

Metabolic bone changes after intradialytic resistive exercise in regular haemodialysis patients

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Abstract

Introduction. Mineral bone disease is a crucial factor that contributes to mortality and morbidity in haemodialysis patients. Intradialytic resistance exercise training can be valuable in stimulating bone formation. The aim of this study was to evaluate the metabolic bone changes after intradialytic resistive exercise training in regular haemodialysis patients.

Methods. The study involved 60 patients on regular haemodialysis, aged 20–60 years. The patients were divided into 2 groups: a high parathyroid hormone group (parathyroid hormone over 800 pg/ml) and a low parathyroid hormone group (parathyroid hormone below 200 pg/ml), both groups randomly assigned into study and control groups. They received intradialytic resistive exercise 3 times per week for 3 months. Calcium, phosphorus, and parathyroid hormone were evaluated before and after the exercise period.

Results. The training protocol proved to be effective in improving bone metabolism parameters, as there were statistically significant differences in the high parathyroid hormone exercise group. Parathyroid hormone and phosphorus decreased and calcium increased ($p = 0.001$, $p = 0.012$, and $p = 0.025$, respectively). In the low parathyroid hormone exercise group, phosphorus decreased significantly ($p = 0.030$) and calcium increased, although not significantly ($p = 0.111$), while parathyroid hormone non-significantly increased in the exercise group ($p = 0.770$), with a significant increase in the control group ($p = 0.007$). These results supported the positive effects of intradialytic resistive exercise in improving bone metabolism.

Conclusions. Intradialytic resistive exercise training improves bone metabolism in haemodialysis patients.

Key words: haemodialysis, intradialytic resistive exercise, parathyroid hormone, bone metabolism

Introduction

Patients suffering from chronic kidney disease (CKD) significantly exhibit calcium and phosphorus metabolism disorders, reduced activation of vitamin D, and elevated serum levels of parathyroid hormone (PTH). This usually leads to mineral and bone metabolism disorders [1]. Haemodialysis is typically administered 3 days a week for 3–6 hours per visit; this routine continues throughout the life of patients or until kidney transplantation is successful [2]. Moreover, dialysis requires immobilization for 12–18 hours a week, thereby directly contributing to sedentary activity, which can further aggravate haemodialysis patients' medical condition [3].

Among haemodialysis patients, there are several approaches used to promote the health of bone; physical training tends to be one of them. In addition, physical training and exercise can improve various measures of physical function in patients with CKD [4].

PTH is the main hormone that controls the metabolism of calcium and is involved in catabolic and anabolic bone acts. Physical exercise can affect PTH concentration [5].

While there are many concerns about the beneficial effect of exercise during haemodialysis, other researchers predict the benefits of both dialysis and exercise through intradialytic exercise [6]. Bessa et al. [7] reported that intradialytic exer-

cises were successful, safe, and advantageous for patients with haemodialysis.

There is a gap in knowledge about maintaining bone quality and preventing bone loss, as well as the role of exercise in haemodialysis patients. The purpose of the study was to evaluate the metabolic bone changes after intradialytic resistive exercise in regular haemodialysis patients.

Subjects and methods

Design

This study was designed as a randomized, controlled, parallel trial. The measured variables were calcium, phosphorus, and PTH concentrations. The study was conducted between July 2018 and July 2019; data were collected twice: before and after the exercise intervention.

Participants

A total of 60 patients (24 males and 36 females) on regular haemodialysis were recruited from the Nephrology and Dialysis Centre, Faculty of Medicine, Cairo University, Egypt. The subjects were aged 20–60 years. They were evaluated for their eligibility to participate in the study. All patients were informed about the purpose of the study.

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The inclusion criteria were as follows: having received haemodialysis for at least 6 months 3 times per week, either gender, age of 20–60 years, no participation in any exercise program. The potential participants were excluded if they met one of the following criteria: history of malignancy or autoimmune diseases, uncontrolled arterial hypertension, deep vein thrombosis, ischaemic cardiomyopathy, amputation, epilepsy, acquired immunodeficiency syndrome, arrhythmias, precordial pain, femoral fistula, severe dyspnoea, excessive pallor, uncontrolled diabetes, use of medications that might influence PTH, calcium, or phosphorus levels, orthopaedic or neurological compromising, reasons to be in a catabolic state (including human immunodeficiency virus), cognitive alterations affecting the participation in the program.

Randomization

Eligible patients were divided into 2 groups. Group 1 (low PTH group, PTH below 200 pg/ml) involved 20 patients, randomly assigned by using a computer-based randomization program into 2 equal and matched subgroups (group 1a, study group, received a program of intradialytic resistive exercise in addition to the haemodialysis sessions, and group 1b, control group, received usual haemodialysis sessions only). Group 2 (high PTH group, PTH over 800 pg/ml) involved 40 patients, randomly assigned by using a computer-based randomization program into 2 equal and matched subgroups (group 2a, study group, received a program of intradialytic resistive exercise in addition to the haemodialysis sessions, and group 2b, control group, received usual haemodialysis sessions only). The patients were blinded about which group they were allocated to by an independent researcher. There was no dropping out of subjects after randomization.

Intervention

All participants were given a brief demonstration about the study and the tasks to be performed. The study groups received a program of intradialytic resistive exercise training 3 times a week for 12 weeks in addition to the haemodialysis sessions, and the control groups received usual haemodialysis sessions only.

Instrumentation

The Cobas® 6000 analyser series (Roche Diagnostics, Mannheim, Germany) was used for biochemical analyses of calcium, phosphorus, and PTH. Sand bags of various weights served to determine the one-repetition maximum (1RM) for each exercise; they were also applied in the resistive training program.

Procedures

Evaluation procedures

Blood samples were collected before and after 12 weeks of intradialytic resistance exercise from each patient in the morning, after fasting overnight, and before the dialysis session; blood was collected in BD Vacutainer® EDTA tubes. The collected blood was centrifuged at $3000 \times g$ for 15 minutes to get plasma, then aliquoted into tubes and kept at -80°C until analysis. Serum concentrations of calcium, phosphorus, and PTH were analysed with the Cobas® 6000 analyser series [8, 9].

Sand bags of several weights (0.5, 1, and 2 kg), made in China, were used to determine 1RM for the exercise training, and also applied in the resistive training program. The 1RM is simply defined as the maximal weight that an individual can lift for only one repetition [10, 11].

Treatment procedures

The resistive exercise program consisted of 3 parts. Warming-up and cooling-down lasted for 3–5 minutes and consisted in lower limbs active free exercise from the supine position. The main part was the resistive exercises of lower limbs from the supine position using weights in the form of sand bags.

Training parameters

The intervention groups performed exercise training during the first 2 hours of haemodialysis sessions using free leg weights. The patient assumed a supine lying position on the treatment plinth and performed the exercises for every lower limb separately while the other limb was supported in an extension position. Resistance was placed at the malleoli level in the distal third of the leg. The program constituted of 2 resistive exercises: (1) hip and knee flexion and extension with dorsiflexion of the foot (the patient performed flexion followed by extension of the lower limb); (2) hip abduction and adduction (the patient performed abduction followed by adduction of the lower limb). Both exercises were resisted by weights, with 40–50% of the 1RM load [11].

The participants performed trials without any load for adaptation. Further, they attempted their trials using 0.5 kg, with gradually increasing weight by 0.5 kg, until failure occurred. The 1RM load was evaluated every 2 weeks and adjusted for each patient. The training program consisted of 3 groups of 15 repetitions in every lower limb with a 1-minute rest between the groups and a 2-minute rest between the exercise types, 3 times per week for 12 weeks.

Statistical analysis

The Statistical Package for the Social Sciences computer program (version 20 for Windows; SPSS Inc., Chicago, USA) was used for the data analysis. Comparisons between mean values of the subject's characteristics for the 2 groups (groups 1 and 2) and each subgroup were performed with ANOVA. MANOVA was applied to compare within-group effects for the studied variables. Data were expressed as mean \pm SD. The significance level was set at $p < 0.05$.

Ethical approval

The research related to human use has complied with all the relevant national regulations and institutional policies, has followed the tenets of the Declaration of Helsinki, and has been approved by the Ethics Committee of the Faculty of Physical Therapy, Cairo University (P.T.R.E.C/012/001266). The study protocol was registered at Pan African Clinical Trials Registry (PACTR201812776161905).

Informed consent

Informed consent has been obtained from all individuals included in this study.

Results

Demographic data of the patients

As shown in Table 1, the paired *t*-test revealed that there was no statistically significant difference between the sub-groups in the patients' general characteristics ($p > 0.05$).

Effect of intradialytic exercise in low PTH groups

As presented in Table 2, there was no statistically significant difference in the mean values of PTH between pre- and post-study assessments within group 1a (study group of low PTH) ($p = 0.770$), while there was a statistically significant increase in the mean values of PTH within group 1b (control group of low PTH) between pre- and post-study assessments ($p = 0.007$). Regarding calcium, there was no statis-

tically significant difference between pre- and post-study mean values within any group ($p > 0.05$). With reference to phosphorus, there was a statistically significant decrease in the mean values within group 1a between pre- and post-study assessments ($p = 0.030$), while there was no statistically significant difference within group 1b ($p = 0.517$).

Effect of intradialytic exercise in high PTH groups

As demonstrated in Table 3, there was a statistically significant decrease in the mean values of PTH within group 2a (study group of high PTH) between pre- and post-study assessments ($p = 0.001$), while there was no statistically significant difference within groups 2b (control group of high PTH) ($p = 0.243$). Regarding calcium, there was a statistically significant increase in the mean values within group 2a between pre- and post-study assessments ($p = 0.025$), while

Table 1. Demographic data of patients in both groups

General characteristics	Group 1 (low PTH) Mean \pm SD		<i>p</i>	Significance	Group 2 (high PTH) Mean \pm SD		<i>p</i>	Significance
	Group 1a	Group 1b			Group 2a	Group 2b		
Age (years)	47 \pm 14	47.5 \pm 9.4	0.927	NS	43.1 \pm 12.2	41.5 \pm 12	0.688	NS
Weight (kg)	78.4 \pm 11.5	78.6 \pm 14.3	0.973	NS	75.8 \pm 10.4	76.4 \pm 7.2	0.820	NS
Height (cm)	164.2 \pm 7.7	164.6 \pm 8.9	0.916	NS	161.9 \pm 7	163.2 \pm 7.4	0.571	NS
BMI (kg/m ²)	29.2 \pm 4.6	28.8 \pm 3.5	0.824	NS	28.9 \pm 3.3	28.7 \pm 3	0.901	NS
Hb (g/dl)	10.5 \pm 1.7	10.8 \pm 1.8	0.703	NS	10.3 \pm 1.2	10.6 \pm 1.6	0.809	NS
Urea (mg/dl)	138.7 \pm 40	128.8 \pm 35.9	0.569	NS	135 \pm 40.9	126.3 \pm 33.7	0.880	NS

PTH – parathyroid hormone, BMI – body mass index, Hb – haemoglobin, NS – non-significant

Table 2. PTH, calcium, and phosphorus values in low PTH groups

Low PTH group	Pre-study Mean \pm SD	Post-study Mean \pm SD	Change	<i>p</i>	Significance
PTH (pg/ml)					
Group 1a	155 \pm 58	177 \pm 41	14.2%	0.770	NS
Group 1b	127 \pm 54	351 \pm 111	176%	0.007	S
Calcium (mg/dl)					
Group 1a	7.2 \pm 1	7.8 \pm 0.6	8.3%	0.111	NS
Group 1b	7.6 \pm 0.8	7.6 \pm 1.1	0%	0.978	NS
Phosphorus (mg/dl)					
Group 1a	5 \pm 1.4	3.8 \pm 1.6	-24%	0.030	S
Group 1b	4.6 \pm 1.4	5 \pm 1.8	8.7%	0.517	NS

PTH – parathyroid hormone, S – significant, NS – non-significant

Table 3. PTH, calcium, and phosphorus values in high PTH groups

High PTH group	Pre-study Mean \pm SD	Post-study Mean \pm SD	Change	<i>p</i>	Significance
PTH (pg/ml)					
Group 2a	1416 \pm 490	770 \pm 206	-45.6%	0.001	S
Group 2b	1581 \pm 463	1702 \pm 592	7.7%	0.243	NS
Calcium (mg/dl)					
Group 2a	7.5 \pm 1.2	8.1 \pm 0.7	8%	0.025	S
Group 2b	8.1 \pm 1.2	8.1 \pm 1.2	0%	0.849	NS
Phosphorus (mg/dl)					
Group 2a	5.1 \pm 1.6	4.5 \pm 1.3	-11.8%	0.012	S
Group 2b	5 \pm 1.6	5 \pm 1.5	0%	0.904	NS

PTH – parathyroid hormone, S – significant, NS – non-significant

there was no statistically significant difference within group 2b ($p = 0.849$). With reference to phosphorus, there was a statistically significant decrease in the mean values within group 2a between pre- and post-study assessments ($p = 0.012$), while there was no statistically significant difference within group 2b ($p = 0.904$).

Discussion

The study reported here was conducted with haemodialysis patients in order to evaluate the effect of an intradialytic resistance exercise program on bone metabolism. The results revealed that in the high PTH group, PTH and phosphorus decreased significantly and calcium increased significantly in the exercise group, indicating an improvement in the bone metabolism parameters. In the low PTH group, PTH increased significantly in the control group, with a non-significant increase in the exercise group; calcium increased (although not significantly) and phosphorus significantly decreased in the exercise group, indicating an improvement in bone metabolism.

Parathyroid hormone

Serum PTH levels have been utilized as a surrogate measure of bone turnover, used in combination with serum calcium, phosphorus, and alkaline phosphatase levels to assess, diagnose, and direct the management of CKD mineral and bone disorders [12, 13].

In patients with end-stage renal disease, elevations of parathormone levels are caused by acidosis, calcitriol tolerance, increased blood phosphorus, decreased blood calcium due to reduced synthesis of 1,25(OH)₂D₃ and deficiency of 1-alpha-hydroxylase [14].

Marinho et al. [15] reported that after 2 months of resistance exercise training during dialysis, a substantial elevation in 1,25(OH)₂D₃ was observed in the exercise group, which was proposed to be due to the elevation of its production by the renal 25-hydroxyvitamin D 1-alpha-hydroxylase, likely induced by the resistance exercise [16]. Participants with osteoporosis showed a significant improvement in serum calcium levels after 12 weeks of exercise training. It was stated that the mechanical loading produced by exercise training could be a major contributor in bone mineralization [17].

Since chronic renal failure patients' bones might exhibit parathyroid resistance, the PTH level must be 2–3 times the normal level to keep healthy bone turnover [18]. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative reported in 2003 the recommended treatment guidelines for bone metabolism and disease, which were 150–300 pg/ml for PTH, 8.4–9.5 mg/dl for calcium, and 3.5–5.5 mg/dl for phosphorus [19, 20]. Resistance exercise could be able to lower PTH levels in patients suffering from CKD. The levels of PTH could differ depending on the intensity and duration of the activity after physical exercise [5].

The results agreed with the study by Marinho et al. [21], which showed that after 24 weeks of an intradialytic resistance exercise training program, PTH decreased from 650.7 ± 324.3 to 426.4 ± 238.5 pg/ml in the exercise group.

Also, in the study conducted by Marinho et al. [21], a significant relationship between PTH and femoral bone mineral density was noticed in the exercise group after intradialytic resistance training in haemodialysis patients. PTH levels were high relative to baseline but decreased after the intervention, and the femoral neck improved at the same time.

The findings were also compatible with those of significant improvements in bone remodelling biochemical markers after moderate exercise training [22], and in contrast with the study stating a significant improvement in bone mineral density without bone markers change comprising PTH [23].

Calcium

Serum calcium was stated to significantly contribute as a biomarker to evaluate bone metabolism [24]. The reduction in calcitriol significantly influences the calcium absorbed by intestine, helping to lower serum calcium and stimulate PTH [25, 26]. During periods of intense exercise, endocrine bone regulators such as PTH, vitamin D, and calcium may also be influenced and may enhance bone metabolism [27].

Marinho et al. [21] reported that a negative correlation between serum calcium and baseline serum PTH was found among a haemodialysis exercise group. PTH is responsible for controlling and maintaining the calcium level in the blood [28]. On assessing the influence of exercise on the roles of trace elements in bone health, a study on osteoporosis clarified that participants showed a significant improvement in serum calcium levels after 12 weeks of exercise training [22].

In contrast, a study by Liao et al. [23] revealed that after 3 months of intradialytic exercise, the patients in the exercise group showed significant improvements in inflammatory cytokine levels and 6-minute walk distance, with no obvious differences in biochemical data including calcium and haematocrit.

Phosphorus

Mineral and bone disorder influences most CKD patients and is described by imbalances in serum blood levels of calcium, phosphorus, and PTH [20, 29]. A study performed by Marinho et al. [21] showed that after 24 weeks of intradialytic resistance exercise, serum phosphorus levels decreased from 5.2 ± 1.4 to 4.8 ± 1.6 mg.

In contrast, in a study investigating the effect of intradialytic exercise on bone mineral density, Liao et al. [23] stated that the improvement in bone mineral density was not by changing the metabolism of phosphate or PTH.

Physical training could influence bone health and quality both directly, through mechanical load, and indirectly, through the stimulation of various endocrine axes [30]. Mechanical loads are converted into biological signals that eventually guide bone turnover. Osteocytes sense mechanical loading and transform these signals into a chemical response. After that, the osteocytes release signalling particles that regulate the recruitment of osteoblasts or osteoclasts, leading to the adaptability of bone mass and structure [31]. Physical exercise can modulate levels of bone markers and positively affect bone quality and mass through controlling the production of hormones and cytokines engaged in the process of bone remodelling [32].

Intradialytic resistance exercise had a positive effect on bone metabolism, which was obvious in a significant decrease of PTH values in the high PTH group, and in maintaining it from a significant increase in the low PTH group (within or close to the recommended K/DOQI guidelines values for bone metabolism [19]). Furthermore, the increase in serum calcium (significant in the high PTH and non-significant in the low PTH group) and the significant decrease in serum phosphorus levels could be contributed to the metabolic bone changes after the exercise.

Limitations

Our study has some limitations. The first one is its short period; that is why long duration studies are recommended to assess the long-term effects of intradialytic resistive exercise training in haemodialysis patients. Other limitations could be those related to psychological, physiological, and potential cultural issues.

Conclusions

It was concluded that intradialytic resistive exercise training lasting 12 weeks improved bone metabolism in patients undergoing haemodialysis.

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Disclosure statement

No author has any financial interest or received any financial benefit from this research.

Conflict of interest

The authors state no conflict of interest.

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