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Exercise training in dialysis patients: impact on cardiovascular and skeletal muscle health

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ABSTRACT

Dialysis patients show a high rate of reduced functional capacity, morbidity and mortality. Cardiovascular disorders, muscle atrophy and malnutrition play an essential role among the aetiological factors. Sedentary lifestyle characterizes them and contributes to the aggravation of the disorders. On the contrary, exercise training is an important preventive and therapeutic tool both for cardiovascular problems and for the appearance of muscle atrophy in dialysis patients. Regular exercise causes both central (cardiac) and peripheral (muscular) adaptations, improving functional capacity. In particular, circulatory system clinical trials in haemodialysis (HD) patients documented that exercise has favourable effects on heart function, promotes balance on the cardiac autonomic nervous system and contributes to the management of arterial hypertension. In the muscular system, it prevents muscle atrophy or contributes significantly to its treatment. The main preventive mechanisms of the beneficial effect of exercise on the muscles constitute the inhibition of the apoptotic processes and protein degradation. Exercise training in HD patients leads to an increase of muscle fibers, mitochondria and capillaries, and the combination of regular exercise and dietary strategies is even more effective in preventing or treating muscle atrophy. Finally, an improvement in functional capacity and quality of life was found also in peritoneal dialysis patients following exercise training.

Keywords: cardiovascular disease, dialysis, ESKD, exercise, muscle mass, nutrition, physical function

INTRODUCTION

Exercise capacity, which is an important prediction of all-cause mortality in both health and disease, is significantly reduced in chronic kidney disease (CKD) patients on dialysis. Furthermore, sedentary individuals on dialysis have a 62% higher risk of dying when compared with non-sedentary patients [1]. The common pathway for all the physical activity derangements are cardiac (central) and muscle (peripheral) dysfunction, as well as malnutrition. A recent metanalysis supported that exercise in haemodialysis (HD) patients improved cardiovascular function, functional capacity and quality of life (QoL) [2].

FUNCTIONAL AND PREVENTIVE MECHANISMS OF EXERCISE ON THE CARDIOVASCULAR SYSTEM

Dialysis patients show a very high rate (>60%) of cardiovascular problems, such as hypertension, coronary heart disease (CHD),

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congestive heart failure (CHF) and arrhythmias, which remain the major causes of morbidity and mortality [3]. CHD is associated with traditional (e.g., diabetes, hypertension and sedentary lifestyle) and nontraditional (e.g., bone disease, anaemia, inflammation and oxidative stress) risk factors, as well as dialysis-related factors [4]. It was supported that reductions in level of physical activity over time in dialysis patients could lead to increased risk of arteriosclerosis [5]. A sedentary lifestyle in HD patients promotes the procedure of increased oxidative stress and inflammation, enhancing coronary endothelial dysfunction, vessel calcification and arteriosclerosis [6, 7]. Indirectly, the association between inactivity and abnormalities in lipid and lipoprotein metabolism as well as in the blood coagulation system could play an essential role for the early appearance of coronary thrombosis and atherosclerosis. Arterial hypertension is common and often unsuccessfully controlled in dialysis patients [8]. Blood pressure (BP) measurements before or after HD display a U-shaped association with cardiovascular events and survival, a phenomenon described as 'reverse epidemiology of hypertension' [8].

Nevertheless, hypertension accelerates the development of CHD by two ways: firstly, it causes endothelial damage, and secondly, it increases the cardiac afterload, resulting in left ventricle hypertrophy (LVH) and diastolic dysfunction. A sedentary lifestyle enhances the appearance of arterial hypertension, by affecting pathophysiological mechanisms at different levels in CKD [9]. Most HD patients have high serum triglycerides and low high-density lipoprotein (HDL) levels. An inactive lifestyle leads to increased blood cholesterol levels and the accumulation of visceral fat. Diabetes is very prevalent in the HD population. Extensive exposure to hyperglycaemia and increased insulin resistance lead to endothelial dysfunction [4]. Oxidative stress and inflammation, both main disorders in diabetic nephropathy, are the most severe pathophysiological mechanisms leading to coronary atherosclerosis [10]. A low level of physical activity increases insulin resistance and deteriorates the control of glycaemia [11].

LVH is one of the most prevalent cardiovascular complications in CKD; it is classified as cardiorenal syndrome type 4 and leads to CHF [12]. It has been reported that a 10% decrease in LV mass translated into a 28% decrease in cardiovascular mortality risk in HD patients [13]. Pathophysiologic mechanisms of LVH have been divided into three sections: (i) related to afterload, caused by arterial stiffness, (ii) related to preload, by volume overload and (iii) related to haemodynamic reasons, such as activation of the intracardiac renin–angiotensin system. Angiotensin II exerts a direct hypertrophic action on cardiomyocytes [9]. Uraemic toxins, such as high parathyroid hormone levels, hypo- or hypercalcaemia and hyperphosphataemia, are associated with LVH and cardiovascular calcifications [13]. Potentially reversible risk factors present during dialysis therapy include anaemia, hypoalbuminaemia and hypertension [14]. Oxidative stress and xanthine oxidase activation, as well as the phosphodiesterase-5 pathway, may also be involved in the development of LVH in CKD patients [12, 13]. Myocardial hypertrophy causes the activation of cellular apoptotic signals and increases extracellular matrix production up to fibrosis [12]. LVH causes progressive impairment in contractility, stiffening of the myocardial wall and diastolic dysfunction, and leads to dilated cardiomyopathy, known as 'uraemic cardiomyopathy', and CKD [13].

Dysfunction of the cardiac autonomic nervous system, as impairment of parasympathetic and enhancement of sympathetic nervous system function at rest, is observed in >50% of HD patients, specifically in diabetic nephropathy [15]. Cardiac autonomic outflow dysregulation in HD patients is mainly the result of central and peripheral uraemic neuropathy [16]. Other possible underlying mechanisms are kidney injury and ischaemia, arterial chemoreflex activation, NO-related mechanisms, reduced renalase secretion and other factors, including the increased renin–angiotensin–aldosterone system activity, and cardiovascular structural remodelling [15, 17]. It was supported that a sedentary lifestyle appears to enhance both sympathoinhibitor and sympathoexcitator mechanisms in the rostral ventrolateral medulla [18]. Heart rate variability (HRV) provides a non-invasive method for the investigation of the autonomic input into the heart. The impaired reflex control of both sympathetic and parasympathetic outflow to the heart and vasculature, and mainly the adrenergic overdrive, leads to reduced HRV [16]. Significantly, decreased HRV is associated with high incidence of arrhythmias and sudden cardiac death in HD patients, particularly in the setting of myocardial ischaemia [16]. There has been a correlation between HRV indices and *Kt/V*, meaning that autonomic dysfunction improved with dialysis therapy [19].

The role of exercise training in primary prevention in HD patients

Studies in HD patients suggest that exercise training prevents cardiovascular diseases, improving arterial compliance, cardiac autonomic control and left ventricular systolic function, as well as ameliorating cardiovascular risk factors [20]. It was reported that exercise training diminishes the oxidative stress, and the concentrations of inflammatory biomarkers like C-reactive protein, cytokines interleukin (IL)-1β, IL-6 and tumour necrosis factor-α, which have been demonstrated as important factors in the development of atherosclerosis [8, 20–22]. Moreover, regular moderate-intensity physical exercise in HD patients ameliorates body weight, has favourable effects on lipid profile, increasing HDL cholesterol and decreasing triglyceride levels, improves glycaemic control and normalizes BP [9, 23–25].

The effects of exercise renal rehabilitation in cardiovascular problems

The cardiorespiratory efficiency, which is estimated by VO_2 peak value, was demonstrated to be low in HD patients. Specifically, VO_2 peak mean values ranging from 15 to 25 mL/kg/min have been reported in several studies [26, 27]. A number of potential mechanisms have been presented to explain the poor aerobic capacity of such patients, including deconditioning, the effects of uraemic toxins, anaemia, muscular atrophy, cardiac dysfunction, metabolic disorders, inappropriate cardiac response to exercise and so on [4, 5, 28, 29].

Combined aerobic and strength exercise training programmes during or outside of dialysis has been shown to lead to significant improvement in aerobic and total exercise capacity in HD patients [28–31]. In addition, physical activities such as self-transportation by walking or cycling to dialysis, or pilates and yoga, have the same beneficial effects [2, 32]. The effects of exercise seem to be dose-responsive [2].

Peripheral (muscular) and central (cardiac) adaptations are proposed for that beneficial effect. Systematic exercise in end-stage CKD has a protective effect on the heart against the progression of CHD by direct mechanisms, such as reducing myocardial oxygen requirements, and increasing its perfusion [20–23]. Moreover, it has beneficial effect on endothelial function, decreasing inflammation indicators [22]. Applying a few weeks of exercise is enough to increase the NO and lead to vasodilation of the coronary arteries as well as other vessels [33]. Decreased myocardial oxygen demand with chronic aerobic exercise in patients with CHD is due to a decrease in heart rate and systolic and mean BP, both at rest and during submaximal exercise. Increased perfusion, owing mainly to a decrease in peripheral vascular resistance, improves arterial compliance as well as enhancing cardiac output during submaximal exercise in HD patients [30]. These favourable adaptations are attributed to a decrease in the tone of the sympathetic nervous system, possibly due to a decrease in the levels of circulating catecholamines, an increase in the action of the parasympathetic nervous system and a suppression of endogenous cardiac output stimulation [16, 31].

Exercise training, mainly the aerobic type, causes increased vagal tone at rest and decreased sympathetic tone in healthy subjects, as well as in CKD, cardiac, type 2 diabetic and other patients [16, 31]. A similar improvement in HRV time- and frequency-domain indices, indicating deterioration of cardiac sympathetic and increase of vagal activity, after a 10-month exercise programme in HD patients was shown in our previous study [16, 34]. The HRV index, mean interbeat (NN) intervals, and standard deviation NN (SDNN) were measured from a 24-h electrocardiographic ambulatory monitoring. At baseline all HRV indices were found to be significantly reduced in HD patients compared with healthy controls. Also, 40% of the patients had arrhythmias (Lown class >II). The patients with a more depressed HRV index had a higher incidence of arrhythmias (60%) compared with those with HRV index >25. Exercise training significantly increased HRV index and SDNN. Furthermore, fewer patients continued to have arrhythmias. Moreover, in another study, we found a significant improvement in the cardiac reflex sensitivity in HD patients following an exercise training programme [35].

There are few studies to support that exercise training improves myocardial function, increasing stroke volume, ejection fraction, left ventricular mass and myocardial contractility, in HD patients with left ventricular dysfunction [30, 36]. Additionally, the beneficial effect of exercise on patients' cardiac functional ability is supported by a better skeletal muscle function [30]. In our previous study [30] following 3 months of intradialytic aerobic exercises for 30 min at 60–70% of maximal heart rate, we observed a significant increase of ejection fraction (%) after a stress echocardiographic study [30]. Significantly, LVEF was found to be correlated with VO_2 peak pre- and post-training. A similar improvement in cardiac function in HD patients following an outpatient exercise training programme has already been detected by Momeni *et al.* [36]. Finally, long-term exercise has a beneficial effect on regulating BP in hypertensive HD patients and contributes to lower mortality [2, 24].

In conclusion, exercise training in HD patients represents an important complementary and cost-effective therapy, providing primary and secondary prevention of cardiovascular complications , acting as a physical 'polypill'.

EFFECTS OF EXERCISE ON SKELETAL MUSCLE MASS AND FUNCTION

Implementation of exercise programmes has the potential to induce favourable changes on body composition, muscle mass and strength, and functional capacity in patients both on peritoneal and extracorporeal dialysis.

Exercise training in HD patients

Studies regarding the effects of exercise training on muscle mass of CKD patients are quite heterogeneous. Most studies conducted on muscle mass estimation have measured either mid-arm and mid-thigh circumference or cross-sectional muscle area by computed tomography or magnetic resonance imaging. Recently, in patients on HD, ultrasonography of the quadriceps femoris muscle has been proposed as a noninvasive method exploitable also at the bedside [37]. A great variety of exercise protocols have been used to study changes in body composition. Successful increase of muscle mass was obtained by moderate to vigorous resistance training, using free weights or elastic bands, performed during the dialysis sessions or in an out-of-dialysis setting [38, 39]. On the contrary, modest or inconsistent changes in muscle mass were found by performing low to moderate intensity intradialytic exercises using ankle weights or elastic bands [40].

Enhancement of apoptotic processes and protein degradation causes skeletal muscle atrophy in CKD patients. Abnormal muscle intracellular signalling that involves the insulin receptor substrate/phosphatidylinositol 3-kinase/Akt pathway finally leads to reduced mammalian target of rapamycin (mTOR) stimulation and decreased protein synthesis. Hence, HD patients are characterized by high rate of muscle proteolysis with impaired protein synthesis [41]: exercise can partially reverse these changes by stimulating pAkt (Figure 1) [42]. Muscle hypertrophy is elicited by progressive resistance exercise that activates the serine/threonine–protein kinase mTOR complex 1, which regulates various cellular processes, including protein synthesis [43]. Kouidi *et al.* [44] studied muscle histology before and after a 6-month exercise programme in seven HD patients. At baseline, a marked atrophy of type II fibres more than type I fibres was observed, together with degenerative changes of mitochondria and reduced capillary density. After exercise training (90 min exercise session, three times a week on the non-dialysis days), type II fibres and average fibre area increased by 51% and 29%, respectively. Improvements of capillaries and mitochondria were also observed. In a similar study conducted on HD and continuous ambulatory peritoneal dialysis (PD) patients, Sakkas *et al.* [45] obtained comparable results after a 6-month aerobic exercise training programme; the average cross-section fibre area increased by 46% after training, and the proportion of atrophic fibres type I, type IIa and type IIx decreased (from 51% to 15%, 58% to 21% and 62% to 32%, respectively). An improvement

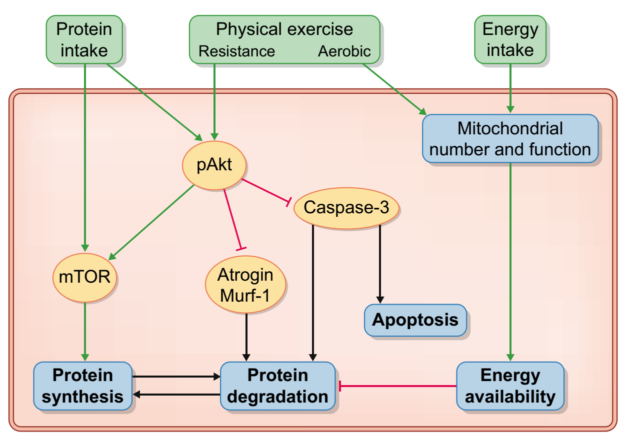

FIGURE 1: Possible mechanisms of interaction exerted by nutrition and physical exercise on muscle protein metabolism.

of the muscle capillary network was also observed. Kirkman *et al.* [46] showed that a 12-week period of an intradialytic progressive resistance exercise training resulted in an increase in thigh muscle volume. Moreover, endurance exercise results in an increase in mitochondrial number and protein synthesis rate, which could lead to an improvement of the aerobic capacity. Endurance exercise has been shown to activate signalling pathways associated with the increase of calcium concentration in the cell cytosol, an increased ATP turnover and the production of reactive oxygen species that promote mitochondrial adaptations [47]. The development of these adaptations needs several weeks of exercise training and the extent of mitochondria adaptations is linked to the exercise intensity [48].

The structural findings described above contribute to the improvement of the functional parameter. Muscle strength changes can occur earlier with a resistance exercise programme due to the rapid neural changes that allow muscle activation and subsequent increase in strength [49].

Table 1 shows a summary of randomized controlled trials (RCTs) on exercise programmes in patients undergoing HD. Below are the main results of these studies. Abdelaal and Abdulaziz [50] found that both aerobic exercise training and resistance exercise training had favourable effects, with aerobic exercise having higher short- and long-term favourable effects on the physical performance and functional balance than resistance training in 60 patients on maintenance HD. Similar conclusions were found by Orcy *et al.* [51] when comparing the effects of combined resistance and aerobic exercise with a resistance program alone on functional performance among HD patients. Interesting results were found also with intradialytic exercise programmes. Bohm *et al.* [52] compared the effects of intradialytic cycling versus a pedometer programme and found that both improved physical function, physical activity and QoL, while neither intervention had a significant effect on aerobic capacity.

In a stepped-wedge RCT study, 171 HD patients underwent progressive resistance training for 12–36 weeks using elastic resistance bands during the first hour of the HD session. The authors found an improvement of muscle strength and physical function, 30-s sit-to-stand (STS) test, 8-foot timed up and go (TUG) test, during resistance exercise periods, whereas a decline during non-exercise periods was observed [54].

Johansen *et al.* [61] tested the effect of nandrolone decanoate and resistance exercise on lean body mass of patients on HD. They found an anabolic effect of the combined treatment with an improvement of lean body mass measured by DEXA. No significant changes in lean body mass were found after resistance training alone but an improvement in self-reported physical functioning was described [61].

An improvement in patient's physical functioning was found also by Segura-Orti *et al.* [57] after a 24-week resistance training during HD: a significant change was found in right knee extensor muscles dynamometry and in the physical performance tests [STS and 6 min walking test (6MWT)] and metabolic equivalent tasks (METs) [57].

Out-of-dialysis exercise training was investigated in the EXerCise Introduction To Enhance performance in dialysis patients trial (EXCITE) [53]. This randomized, controlled, multicentre trial aimed to evaluate the effects of home-based low-intensity physical exercise programmes adapted to the baseline performance capacity of each patient. The 6MWT and STS performances significantly improved, together with self-reported QoL, in the exercise group but not in the control group [53].

In a sub-analysis limited to patients >65 years of age, cognitive function also improved, while it significantly declined in the control group [63].

Findings from a recent meta-analysis of 20 RCTs including 667 participants indicated an increased aerobic capacity, walking capacity and health-related QoL following aerobic exercise or combined exercise performed three times per week for at least 2–12 months [2].

Lu *et al.* [64] investigated the effect of exercise on muscle fitness, including muscle mass, muscle strength and physical performance. A total of 21 RCTs were included in this meta-analysis, which showed that regular resistance training with intensity variable from moderate to high may improve body composition, muscle mass and strength in HD patients. An amelioration of physical performance was observed both with aerobic and resistance training [64]. Exercise of moderate intensity, regardless of modality (intra- or inter-dialytic, endurance, resistance or a combination of both) resulted in improved physical function as assessed by 6MWT, STS tests, handgrip strength, TUG, step and stair climb tests, balance tests and sit-and-reach test [65].

Salhab *et al.* [66] examined the efficacy of aerobic intradialytic exercise on the QoL evaluated with the 36-Item Short Form Survey (SF-36) and other parameters such as dialysis efficiency, inflammatory status, mortality and hospitalization rate [66]. The results of the meta-analysis (12 studies were selected for quantitative analysis) showed a significant positive effect on the QoL physical component score of SF36 and on mental component score, but not on serum phosphorus or *Kt/V*. A limitation of this meta-analysis is represented by a limited number of studies included, the heterogeneity in the exercise programmes and the limited data for several outcomes [66].

This topic was investigated also by Ferrari *et al.* [67] in a meta-analysis of 50 studies involving 1757 HD patients. Aerobic, resistance and combined training during HD demonstrated positive effects on functional and clinical parameters in end-stage kidney disease (ESKD) patients [67]. Recently, Zhang *et al.* [68] conducted a meta-analysis to define a protocol for systematic review and meta-analysis of the literature to study the therapeutic efficacy of exercise interventions for patients undergoing HD on fatigue and health-related QoL that could contribute to limit the bias due to heterogeneity of exercise protocols and outcomes.

Combining exercise and nutritional intervention

The reduction of skeletal muscle mass in CKD patients is accelerated by HD commencing when a mismatch between increased protein requirement and inadequate dietary nutrient intake occurs in combination with increased protein catabolism and low physical activity. As already mentioned above, regular exercise may favour protein synthesis and anabolism, counteracting progressive loss of lean body mass. However, similar to elderly subjects, a reduced muscle protein synthetic response to feeding was reported in HD patients on the non-dialysis days [41]. It is conceivable that coupling physical exercise and protein intake can attenuate or even prevent muscle loss in HD patients more effectively than nutritional intervention or exercise programmes alone. Dong *et al.* [56] found an improvement in body weight and muscle strength when resistance exercise was combined with intradialytic nutritional supplementation; no effect on lean body mass was found when considering exercise training or nutritional supplementation separately. Majchrzak *et al.* [69] performed protein kinetic studies with stable isotope in HD

Table 1. RCTs published after 2000, including dialysis patients and regarding the effects of exercise on muscle structure and function

Author. ref.	Participants, n (Group)	Intervention	Exercise program (Duration)	Primary end point	ITT	
Abdelaal and Abdulaziz [50]	20 (I) 21 (I) 25 (C)	Aerobic exercise Resistance exercise	3 months	Physical performance and functional balance	Yes	Favourable effects with both aerobic and resistance exercise; aerobic exercise has higher short- and long-term favourable effects on physical performance and functional balance than resistance training
Manfredini *et al.* [53]	151 (I) 145 (C)	Home-based exercise	6 months	Functional capacity and QoL changes	Yes	Improvement of distance covered during the 6MWT, STS test, cognitive function score, quality of social interaction score kidney disease component of the KDQOL-SF in the exercise group but not in the control group
Bennet *et al.* [54]	51 (I_1) 61 (I_2) 59 (I_3)	I_1: 36 weeks programme I_2: 24 weeks programme I_3: 12 weeks programme Progressive resistance intradialytic training using resistance elastic bands	12 months	30-s STS test, the 8-foot TUG test and the four-square step test		Improvement of muscle strength and physical function, STS test, TUG, during resistance exercise periods, decline during non-exercise periods
Bohm *et al.* [52]	30 (I) 30 (I)	Intradialytic exercise (cycling), home-based walking	6 months	Aerobic capacity (6MWT, VO_{2max})	Yes	Both improved physical function, physical activity and QoL No significant effect on aerobic capacity
Orcy *et al.* [51]	13 (I) 13 (C)	Resistance + aerobic training Resistance training alone	10 weeks	Functional performance (6MWT)	Yes	Significant improvement of 6MWT in the I group
Song and Sohng [55]	20 (I) 20 (C)	Progressive resistance training	3 months	Skeletal muscle mass, grip, leg muscle strength and QoL	Yes	Increase of muscle strength and of QoL
Dong *et al.* [56]	15 (I) 17 (C)	Resistance training + intradialytic nutrition (both group receiving nutritional supplementation)	6 months	Body composition (lean body mass)	No	No statistically significant differences between the I and C groups as regard lean body mass and body weight Improved body weight and muscle strength during the study when treatments were combined
Koh *et al.* [28]	27 (I) 21 (I) 22 (C)	Intra-dialytic cycling, home-based walking	6 months	Distance walked during a 6MWT	Yes	No differences between intradialytic or home-based exercise training and usual care for either physical function
Segura-Orti *et al.* [57]	19 (I) 8 (I)	resistance training low-intensity aerobic training	6 months	(STS test, 6MWT), knee extensor muscles (isometric dynamometry)	Yes	Improvement of physical functioning; significant change in right knee extensor muscles dynamometry, STS, 6MWT and METs
Kopple *et al.* [58]	10 (I) 15 (I) 12 (I) 14 (C)	Endurance training, strength training, endurance plus strength training	5 months	Body composition (body cell and fat mass); mid-thigh cross-sectional area skeletal muscle protein mRNA	No	Decrease in body fat, increase in fat-free mass Significant increase of muscle protein Decrease of muscle mRNA for myostatin

(continued)

Table 1. (continued)

Author. ref.	Participants, n (Group)	Intervention	Exercise program (Duration)	Primary end point	ITT	
Cheema *et al.* [59]	24 (I) 25 (C)	Intensive resistance training	3 months	Thigh muscle cross-sectional area, intramuscular lipid infiltration muscle quantity and quality	Yes	No significant difference in muscle cross-sectional area change between groups Significant improvements in muscle strength, mid-thigh and mid-arm circumference, body weight
Yurtkuran *et al.* [60]	19 (I) 18 (C)	Yoga-based exercise	3 months	Pain intensity, fatigue, sleep disturbance	Yes	Improvement in strength, fatigue, pain, sleep disturbances
Johansen *et al.* [61]	20 (I) 20 (I) 19 (I) 20 (C)	Resistance exercise training training exercise + nandrolone nandrolone	3 months	Body composition (lean body mass), muscle size, physical performance	Yes	Anabolic effect with combined treatment, improvement of lean body mass. No significant changes in lean body mass after resistance training alone. Improvement in self-reported physical functioning
Koufaki *et al.* [62]	18 (I) 15 (C)	Cycling	3 months	Aerobic and functional capacity	Yes	Improvement of peak exercise capacity. Measurements of functional capacity suggest that longer time might be needed to induce peripheral adaptations

I, intervention group; C, control group; ITT, intention-to-treat analysis; KDQOL-SF, Kidney Disease Quality of Life Short Form

patients after oral nutritional supplementation or oral dietary supplementation combined with resistance exercise. They observed that activity significantly increased the protein anabolic effects of oral intradialytic nutritional supplementation. In the untrained subjects, resistance exercise coupled with whey protein intake induced higher phosphorylation of mRNA translational signalling proteins than exercise alone, leading to enhanced protein synthesis [70]. Also, activation of mTOR signalling by whey protein intake after resistance exercise occurs in a dose-dependent manner [71].

Exercise in peritoneal dialysis

Few studies have investigated the prevalence of sedentary lifestyle, reduced exercise tolerance or the impact of exercise training on performance capacity and muscle function in PD patients. Patients on PD present reduced physical capacity and activity measures when compared with the general population [72]. In elderly PD patients, the percentage of sedentary lifestyle is high, but similar to that of elderly CKD patients [73]. Physical activity and function was reduced mainly with age. In a cohort of PD patients, Uchiyama *et al.* [74] recently reported that younger age and male gender were associated with higher aerobic capacity and muscle strength. In contrast, skeletal muscle index (measured by DEXA) was positively correlated with muscle strength but not with aerobic capacity. The authors found a strong positive correlation between aerobic capacity (measured by the incremental shuttle walk test) and health-related QoL scores. Koufaki *et al.* [62] showed an improvement in peak exercise tolerance, exercise capacity both in HD and PD patients after a 3-month aerobic cycling programme. The authors suggested that long exercise training time might be needed to induce peripheral adaptations resulting in an evident improvement of functional capacity. Increase of VO_2 peak and QoL outcomes in PD patients were also reported by Lo *et al.* [75] after 12 weeks of structured aerobic exercise [76].

Adherence to exercise protocols

Compliance with exercise programs was not always investigated in RCTs. Carmack *et al.* [77] found a compliance of 84.2% to an individualized exercise protocol consisting of ergometer cycling three times/week for 20–30 min during dialysis session. Frey *et al.* [78] implemented an exercise programme where the patients cycled on stationary bicycle ergometers during the second hour of dialysis treatment (three times per week). Exercise time was progressively increased in the first 4 weeks to 45 min, and then maintained at 45 min during the following 4 weeks. Patients in the control group remained sedentary throughout the 12-week study. Kouidi *et al.* [31] found 88.3% compliance to a 10-month intra-dialytic mixed cardiovascular and resistance training programme. In the RCT by Chen *et al.* [40], patients followed a 6-month supervised resistance exercise training programme. The training sessions were performed twice a week during the second hour of HD. The control group did stretching exercises and continued their usual activities. The compliance was 89 ± 14% in the treatment group and 90 ± 17% in the control group. Koh *et al.* [28] randomly assigned 70 HD patients to a supervised intra-dialytic exercise group and an unsupervised home-based exercise group. Twenty-two patients who did not exercise formed the control group. Compliance to exercise programmes was 75 ± 19% in intradialytic exercise-group and 71 ± 13% in the home-based exercise group. Compliance to the exercise sessions was evaluated in the last 4 weeks and it was the 83% in the treatment group. Manfredini *et al.* [53] found a 87.5% overall adherence to a 6-month home-based, low-intensity exercise protocol, and they reported as main determinants of low adherence a scarce interest, orthopaedic limitations, intercurrent nonorthopaedic problems and concerns related to work activities.

Possible alternative to active exercising

Unfortunately, several barriers to exercising exist in dialysis patients [79]. When exercise programmes are not available, or patient incapacity or unwillingness occur, alternative strategies as neuromuscular electrical stimulation (NMES) might be considered. A meta-analysis of eight studies including 221 patients showed that NMES applied during HD sessions enhanced functional capacity as assessed by the performance at the 6MWT and peak workload during incremental exercise [80]. An increased knee extensor muscle strength and handgrip strength emerged, but muscle mass and muscle structure did not change, nor did cardiovascular outcomes. NMES may be a safe, practical and effective chance to improve muscle strength, especially in those patients at risk of complication during intradialytic exercise or who are unwilling to join active exercise programmes [80].

In summary, exercise training programmes, regardless of the modality, are effective in improving cardiovascular aspects, physical function, and muscle strength and mass. Additional effects are represented by amelioration of mood, increased appetite and nutrient intake, and a better QoL. Overall, a virtuous circle is created: a positive strategy able to prevent progressive loss of muscle mass, and ameliorate body composition, functional and nutritional status in ESKD patients.

CONFLICT OF INTEREST STATEMENT

None declared.

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