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Physical exercise in individuals in hemodialysis: benefits and best indications - systematic review

Exercício físico em indivíduos em hemodiálise: benefícios e melhores indicações - revisão sistemática

Filipe Ferrari[1], Marvyn de Santana do Sacramento[2], Diego Passos Diogo[3], Alan Carlos Nery dos Santos[4], Marcelo Trotte Motta[5], Jefferson Petto[6]

[1]Corresponding author. Social Faculty of Bahia, Federal University of Rio Grande do Sul. Salvador – Porto Alegre, Bahia, Brazil. ORCID: 0000-0001-6929-8392. ferrari.filipe88@gmail.com
[2]Social Faculty of Bahia. Salvador, Bahia, Brazil. ORCID: 0000-0003-0851-9950. marvynsantana@gmail.com
[3]BAHIANA – School of Medicine and Public Health, Adventist Faculty of Bahia, Feira de Santana State University. Salvador – Cachoeira - Feira de Santana, Bahia, Brazil. ORCID: 0000-0001-6395-1549. passosdiogo@hotmail.com
[4]BAHIANA – School of Medicine and Public Health, Salvador University. Salvador - Feira de Santana, Bahia, Brasil. ORCID: 0000-0002-0737-1555. carlos.nery@unifacs.br
[5]Social Faculty of Bahia. Salvador, Bahia, Brazil. ORCID: 0000-0003-4785-3687. trottefisiol@yahoo.com.br
[6]BAHIANA – School of Medicine and Public Health, Social Faculty of Bahia, Salvador University, Adventist Faculty of Bahia. Salvador – Feira de Santana – Cachoeira, Bahia, Brazil. ORCID: 0000-0002-5748-2675. petto@cardiol.br

RESUMO | INTRODUÇÃO: Cresce o número de indivíduos com doença renal crônica (DRC) submetidos à hemodiálise (HD). No Brasil, em 2012, o número de pacientes em HD era de 97.586, com taxa de mortalidade de 19%. O exercício físico (EF) é uma terapia adjuvante capaz de promover controle glicêmico, pressórico e outros ganhos relevantes para o controle da DRC. **OBJETIVO:** Descrever os benefícios sobre a qualidade de vida, os cuidados e os protocolos mais efetivos de exercício físico para indivíduos em hemodiálise. **MÉTODO:** Estudo de revisão sistemática. Consultados artigos dos bancos de dados SciELO e PubMed entre 2005 e 2016, sobre os efeitos fisiológicos do exercício e qualidade de vida de indivíduos em hemodiálise. Os descritores em cruzamento utilizados foram: "hemodialysis" AND "exercises", "haemodialysis" AND "exercises" e "intradialytic" AND "exercises". **RESULTADOS:** Foram selecionados 23 artigos com diferentes programas de EF 8 aeróbios, 6 resistidos, 5 compostos pela associação de ambos e 1 de comparação entre aeróbio e resistido. A amostra variou entre 6 a 103 pacientes. Tempo de intervenção de 2 a 4 meses. Todos os programas aeróbios confirmaram melhorias em um ou mais parâmetros: capacidade funcional, redução da inflamação, melhora da complacência arterial dentre outros. Nos EF resistidos, um dos estudos reportou efeitos deletérios para os pacientes, já aqueles com EF resistido e aeróbico, apontaram benefícios. **CONCLUSÃO:** O EF foi capaz de prevenir o estresse oxidativo, reduzir a pressão arterial e a glicemia, aumentar o volume e a força muscular, além de ganhos na qualidade de vida, entretanto não houve unanimidade sobre o melhor protocolo.

PALAVRAS-CHAVE: Atividade física. Fisiologia renal. Fisiologia do exercício.

ABSTRACT | INTRODUCTION: The number of patients with chronic chronic disease (CKD) on hemodialysis (HD) has increased. In Brazil, in 2012, the number of patients in HD was 97,586, with a mortality rate of 19%. Physical exercise (PE) is an adjuvant therapy capable of promoting glycemic control, blood pressure and other gains relevant to CKD control. **OBJECTIVE:** To describe the benefits of quality of life, care and the most effective protocols of physical exercise for the individual on hemodialysis. **METHOD:** Systematic review study. Consultations of the SciELO and PubMed databases between 2005 and 2016 on the physiological effects of exercise and the quality of life of the individual on hemodialysis. The cross-over descriptors used were: "hemodialysis" and "exercises", "hemodialysis" and "exercises" and "intradialitic" and "exercises". **RESULTS:** 23 articles were selected with different EF programs, 8 exercises, 6 resisted, 5 composed by the association of both, and 1 of a comparison between aerobic and resisted. A sample ranged from 6 to 103 patients. Intervention time of 2 to 4 months. All programs should be improved in relation to functional capacity, reduction of inflammation, improvement of arterial compliance and others. In resisted PE, one of the studies reported deleterious effects for the patients, while those with resisted and aerobic PE showed benefits. **CONCLUSION:** EF was able to prevent oxidative stress, reduce blood pressure and increase blood glucose, increase muscle volume and strength, and gain quality in life, but there was no agreement on the best protocol.

KEYWORDS: Physical activity. Renal physiology. Exercise physiology.

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Introduction

Chronic kidney disease (CKD) is defined by the glomerular filtration rate of <60ml/min/1.73m² or presence of renal damage. The possibility (or renal failure - IR) occurs through abnormal protein excretion in the urine, defined as microalbuminuria when the moderate phase or macroalbuminuria, where an advanced stage of protein excretion and renal damage is observed. The normal rate of albumin excretion in 24 hours corresponds to 20mg. When maintained from 30 to 300mg / day, microalbuminuria is considered. IR is characterized by persistent macroalbuminuria (> 300mg/day), in general, is associated with a progressive decline in glomerular filtration rate, progressing to CKD and cardiovascular disease (CVD) even if the patient has adequate medical management[1].

Expressed to affect 8 to 16% of the world's population. by 2015, it reached one in five men and one in four women between 65 and 74 years of ages, and half of the population aged 75 or over. It believes that its prevalence will increase in the coming decades, driven by an aging population, in addition to the simultaneous increase in the prevalence of diabetes and hypertension[2].

A recent systematic review with meta-analysis included 100 studies, comprising 6,908,440 patients, on the prevalence of CKD. The overall mean of the 5 stages was 13.4% (11.7-15.1%), of these, 10.6% (9.2-12.2%) were in stages 3-5. The prevalence per stage: 1 the stage - 3.5% (2.8-4.2%); 2 the stage - 3.9% (2.7-5.3%); 3 the stage - 7.6% (6.4-8.9%); Stage 4 - 0.4% (0.3-0.5%) and Stage 5 - 0.1% (0.1 to 0.1%). Overall prevalence is brought up, with consistent data pointing to 11-13%, most in the third stage[3].

This disease has become increasingly clear due to its high prevalence and complications. It has just been According to the National Health and Nutrition Examination Survey, conducted between 1999 and 2004 in the United States, about 5% of the population had CKD in stages 1 and 2 and 8% in grades 3 to 4. Also in the US, the US Renal Data System 2015 Annual Data Report brings about 468,000 Americans on hemodialysis (HD). The treatment costs the country approximately $ 31 billion per year. Nevertheless, almost 90,000 of these patients die annually[4].

In Brazil, according to the census of the Brazilian Society of Nephrology 2014, in that year the number of patients observed in HD in the country was 112,004, of which 36,548 were starting treatment. The estimated mortality rate was 19%, corresponding to 21,281 deaths. Of those prevalent in 2012, 31.9% were over 65 years of age and 31.2% were on the waiting list for transplantation. Although the prevalence rates and the incidence of dialysis patients increased, the mortality rate decreased compared to the previous year. Expenses for dialysis treatments exceed 2 billion reais[5].

The risk of mortality is almost 30% lower in individuals with CKD who practice PE regularly compared to those with sedentary habits[6]. However, progression of the disease carries with it numerous physical limitations, so the same recommendations that are made for the elderly (65 years or older) and adults aged 50-64 years with chronic problems can be followed by patients with advanced CKD[7]. Supervised physical exercise (PE) is a powerful tool for glycemic and blood pressure control, muscular atrophy, and quality of life and several other proven benefits in the general population[8]. Therefore, due to the relevance of the topic, we searched the literature for studies that proved the already recognized benefits of PE, especially intradialytic, in patients with CKD.

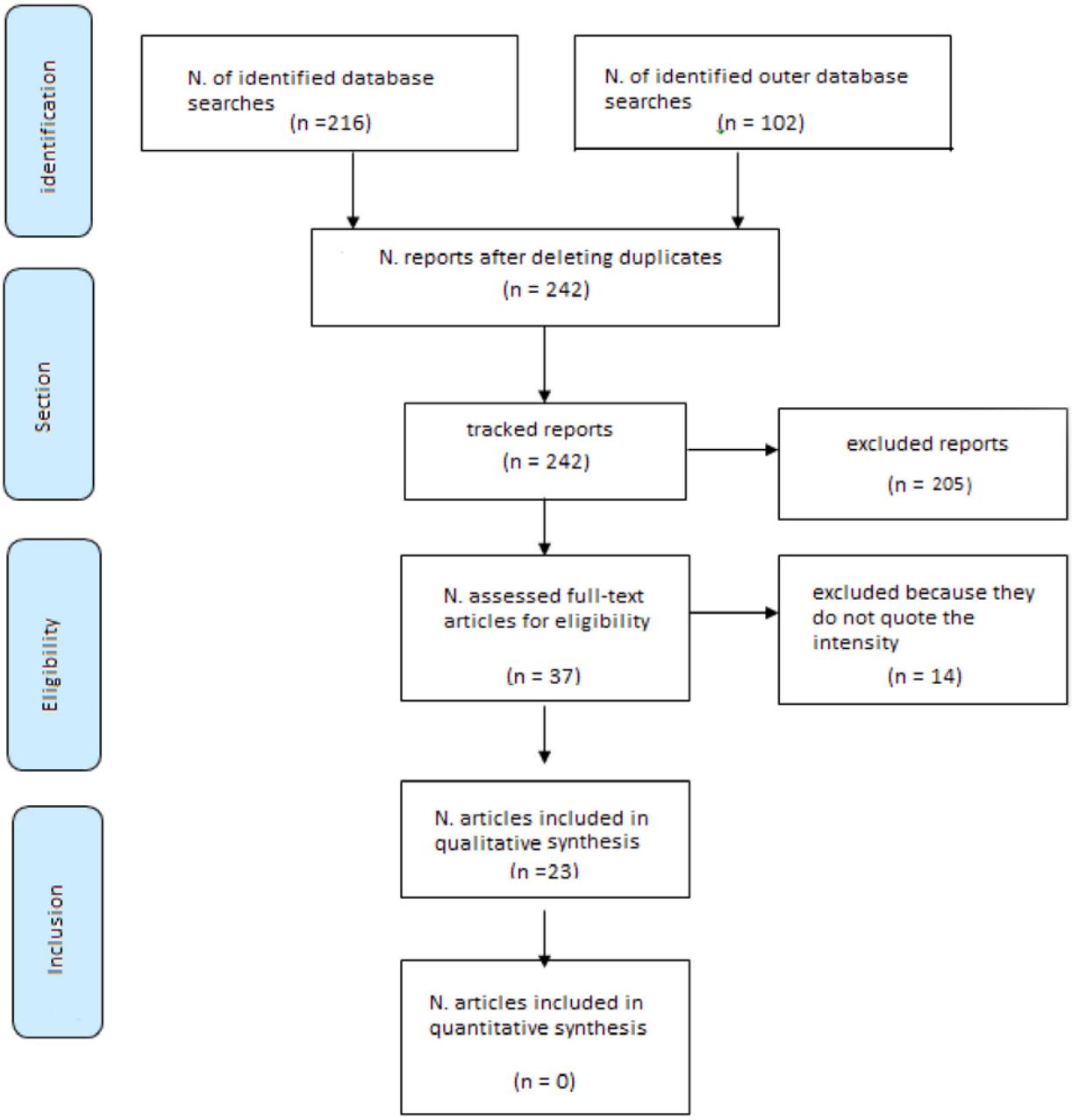
Method

This is a systematic review based on specialized literature through consultation of scientific articles from the SciELO and PubMed database, published between the years 2005 and 2016. For the search, the crosswords of keywords used were: "hemodialysis" AND "exercises", "haemodialysis" AND "exercises" and "intradialytic" AND "exercises".

The studies were included according to the following criteria: to evaluate the Effects of PE - particularly the intradialytic, be it aerobic, resisted or association

of both - on the renal system and the quality of life of the patients. Excluded bibliographic reviews, duplicates, case studies and articles that were not freely available.

Figure 1. Diagram of flow of selection of physical exercise studies in individuals on hemodialysis, 2018



We sought to study and understand the main parameters and responses related to CKD, PE and the correlation between the two, and, whenever possible, the results found.

Eligibility Criteria

The studies included in this study should meet the following criteria: 1) population: adults patients (equal to or more than 18 years of age) diagnosed with CKD; 2) intervention: aerobic exercise, resistance exercise and combination of aerobic and resistance exercises; 3) Comparator Group: usual care; 4) outcome: functional capacity, blood pressure control, strength and muscle mass gain , and quality of life. There was not any restriction on study publication status, language and methodological quality. The articles were analysed according to: intensity, exercise modality, duration and moment of exercise application. The risk of bias in each was analyzed from PEDro scale[9].

Results

A total of 23 articles were selected in the database that met the eligibility criteria and evaluated the effects of different aerobic (8-passive), 8 aerobic (including passive), aerobic and resisted 2, and 5 both at varying intensities.

The sample size varied from 10 to 50 participants in 17 studies (~ 75%), a single discrepancy in the study of Van Vilsteren and Collaborators[10] investigated 103 patients. Once again singular, these authors reported the use of beta-blockers as exclusion criteria. The others, for the most part, considered exclusive cardiovascular events, especially angina.

Regarding the intervention time, there was a certain homogeneity in the protocols, varying from 2 to 6 months in 19 studies (~ 83%). Saitoh[11], da Silva[12], Anding[13] and his colleagues were in disarray at the others, with monitoring of 9 months, 16 months and 5 years, respectively. All aerobic programs confirmed improvements in one or more parameters: functional capacity, reduction of inflammation, improvement of arterial compliance and quality of life. Studies with PE resistance, only Esgalhado and Employees[14] uses session ram single again single of subs acute ICIO force, reported deleterious Effects for patients. However, several studies that applied associated PEs also noted important benefits on quality of life[10,12,13,30,31].

Chart 1. Studies included in the systematic review of physical exercise studies in hemodialysis subjects, 2018 (to be continued)

Aerobic Exercise			
Authorship	**Number of participants**	**Methods**	**Results**
LIAO [15] *et al.*, 2016	40 adults in HD for more than 6 months, 21-65 years	Moderate intradialytic PE on cycle ergometer, 30min / day (5min heating) for 3 months	Reduced inflammation and improved BMI, nutrition, bone density, cardiovascular resistance, and PE tolerance
HRISTEA [16] *et al.*, 2016	16 seniors in HD for at least 3 months	Moderate intradialytic PE on cycloergometer, 3 times per week, progressively increasing from 10min to 30min for 6 months	Increase in performance of the walking test (+ 22%) and self-reported quality of life (+ 53%), with no decline in balance
MOHSENI *et al.*, 2013 [17]	50 adults and the elderly, in HD for more than 3 months	Low-intensity, 2-month, 3-week, 15-minute / day intradialytic PE	After the first month, it increased the Efficacy of HD, thus remained until the end of the study
MUSAVIAN *et al.*, 2015 [18]	16 adults and elderly people in HD, ages 24-75 years	Passive PE in electric mini-bike (30min for 2 months), followed by 2 months of interval, and 2 months of active PE (bicycle off)	Passive PE did not change potassium, calcium and phosphorus, but reduced BP. Active PE significantly decreased phosphorus levels
KOH *et al.*,2010 [19]	70 people in HD	Intradialytic PE (exercise cycle 3x per week) vs.PE performed at home (walk), 6 months	There were no significant differences between the protocols, regarding physical function and vascular parameters
BAE *et al.*,2015 [20]	10 HD DRC carriers	Intradialytic aerobic PE, 3 months, exercise bicycle for 30min during the first two hours of HD	Improvement in quality of life and cardiovascular system and delayed the decline of body composition
TOUSSAINT *et al.*, 2008 [21]	19 patients, mean age of 67 years, in HD for more than 3 months	Intradialytic PE on exercise bicycle, minimum 30min, for 3 months	Improvement in arterial compliance, lower cardiovascular risk measured through type B natriuretic peptide

Chart 1. Studies included in the systematic review of physical exercise studies in hemodialysis subjects, 2018 (continuation)

Aerobic Exercise			
Authorship	**Number of participants**	**Methods**	**Results**
WILUND *et al.*,2010 [8]	17 patients in HD, ages 30-70 years	Intra-aerial PE, 4 months, cycling with increased duration at each session, starting with 5min until reaching 45min	Increased walking performance by 17%, reduced thiobarbituric acid reactive substances by 38%, alkaline phosphatase by 27%, and epicardial fat thickness by 11%
Weathered Exercise			
Authorship	**Number of participants**	**Methods**	**Results**
ESGALHADO*et al.*, 2015 [14]	16 patients aged ~ 44 years, there are about 5 in HD and mean BMI of 23kg / m^2	PE resisted in single session, 60% of 1RM, 3 sets of 10 repetitions in 4 types of exercises in both legs, during 30min	Reduced plasma levels of superoxide dismutase (antioxidant). On the day without PE, on the other hand,
SAITOH *et al.* , 2016 [11]	75 people in HD	PE intradialytic resistance in *leg press*adapted 20min / day at the onset of HD, mild to moderate intensity, for 9 months	Did not cause adverse events. Improved serum albumin levels and protein elimination
MARTIN-ALEMAÑY *et al.* , 2016 [22]	36 patients in HD, mean age 34 years	Resistance PE associated with the intradialytic diet, 40min / day, 2x per week, for 3 months	Protein elimination reduced from ~ 60% to ~ 20% in training or diet groups
BULLANI *et al.*, 2011 [23]	11 people, average 70 years, in HD for more than 3 months	Medial resisted intradialytic PE with elastic bands, 40min / day, 2x / week, for up to 6 months	*Improvement in the performance* of the*Tinetti Test (balance test, +2.2 points), walk test (+44 meters)* and *Timed Up & Go* (-2.1 seconds)
SONG & SOHNG, 2012[24]	40 people in HD	PE of progressive resistance, 3 months, 3 times per week, 30min each session, exercises of upper and lower limbs, with the aid of elastic and sandbags	Improved skeletal muscle mass, adherence to treatment, muscular endurance and quality of life, reducing percentage of fat, total cholesterol and triglycerides
RIBEIRO *et al.*,2013 [25]	60 patients between 40-75 years divided into 4 groups: 1) patients with type 2 DM and CKD; 2) Type 2 DM with sedentary CKD; 3) DRC and PE and 4) sedentary DRC	Intradialytic PE, 2 months of activity at 40% of 1RM, 3 times per week, 3 sets of 12 repetitions with gradual overload every 6 sessions	Diabetics had greater glycemic reduction, compared to sedentary ones. It improved vitality, strength and self-esteem, and reduced the secretion of inflammatory cytokines
JOHANSEN *et al.*, 2006 [26]	20 adults in HD, mostly diabetic and / or hypertensive	Resistant intradialytic PE, 3 months to 60% of 3RM, 3 times a week, ranging from 2 to 3 sets of 8 to 10 replicates	It increased the cross-sectional area of the quadriceps, improved self-reported physical function, and increased quality of life.
CHEEMA *et al.*,2007 [27]	49 people in HD	High-intensity intradialytic resistance PE, for 3 months	Improved the physical function of patients in HD
Kirkman *et al.*,2014 [28]	23 patients in HD and 9 healthy subjects	Intradialytic PE of progressive resistance of high intensity (extension of the legs) *vs.* control therapy (stretching), 3 months	High intensity increased muscle volume and strength (healthy or HD practitioners). However, improvement in physical function was only noticed in healthysubjects .

Chart 1. Studies included in the systematic review of physical exercise studies in hemodialysis subjects, 2018 (conclusion)

Combined Exercises			
Authorship	**Number of participants**	**Methods**	**Results**
AFSHAR *et al.*,2010 [29]	21 men in HD	PE aerobic (cycling) vs.(knee extension, abduction and hip flexion at 60% of 3RM) for 2 months	Reduced serum creatinine in both - more in aerobic PE. Both improved inflammation, but without influence on lipids
VAN VSTERENet *al.*, 2005 [10]	103 people in HD	Aerobic and resisted PE combined, 3 months, 2 to 3 times a week: 60% cycling of 1RM at the onset of HD, and resistance exercises with low weight	Changes in behavior, physical fitness, physiological conditions and improvement in quality of life, physical function and muscular strength
PERES *et al.*,2010 [30]	78 individuals for at least 3 months in HD in Brazil	Combined aerobic and intradialytic PE, 2 months, 3 times per week, 1h / day, with heating; aerobic exercise on the cycle ergometer;strength with weights, balls and elastics; and cooling	Increased walking test performance, VO2max, quadriceps muscle strength, vitality, emotional aspects and mental health
SIMO *et al.*,2015 [31]	22 elderly people in HD	PE aerobic and resisted combined, low intensity, 3 months, 2 times per week, 45-50min: aerobic on cycle ergometer and anaerobic with elastic bands, dumbbells etc.	Improvements in muscle strength and functional capacity, providing better quality of life and breaking the monotony in the treatment
ANDING *et al.*,2015 [13]	50 seniors in HD for more than 4 years	PE aerobic and resisted combined, 2 times a week, 1h during HD: aerobic exercise on the stationary bicycle and resisted in 8 muscle groups	At the end of 1 year, improvements in quality of life, strength and physical function. But only 10 individuals reached the end of 5 years in stable clinical conditions
DA SILVA *et al.*, 2013 [12]	56 individuals, 29-82 years, for more than 3 months in HD	Aerobic and resisted PE combined , 20min / day, 3x / week at the beginning of HD: bicycle at 60-70% FC, strengthening with weights, ball, elastics and stretching, for 16 months	Increased PE tolerance, reduction in HR, RR and pain level, 54m increase in walking test, improvements in quality of life and physical capacity, 28% increase in SF-36 score

All studies were performed in humans, 13 of them were controlled studies, and of the total (23) 14 were randomized studies, configuring more articles within the established confirmation pattern.

Chart 2. Bias risk assessment of physical exercise studies in hemodialysis subjects, 2018

Study	Controlled	Randomized	Scale of P ED ro (max 10)
LIAO *et al.* , 2016 [15]	x	x	4
HRISTEA *et al.* , 2016 [16]	x	x	4
MOHSENI *et al.*, 2013 [17]	x	x	5
MUSAVIAN *et al.*, 2015 [18]			4
KOH *et al.*, 2010 [19]	x	x	4
BAE *et al.*, 2015 [20]			4
TOUSSAINT *et al.* , 2008 [21]			6
WILUND *et al.*, 2010 [8]	x	x	4
ESGALHADO *et al.*, 2015 [14]			5
SAITOH *et al.* , 2016 [11]			5
MARTIN-ALEMAÑY *et al.* , 2016 [22]	x	x	4
BULLANI *et al* ., 2011 [23]	x	x	5
SONG & SOHNG, 2012 [24]		x	5
RIBEIRO *et al.*, 2013 [25]			5
JOHANSEN *et al.*, 2006 [26]	x	x	7
CHEEMA *et al.*, 2007 [27]	x	x	8
Kirkman *et al.*, 2014 [28]	x	x	6
AFSHAR *et al.*, 2010 [29]	x	x	4
VAN VSTEREN *et al.*, 2005 [10]	x	x	5
PERES *et al.*, 2010 [30]			4
SIMO *et al.*, 2015 [31]	x	x	5
ANDING *et al.*, 2015 [13]			5
DA SILVA *et al* ., 2013 [12]			5

Chart 3. Detailed PEDro ladder of physical exercise studies in subjects on hemodialysis, 2018 (to be continued)

Study	1*	2	3	4	5	6	7	8	9	10	11	Punctuation
LIAO *et al.* , 2016 [15]		X		X						X	X	4/10
HRISTEA *et al.* , 2016 [16]	X	X		X						X	X	4/10
MOHSENI *et al.*, 2013 [17]	X	X		X			X	X			X	5/10
MUSAVIAN *et al.*, 2015 [18]	X			X					X	X	X	4/10
KOH *et al.*,2010 [19]	X	X		X						X	X	4/10
BAE *et al.*,2015 [20]	X			X				X	X		X	4/10
TOUSSAINT*et al.* , 2008 [21]	X	X	X	X				X		X	X	6/10
WILUND *et al.*, 2010 [8]	X	X		X			X				X	4/10
ESGALHADO*et al.*, 2015 [14]	X			X				X	X	X	X	5/10
SAITOH *et al.*, 2016 [11]	X			X				X	X	X	X	5/10
MARTIN-ALEMAÑY *et al.* , 2016 [22]		X		X						X	X	4/10
BULLANI *et al.*, 2011 [23]				X				X	X	X	X	5/10
SONG & SOHNG, 2012[24]	X	X		X				X		X	X	5/10
RIBEIRO *et al.*, 2013 [25]	X			X				X	X	X	X	5/10
JOHANSEN *et al.*, 2006 [26]	X	X	X	X				X	X	X	X	7/10

Chart 3. Detailed PEDro ladder of physical exercise studies in subjects on hemodialysis, 2018 (conclusion)

Study	1*	2	3	4	5	6	7	8	9	10	11	Punctuation
CHEEMA *et al.*, 2007 [27]	X	X	X	X			X	X	X	X	X	8/10
Kirkman *et al.*,2014 [28]	X	X	X	X			X			X	X	6/10
AFSHAR *et al.*, 2010 [29]	X	X		X						X	X	4/10
VAN VSTEREN *et al.*, 2005 [10]	X	X		X				X		X	X	5/10
PERES *et al.*,2010 [30]	X			X				X	x		X	4/10
SIMO *et al.*,2015 [31]	X			X				X	X	X	X	5/10
ANDING *et al.*, 2015 [13]	X			X				X	X	X	X	5/10
DA SILVA *et al.*, 2013 [12]	X			X				X	X	X	X	5/10

1-Eligibility criteria; 2- Random allocation; 3-Hidden allocation; 4-Baseline comparability; 5- Blind subjects; 6-Blind therapists; 7- Blind assessors; 8-Adequate follow-up; 9-Intention-to-treat analysis ; 10-Comparisons between groups; 11- Estimate point estimates and variability.
* Value not included in the calculation of PEDro scale.

Discussion

This study revealed heterogeneous aspects regarding the age of the participants and PE protocols diverge over workloads, which can generate r different responses and adaptations. There are no randomized controlled trials comparing different intensities of intradialytic PE. Therefore, these factors must be taken into account in the final results of this research.

Physical inactivity is a major risk factor for CVD, which are susceptible both individuals with CKD as those without the disease[32]. In the general population, exaggerated increase in body weight is widely documented as an independent risk for CVDs. In contrast, falling muscle mass is an important predictor of mortality in individuals with CKD in HD, and the decrease in muscle strength is an aggravating factor for this outcome[33].

There is observational evidence suggesting a reduction in risk factors for CVD in patients with CKD, possibly due to the interaction of a number of cardioprotective benefits: improvement in endothelial function, increased compliance of the artery l , better in inflammation and stress oxidative; reduction of the risk factor profile for CVD (control of SBP, improvement in lipid profile and insulin sensitivity); antiatherogenic protective Effect; anti-ischemic protective Effect; antiarrhythmic protective Effect; antithrombotic protective Effect induced by PE[8,12,14,25,29].

Another point worth mentioning is the increase in pressure levels, which is very common in these patients. Not infrequently, this pressure is not well controlled. PE has been attributed as a non-medicinal therapy of extreme importance in the management of hypertension. Several mechanisms can be attributed to this, such as a greater stimulus to nitric oxide synthase (NOS) [2] and, consequently, a greater synthesis of endothelial nitric oxide during PE. The findings demonstrate that these benefits corroborate the adoption of PE intradialític for patients with CKD[8,34,35]. In addition to these improvements, there is reduction of toxins in the blood, allowing greater tolerance to HD, better Kt / V results - which measures the Efficacy of HD, and decreased amount of fluid removed[36].

Intensity

Preliminarily, for comparison purpose, it is necessary to describe the method of evaluation of the training intensity that was used for the prescription of PE. The Borg Effort scale was chosen by several

authors[11,12,15,16,21,22], usually associated with heart rate monitoring. Other authors measured the intensity of symptoms such as dizziness, headache, palpitations, nausea, anxiety, fatigue or any other adverse Effects[17]. Cracked et al.[14] used the 1RM test, which makes the study results more reliable.Cheema et al.[27] made the measurement from a subjective perception of Effort that varied from "difficult" to "very difficult". Kirkman et al.[28] determined the intensity from an evaluation of 5RM with 2 minutes of recovery between the series. When the subjective perception of Effort was not high, 1RM was predetermined and the training load increased.

With respect to the intensity itself, some authors suggest that the low - intensity PE, both aerobic and anaerobic (including passive PE), assists in the Efficacy of HD[17,18] while other authors observed an improvement in the quality of life in muscle strength, functional capacity and depressive symptoms of the elderly, as well as a reduction in glycemia and secretion of pro-inflammatory cytokines, as well as an increase in vitality[10,12,13,16,20,24,31].

However, several studies advocate the choice of moderate intensity. For example, researchers observed that moderate PE performed with shin guards generated increased cross-sectional area of the quadriceps, improved self-reported physical function[2], muscle strength in 12 weeks of aerobic exercise[17], as well as improvements in the cardiovascular system and delay in the decline of composition body[8], translated by improvement in serum albumin levels (nutritional marker)[15].

Corroborating with these findings, other authors demonstrated a 17% improvement in walking test performance, as well as a 40% reduction in oxidative stress markers, a 30% risk of vascular calcification and in more than 10% the thickness of the epicardium fat - highly inflammatory to the heart[8]. Reduced serum creatinine was also reported. However, there was no influence on lipids - probably due to the short duration of the study, which did not lead to changes in body weight[29].

This intensity was also efficient for the elderly, being able to improve the quality of life, strength and physical function[13] so important for this population that, frequently, presents sarcopenia, due to aging[14].

Besides the loss of mass and muscle strength, moderate PE contributes to higher levels of anti-inflammatory cytokines, decreasing bone loss and fractures in patients with CKD and a significant increase in the number of endothelial progenitor cells[15].

However, the study by Esgalhado et al.[14], who evaluated only one moderately resisted PE session for 30 minutes, reported that acute PE reduced plasma levels of superoxide dismutase (SOD) - an enzyme with important antioxidant properties. Another factor that draws attention is that in the day without the exercises, by contrast, SOD was potentiated.

Song & Sohng[24] evaluated the Efficacy of moderate to high intensity of PE, and concluded that this progressive intensity increased skeletal muscle mass, adherence to treatment, muscle endurance and quality of life, further reducing the percentage of fat, total cholesterol and triglycerides. With regard to high intensity PE, Cheema et al.[27] have suggested that individuals with terminal CKD can benefit from it, improving skeletal muscle quality and overall health, also increasing muscle volume and strength1.

However, mortality risks are known to be greater for those with functional impairment, and 75% reported severe limitations for severe FB, while 42% had the same complaint for moderate FB. As a consequence, the relationship between mortality and intensity of PE was noted: among those with severe limitations, 37.9% resisted moderate FT and 27.8% FT - 53.6% and 52% of those with little or no limitation[6].

Based on our conception and clinical practice, as well as in the analysis of studies, all intensities can and should be performed. However, it would be more appropriate and safe to initiate HD programs with mild to moderate intensity from a careful and individualized assessment and prescription, progressing to moderate to high intensity when the patient is prepared for such a change, without offering risks to the individual.

Duration and frequency of the exercise application

HD sessions are usually performed 2 or 3 times a week. Likewise, this was the frequency applied by the vast majority of PE programs - more than 95%

of them were carried out 2 or 3 times a week. In relation to mortality in this high-risk population, data from more than 2,500 patients were analyzed in the Dialysis Morbidity and Mortality Wave 2 studies. The highest survivals were observed in those who said they exercised between 2 and 5 days per week, but only 24% of individuals were in this group[32].

Regarding duration, it is important to note that some studies did not explain this variable; of the others, the most used 30 minutes as the standard duration - although some use longer periods[8,13,22,30]. Three basic types of PE program can be applied to these patients: a supervised outpatient program at a rehabilitation center, a home-basedprogram, and intradialytic PE.

In terms of ensuring the prescribed intensity and duration of RU, the supervised outpatient program is the most effective but is associated with the highest rates of circumvention. Hence the importance of an individualized prescription, where one can measure the benefits and adverse Effects of each protocol. Some results indicate that interdialytic PE is the most effective, but even with less Effectiveness, it is preferable because of the greater adherence[37].

Due to the delay in treatment, each HD session takes about 4 hours, the monotony is almost inevitable. This favors the applicability of intradialytic programs: 90% of the studies analyzed the effect of PEs during HD. The implementation is easier, since the patient is obligatorily in the environment where the PE will be performed, monitored and under the supervision of professionals, thus less conducive to procrastination.

In addition, studies have reported that 76% of patients fall asleep during the HD sessions. In addition, it is known that the mortality risk of patients sleeping more than 9h / day is up to 50% higher when compared to those who sleep between 6 and 7 hours. Thus, an additional benefit of intradialytic PE is to keep patients awake and active[19].

Song & Sohng[24] evaluated the benefits of PE performed immediately prior to HD, when the individual is already at the clinic where the session will be held. This moment was chosen, according to the authors, due to the Korean practice of performing analysis with the patient lying down, which makes it difficult to attach an instrument to the PE and its own execution.

On the other hand, the risk of episodes of hypotension during intradialytic FB prevents many patients from performing PE with durations and intensities similar to what they could do on days without HD. Comparing PE performed at home with the outpatient clinic, the first one was more efficient in the 6-minute walk test result. It has also been shown that interdialytic PE may bring higher increases in VO2max than intradialytic PE (34.1% vs. 17.8%), although adherence is probably lower[38].

It is imperative that the PE protocol, when intradialytic, does not exceed the first two hours of HD, to avoid physical stress in the second half of the session, when the hemodynamic conditions of the patients are unfavorable. A certain uniformity is observed in the evaluation period of the protocols; about 70% of the reviewed studies analyzed the Effects of 2 to 4 months of PE. However, comparing the Effect of this variable on the change in VO2max, a 35% improvement was found in studies of 6 months or more, against 16% in studies of shorter duration, on average (work lasting 3 months resulted in an increase of 12%), bringing the importance of a longer duration of PE during HD[38].

Thus, it is suggested that the PE performed for at least 6 months transmits more significant improvements, and it is known that an increase of 3.5 ml / kg / min in VO2max is associated with a decrease in cardiovascular risk and mortality[38]. The increase in VO2max from PE was also associated with a significant increase in hematocrit and hemoglobin levels, a 23% decrease in triglycerides and a 21% increase in HDL-c, as well as an 18% increase in the rate of disappearance of glucose, despite a 52% decrease in fasting insulin levels, which translates into improved insulin sensitivity[39].

A longitudinal study[21] compared the Effects of 3-month intradialytic training at different times: short term (shortly after 3 months of PE) and long term (4 months after PE cessation). The differences were statistically significant, in favor of PE, in serum markers (C-reactive Protein and albumin), as well as the positive impact on VO2max, a marker of physical capacity whose consequences were extolled

previously. The study reinforces the importance of regularity in the practice of PE over the patient's overall health, especially in reducing the risk of cardiovascular death.

Modality

Different types of PE can be offered to patients with CKD: Aerobic[8,15-21], weathered[11,14,22-27] or a combination of both[10,12,13,30,31].

Except for a study[7], all research that investigated the Effects of aerobic intradialytic PE, they used the bikes or cycle ergometers. This is due, in addition to the ease of execution, by the practicality of the coupling of the equipment to the dialysis apparatus.

A pilot study clearly showed that supervised aerobic PE greatly increases the quality of life of these individuals. The practice of only 45 minutes per week of aerobic PE over an one-year period has already been able to cause a significant improvement in physical disability and arterial stiffness in this population, giving it substantial cardiovascular benefits[40]. PE proved beneficial in atrophy of the fibers, increasing by 46% the cross-sectional area of the fiber and improves capillarization in skeletal muscle of patients with renal insufficiency[41].

Afshar et al.[29] showed a greater reduction, and statistically significant, of serum creatinine and C-reactive protein in the aerobic group, compared to the group that performed PE of resistance. However, studies comparing PE combined aerobic and aerobic isolated force with PE studies were observed gains Medi the s 28.6% versus 23.2% VO2max, respectively[38].

The aerobic PE protocols report cardiovascular impacts and quality of life. However, only those who applied resisted PE protocols[25] or with the association of resisted and aerobic PE[30], improved strength and muscle mass, so peculiar to resistance training[42], which brings the same relevance of this type of PE to this one population, whose muscular strength is lower than in sedentary populations without CKD[43].

PE was able to reduce the mRNA myostatin (growth factor that inhibits the growth of muscle tissue) by 51%, while the levels of IGF-IR mRNA (growth factor receptor, insulin - like type 1), increased 41%. These changes may indicate mechanisms by which PE improves muscle capacity[45].

Despite episodes of muscular pain (which were spontaneously healed), resisted PE was safe and, at 9 months, did not cause any adverse events or injuries in the patients. On the contrary, this type of exercise proved to be important in relation to s nutritional and changes metabolic, improving serum albumin levels and the elimination of proteins[11], common feature in HD patients (affects up to 75% of them) and greatly increases the risks of cardiovascular morbidity and mortality[46].

However, when resisted PE was practiced less frequently (twice a week), the same Effect was not noticed. In a study that analyzed this type of FB associated with an intradialytic diet, it was concluded that the prevalence of this comorbidity, which was initially almost 60%, effectively reduced to less than 20%, both in the trained group and in the group that followed only the diet[22]. Ie, the addition of PE did not appear to increase the acute anabolic Effects of nutritional supplementation, perhaps for the low frequency of the PE, since the recommendation that there are positive changes in clinical outcomes is less 3 times a week[47].

In sum, the combination of both types of exercise seems to be the most efficient for these patients, although the combined training may be more complex and compliance with this type of PE is scarcer. When adopting this type of protocol, the endurance PE is usually performed before the aerobic because some patients would be unable to advance to the resisted PE due to fatigue after a relatively long time of the aerobic physical exercise. In order to avoid this, some programs apply intradialytic aerobic PE and resisted PE before or after HD[43].

Contraindications

The progression of CKD causes severe limitations. Individuals undergoing HD have a considerably lower tolerance PE lower functional capacity, toughness and strength, and increased muscle wasting and fatigue than healthy people or those with even less severe CKD who do not yet require HD[48]. Many of them can only perform physical activities that require 50% or

less of their maximum oxygen consumption; such a low level that makes it difficult even to perform basic tasks of daily life[44]. This makes about a quarter of the patients considered ineligible for studies with physical training[38].

Thus, not all chronic kidney patients have or can achieve regular PEs. According to the American College of Cardiology Foundation in conjunction with the American Heart Association, several contraindications are specific among these, symptomatic cardiac arrhythmias, pulmonary congestion and peripheral edema[48]. Some patients tested showed different responses with PE, such as ST-segment depression, hypertensive episodes or significant ventricular ectopy. However, it is essential to mention that these responses occurred in persons with previous heart disease[6].

Therefore, despite the benefits that some studies point towards the intense PE[27,28], it should always be extremely cautious and prescribed by a trained professional who knows the possible adverse Effects that this type of training can lead to people in HD. A thorough medical examination, with a correct history, covering the patient's clinical history, physical examination, electrocardiogram and laboratory tests are fundamental before beginning the practice of PE.

Several studies have found that, after the first two hours of HD, PE can cause or worsen cardiovascular decompensation[43,49]. Thus, PE at the end of HD is contraindicated for those susceptible to hypotension or who have large volume of fluid removed, since complications arose when this volume was greater than 2.5L[45]. Despite the negative association between systemic arterial hypotension and HD, no evidence suggests that PE causes any myocardial damage. In addition, no serious adverse event was reported after 28,400 hours of intradialytic PE, as concluded a major systematic review and meta-analysis involving 565 patients[22].

Conclusion

Overcoming the generally reduced physical function of patients in HD, the intradialytic PE program in most cases proved to be Efficient and easy to apply. Even when low intensity, even passively, had extremely positive impacts on the quality of life of these individuals. It is desirable, then, that PE programs are implemented for HD patients, including those with comorbidities.

In summary, almost all the studies that deal with the subject demonstrate beneficial Effects of PE not only for physical functioning (including VO2max and muscle strength), but also for the improvement of hematological indices, inflammatory cytokines, nutritional status, mental health and general health.

However, is not clear if the benefits are limited to patient's stable, since several studies have this factor as a criterion for inclusion of participants for research. Therefore, individualized protocols for elderly or comorbid patients need to be further studied.

Even with so many benefits exposed, the practice of PE in individuals with CRI in HD has not yet become a routine practice. What is the reason for the low adherence and applicability of PE in these patients? One of the hypotheses to be considered may be mistrust and even lack of knowledge on the part of the nephrologists about the documented results. Most individuals who are on HD treatment with advanced CKD are over 50 years of age. This can be an obstacle, as many may be seen as unable to fit into an intradialitic PE program. Due to a lack of motivation and comorbidities, the dissemination of an educational nature about the Effects of intradialytic FB is also scarce, thus preventing the scope of this therapy.

Reports indicate that adverse events can occur more frequently when performing high intensity PE, compared with those of moderate intensity. Therefore, in view of the various comorbidities that HD patients may present, it is first recommended

that complete evaluations be performed on patients prior to initiating a PE program for obvious safety reasons. It is suggested that the prescription of PEs be made progressively, and in this practice 5 to 10 minutes of heating should be included. It is interesting that the PE intensity is prescribed from the Borg Effort rate, which did not occur in all the studies we evaluated.

Despite the fact that the literature is recommending more and more the practice of PE during HD sessions, it is necessary to consider the variables that are possible risk factors in this population, such as medication use, obesity, hypertension, diabetes, age, HD, among others. Therefore, it is imperative that the PE is prescribed with caution, in an individualized way it is monitored. We suggest PE, whether aerobic, resistance or the association of both, as an adjuvant therapy that should complement treatment in CKD. In short, regular PE should be mandatory and not optional for these patients.

Through this review, all the intensities, durations and modalities of PE in HD seem to generate benefits, however, there is still no unanimity as to what the optimal protocol would be in order to promote the best possible responses and adaptations, and the magnitude of this response still lacks comparative analysis in the studies. Subsequent evaluations with larger samples should be performed in order to prove and draw up more detailed and specific protocols that will greatly assist in a more Effective dialysis treatment.

Limitation of the study

In addition to the limitations inherent in each study that composes this review, some of them are not meticulous in describing the protocols. Among these shortcomings, part of the work does not mention the duration of the RUs. Others fail to express the intensity. The existence of different ways to measure this magnitude, the intensity can be measured by the Borg scale or based on heart rate, for example, makes the comparison between results less accurate. Without mentioning the heterogeneity regarding prescriptions: different intensities, durations and modalities are factors that potentially influence the Efficacy of PE. In addition, participants selected in the studies were generally the healthiest HD patients and therefore, it is difficult to generalize the results. Another limit would be the small sample size.

Studies presented moderate quality according to the PEDro scale, which evaluates the methodological quality, obtaining 5 points in the global average. In addition, this work was not evaluated in statistical character. Despite these limitations, it presents good resources for clinical practice, given the really considerable number of studies involved.

Contributions

Ferrari F, Diogo DP, Motta MT, Petto J participated in the conception and design of the research. Lacerda FFR , Sacramento MS, Santos ACN, Petto J participated in the drafting of the manuscript. All authors participated in the critical review of the manuscript for content .

Conflicts of interest

No financial, legal or political conflict involving third parties (government, business and private foundations, etc.) was declared for any aspect of the work submitted (including but not limited to grants and funding, advisory board, study design, manuscript preparation , statistical analysis, etc.).

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