysis comparing the study groups and control group in terms of the number of steps performed (Table 4). It was observed that all groups showed statistical significance between the number of steps performed, both during 0-3 and 4-6 months. Post-hoc analysis also showed the relationship between individual groups in the analysis of the tested parameter.

Table 4. Comparative characteristics of the study groups (N-S; S-N) and control group by number of steps

		N-S (N=16)	S-N (N=17)	C (N=32)	*P*-value
Steps 0-3 mth	avg. (SD)	3 786,2 (2 216,3)	4 345,9 (1 410,3)	6037,8 (771,7)	0,0001[1] [2]0,0001[a] [2]0,0024[b]
	range	1444,2-9 596,3	2377,2-6 652,0	5080,3-8 671,6	
	median	3400,8[a]	4073,1[b]	5862,1[a,b]	
Steps 4-6 mth	avg. (SD)	4691,1 (2532,5)	3817,5 (1421,0)	6162,9 (651,2)	0,0001[1] [2]0,0003[a] [2]0,0001[b]
	range	2500,4-11 998,0	1538,7-6 687,1	5213,5-7 781,5	
	median	4 110,8 [a]	3460,1[b]	6133,3 [a,b]	

The correlation between the number of steps in the study and control groups and the concentration of sclerostin and interleukin was examined after 3 and 6 months. It was shown that in the control group both SCL and IL-6 levels negatively correlated with the number of steps both after 0-3 months and after 4-6 months. Analyzing the study groups, it was shown that SCL concentration negatively correlated with the number of steps after 4-6 months, but this correlation was observed only in the S-N group (Table 5).

Table 5. Correlation analysis of the number of steps in the study and control groups and the concentration of sclerostin and interleukin after 3 and 6 months (R – correlation coefficient)

			N-S (N=16)	S-N (N=17)	C (N=32)
SCL	Steps 0-3 mth	R	-0,24	-0,34	-0,79
		P-value	0,3743	0,1681	0,0001
	Steps 4-6 mth	R	-0,01	-0,65	-0,65
		P-value	0,9569	0,0037	0,0001
IL-6	Steps 0-3 mth	R	-0,34	-0,47	-0,39
		P-value	0,2001	0,0504	0,0281
	Steps 4-6 mth	R	-0,15	-0,26	-0,48
		P-value	0,5792	0,3033	0,0059

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Correlations between the number of steps in the study and control groups were also analyzed in terms of age, body weight, BMI (Table 6). It was shown that in the control group waist circumference and age of patients negatively correlated with the number of steps both after 0-3 and 4-6 months.

Table 6. Correlation analysis of the number of steps in the study and control groups in terms of age, body weight, BMI (R – correlation coefficient)

Steps		Group S-N		Group N-S		Group C	
		3 mth	6 mth	3 mth	6 mth	3 mth	6 mth
Body weight	R	0,14	0,05	0,12	-0,07	-0,32	-0,23
	P-value	0,5758	0,8292	0,6522	0,7907	0,0720	0,2117
BMI	R	0,27	0,20	0,22	-0,01	-0,32	-0,25
	P-value	0,2798	0,4233	0,4117	0,9569	0,0744	0,1753
Waist circumfe rence	R	0,19	0,29	0,19	-0,06	-0,41	-0,40
	P-value	0,4500	0,2446	0,4772	0,8156	0,0185	0,0237
Age	R	-0,38	-0,14	-0,49	-0,25	-0,42	-0,38
	P-value	0,1167	0,5859	0,0553	0,3478	0,0157	0,0320

Discussion

The literature describes many benefits of exercising and increasing regular physical activity for the health and well-being of patients with chronic kidney disease [22-25]. Despite this fact, the level of physical activity in this group of patients is significantly lower compared to people with normal renal function [26.27]. The presented work showed that despite the introduced intervention, the total number of steps performed was significantly lower in periods of 0-3 and 4-6 months in groups S-N and N-S compared to C. Similar relationships have been found in publications of other authors [28, 29]. This could be influenced by complications associated with chronic kidney disease and renal replacement therapy, as well as by a lack of motivation to exercise [30-33].

There are many works in which, similarly to the conducted research project, pedometers or accelerometers were used in AF studies as well as tools for monitoring and motivating of renal replacement patients to exercise [34-37]. It is important that in the presented studies out of 53 patients qualified by a nephrologist only 43 persons entered the study. In the study group there were no patients who stopped performing the intervention. The only exception resulting in

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cessation of physical activity were independent factors, such as kidney transplantation to a patient treated with renal replacement therapy or death. Prescribed physical exercise performed by hemodialysis patients was completely safe and did not adversely affect their health.

Mechanical stress is a key regulator that controls bone formation and remodelling involving osteocytes. Sclerostin is produced and released by mature osteocytes on the bone surface, where it inhibits osteoblast transmission and signals activating differentiation from mesenchymal cells, thereby inhibiting new bone formation. There are few publications in the literature on the effect of physical training on the concentration of SCL in peripheral blood [38-40]. In turn, Frings-Meuthen et al. when examining SCL concentration in young healthy men, observed an increase in the concentration of this protein after 14 days of immobilization in the supine position [41]. These observations were confirmed in the work of Gaudio et al. who checked the influence of immobilization on SCL concentration in postmenopausal women [42].

For example, Ardawi et al. assessed the impact of walking or exercise on SCL concentration and showed that the concentration of this protein decreased with increasing duration of physical activity [40]. It can therefore be concluded that the concentration of sclerostin in the blood may drop after properly planned physical training. In addition, this protein plays a significant role as a stimulator of osteoblastogenesis, and its concentrations or differences in serum concentrations can be considered a potentially important parameter in monitoring and predicting the further course of therapy.

In this study, for the first time, an attempt was made to assess the relationship between regular physical activity expressed in the number of steps and sclerostin concentration in patients receiving renal replacement therapy by hemodialysis. A negative correlation between SCL level in blood after the 6th month of the research project and the total number of steps performed in the S-N and C groups after 4-6 months was presented. It was also shown that the concentration of SCL in S-N group decreases with an increase of the number of steps performed on HD-free days over a 4-6 month period.

In the available literature, no research was found that would be based on a similar analysis in the group of patients treated with hemodialysis. Preliminary studies have shown that there may be a relationship between physical activity expressed in the number of steps and sclerostin concentration in patients treated with hemodialysis. It is worth considering performing similar studies not only in the group of hemodialysis patients, but also among patients treated with other methods of renal replacement therapy.

IL-6 levels are often elevated in patients with CKD, especially those treated with dialysis. Lack or reduced physical activity may result in an increase in inflammation among people with

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chronic kidney disease [43]. In turn, regular exercise is particularly important in people with chronic kidney disease because it has anti-inflammatory effects [44].

Many studies have been published on the relationship between physical activity and IL-6 concentration in hemodialysis patients, but no studies evaluating the correlation between the number of steps performed and the concentration of this cytokine in hemodialysis patients have been found.

This study evaluated the relationship between regular physical activity expressed in the number of steps and IL-6 concentration in hemodialysis patients. The concentration of this cytokine did not change significantly in relation to the number of steps performed in the examined groups. Similar results were obtained by other authors who assessed the effect of exercise performed during the procedure on IL-6 concentration [45-59]. Prescribed physical activity in the group of patients treated with hemodialysis may have been too short, the occurrence of chronic inflammation or high individual variability among patients on dialysis could have affected the absence of significant changes in IL-6 levels. In the control group, the IL-6 concentration decreased with the increase in the number of steps at all time points (after 3 and 6 months of studies). Similar results confirming the relationship between physical activity and the concentration of inflammation markers were obtained in other studies [50-52]. Adequate physical activity reduces the level of inflammation markers.

As a result of the analysis, no significant correlations were found between performing the intervention and body weight, as well as BMI in the examined groups. Similar results were obtained by Dungey et al. who analyzed the impact of regular exercise during hemodialysis on anthropometric parameters [49].

The study showed that there is a negative correlation between the total number of steps performed and waist circumference in the control group. Research by Huang et al. showed that people who exercise systematically have a lower waist circumference [53].

There are few publications assessing the impact of exercise on anthropometric parameters in hemodialysis patients, such as BMI and body weight [54], which may be due to problems arising from the overhydration of patients in the period between dialysis.

Regular physical activity positively affects the physical and mental functioning of a person. Studies have shown that with age deterioration of the body's cognitive functions, sarcopenia or a decrease in bone mineral density may occur. Age is a good predictor of health condition. However, there is a large individual variability showing that some elderly people are in good health, while others are weak or disabled [55]. In this study, a negative correlation between age and physical activity, expressed in the number of steps was confirmed only in the control group.

The absence of these relationships among the participants of the study group may be due to their chronic kidney disease, conducted renal replacement therapy or post-dialysis complications, such as fatigue.

Conclusions

The studies showed that intensified, regular physical activity expressed in the number of steps may have an impact on lowering the concentration of the biochemical parameters tested (sclerostin, interleukin 6), but it does not affect the BMI, body weight, waist circumferences in the group of patients treated with hemodialysis. In turn, in the group of patients without end-stage kidney disease, a bigger number of steps performed is associated with lower values of both interleukin 6 and sclerostin levels. The key factor is to encourage patients with end-stage renal disease who are being treated with hemodialysis to exercise regularly, as they show significantly lower physical activity compared to patients with normal renal function.

Limitations

The obtained results were influenced by the worsening condition of patients with CKD, renal replacement therapy and the occurrence of various comorbidities. In the study of patients with chronic kidney disease treated with hemodialysis, it was difficult to find people willing to participate in the project assessing their AF. It was also necessary to choose physical activity in a way, which allowed the participants to be able to perform the recommended intervention. The size of the study group during the research project decreased for independent reasons, such as kidney transplants and deaths among project participants. In the study, the psychological aspect of having a pedometer could have made the hemodialysis patients more willing to perform physical activity, even when they did not have the recommended intervention. This could have been an independent factor influencing the course of the study. In the continuation of research, it is necessary to increase the size of the study group, which would allow a more accurate analysis of these relationships.

Conceptualization, A.T.S./G.D./M.M.M.; Data Curation, A.T.S/V.D.; Investigation, A.T.S./G.D.; Formal Analysis, A.T.S./A.R.; Software A.R/K.S; Methodology, A.T.S/V.D./A.R.; Project Administration, A.T.S.; Writing – Original Draft Preparation, A.T.S.; Writing – Review & Editing, A.T.S/G.D./M.M.M./V.D./K.C./A.R./I.R./; Supervision, G.D.

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