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NEPHROLOGY - REVIEW

The impact of exercise on physical function, cardiovascular outcomes and quality of life in chronic kidney disease patients: a systematic review

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Abstract
The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is increasing steadily. CKD does not only relate to morbidity and mortality but also has impact on quality of life, depression and malnutrition. Such patients often have significantly decreased physical activity. Recent evidence suggests that low physical activity is associated with morbidity, mortality, muscle atrophy, quality of life impairment, cardiovascular outcomes and depression. Based on this, it is now recommended to regularly improve the physical activity of these patients. Furthermore, studies have shown the beneficial effects of various exercise programs with respect to outcomes such as low physical activity muscle atrophy, quality of life, cardiovascular outcomes and depression. Despite these encouraging findings, the subject is still under debate, with various aspects still unknown. In this review, we tried to critically summarize the existing studies, to explore mechanisms and describe future perspectives regarding physical activity in CKD/ESRD patients.

Keywords Exercise · Quality of life · Chronic kidney disease · End-stage renal disease

Introduction

Chronic kidney disease (CKD) is currently recognized as a global public health concern, with a substantial amount of end-stage renal disease patient in need for renal replacement therapy or kidney transplantation [1–3]. Apart from increased morbidity and mortality, the CKD causes decreased quality of life, malnutrition, impaired cognitive function, deteriorated sleep and increased depression rate among CKD patients [4, 5].

Patients with CKD/ESRD are often inactive. This has both a physiologic and a psychological basis. With routine dialysis interventions performed three times per week for 4–5 h per session, physical activities of dialysis patients are significantly limited, resulting in functional disability and inactivity [6, 7]. Furthermore, the patients have protein energy wasting and also muscle atrophy which also limits their physical activity [8]. As these patients are also depressive, most of them have limited energy and a decreased will for daily activities [9]. Each of these conditions (decreased quality of life, depression, decreased physical activity, muscle atrophy) per se is also related to increased morbidity and mortality [10–12]. Given the fact that low physical activity

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is frequent and related to morbidity and mortality, the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines recommends to routinely counsel dialysis patients on increasing their physical activity levels [13, 14]. It was suggested that exercise has also a direct effect on glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) [15].

Various studies have proven exercise to have impact on physical activity, quality of life, depression and cardiovascular function [16–20]. These data stimulate researchers to perform studies regarding the effects of aerobic and/or anaerobic exercise in CKD and ESRD patients. Bearing these issues in mind, in this review we tried to summarize the studies regarding the impact of exercise in CKD and ESRD patients including hemodialysis and peritoneal dialysis patients.

Methods

Data sources and literature search

A literature search was performed using electronic databases MEDLINE, Ovid/MEDLINE (1988–2017), PubMed/MEDLINE, Embase and ISI Web/Web of Science for published studies from January 1988 to April 2017. We searched for relevant studies using the keywords "chronic kidney disease," "not on dialysis," "predialysis," "uremia," "hemodialysis," "peritoneal dialysis," "end stage renal disease," "exercise," "quality of life," "physical activity," "depression," "muscle atrophy," "cardiovascular events" and "all-cause mortality" limiting the search. Only research articles involving humans and published in English were included. Neither unpublished data nor abstracts were included (Fig. 1).

Study selection

Eligibility criteria for inclusion in this review were: randomized or observational design, patients with CKD and ESRD (both hemodialysis and peritoneal dialysis), exercise

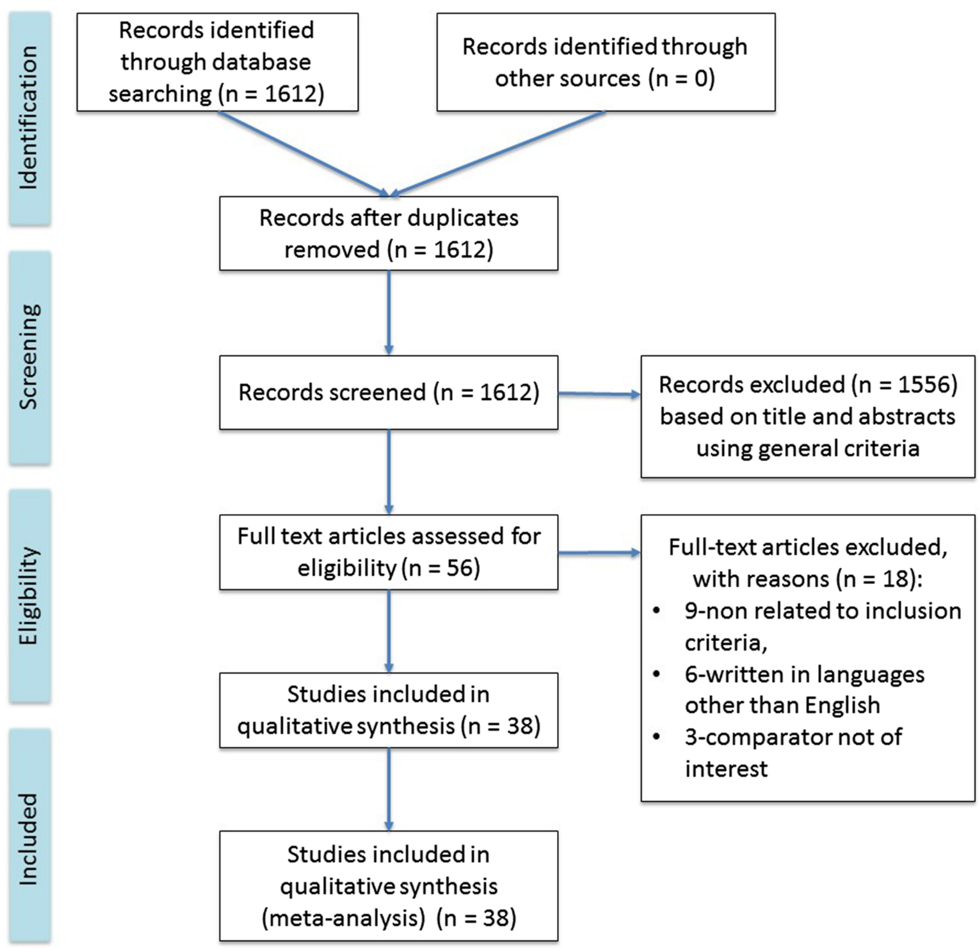

Fig. 1 Flow diagram of the study selection process

test performed, reports of quality of life, "physical activity," "depression," "muscle atrophy," "cardiovascular events" and "all-cause mortality."

The quality of the studies was assessed by the Newcastle–Ottawa scale [21]. This scale used selection of the study groups, the comparability of the groups and the assessment of outcome. Stars were given for each quality item to serve as a quick visual assessment, and the highest quality studies are awarded up to nine stars (Table 1).

Outcome measures

We assessed the association between any exercise program (endurance, resistance or combination) with "physical activity," "depression," "muscle atrophy," "cardiovascular events" and "all-cause mortality."

Results

There are currently 38 studies, 22 observational [6, 22–43] and 16 randomized [16, 20, 29, 44–54], investigating the relationship between exercise and the change in body composition, arterial stiffness, blood pressure (BP), physical function, muscle performance, cardiopulmonary exercise performance and/or quality of life. Studies involving ESRD patients and CKD patients are summarized in Tables 2 and 3, respectively. The majority of these studies were performed in HD [6, 22–33, 44, 47, 48, 52, 53], while 6 were done in CKD not on dialysis [16, 20, 34, 35, 50, 51], 2 in both HD and PD [45, 46] and 1 in transplanted patients [49]. The exercise period varied between 4 weeks [22] and 5 years [28]. The types of training involved in these studies were heterogeneous: *only aerobic*—cycle ergometer or stationary bike [6, 22, 23, 25, 29–31, 44, 47, 49, 52], walking [16, 45, 46] or a combination of different aerobic methods [20, 26, 51]; *only anaerobic* [24, 34, 47, 52, 53]; *both aerobic and anaerobic* [27–30, 32, 48–50]. There was also a study that used a virtual reality exercise program [33].

Exercise and body composition

Four studies evaluated this relationship [6, 16, 33, 53]. Three studies used bioimpedance to assess body composition [6, 33, 53], while the last one used dual-energy X-ray absorptiometry [16]. While some of these studies showed that there was no improvement in muscle mass [6, 16], body fat mass [6], fat percentage [6, 16], arm muscle mass [33] or body fat rate [33], some showed a significant increase in skeletal muscle mass [33, 53], leg muscle mass [33] or decrease in body fat rate [53].

Exercise and arterial stiffness

Three studies examined this association [20, 49, 50]. Mustata et al. [20] showed that in patients with CKD stages 3 and 4, with different aerobic exercises for 12 months the augmentation index is improved in the exercise group. Similarly, in CKD non-dialysis patients, Greenwood et al. observed a reduction in the pulse wave velocity, both in 6 and 12 months, by using a combined aerobic and anaerobic training as compared to a usual-care group [50]. Later, the same group also showed that in transplanted patients, either an aerobic or anaerobic type of exercise for 12 weeks significantly reduced the pulse wave velocity as compared with a control group [49].

Exercise and blood pressure

This relationship was evaluated in 5 studies [16, 23, 25, 32, 50]. Henrique et al. [23] showed that a 12-week program of 30 min on cycle ergometer in the first 2 h of each hemodialysis session significantly reduces average systolic, diastolic and mean BP (assessed with ambulatory BP monitoring) despite maintaining the same doses of antihypertensive drugs and dry weight of patients. Musavian et al. [25] revealed that passive intradialytic pedaling exercise (and not active pedaling) was associated with an improvement in diastolic BP as compared with the control group. There was no benefit of passive or active pedaling in regard to systolic BP. Aoike et al. [16] also showed that walking for 30 min for 12 weeks is associated with an improvement in both systolic and diastolic BP control. However, the remaining studies did not find any benefit for BP control by using a combined aerobic and anaerobic training [32, 50].

Exercise and physical function

This relationship was evaluated in 18 studies [6, 16, 22–24, 26–30, 32, 34, 45–47, 49, 51–53]. Numerous tests were used to assess physical function, the more frequent being: the six- [6, 16, 23, 24, 26–29, 34, 45–47, 51] or 10-min [22] walk test; sit-to-stand test [27–30, 45, 47, 48, 50, 51, 53]; timed up and go test [16, 22, 28, 34]; and stair climb time [22, 32, 52].

In regard to the walk test, an improvement in the distance walked in the specific time interval (6 or 10 min) was observed in the majority of the studies [6, 16, 23, 26, 27, 29, 34, 45, 46, 51]. Anding et al. [28] observed a beneficial effect only at 12 months, but not at 6 months of follow-up. There were 2 studies that did not find a statistically significant improvement of this test with exercise [24, 47]. Similar findings were also observed for the sit-to-stand test. Exercise was associated with a significant increase in the number of repetitions or the time to perform a number of repetitions in

Table 1 Newcastle–Ottawa quality assessment of the included trials

Trial, (year)	Case cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Outcome assessment	Duration of follow-up	Adequacy of follow-up	Total score
Bae et al. [6]	*	*	*	*	*	*	*		7
Thomas et al. [22]	*	*	*		*	*	*	*	7
Mooreet al. [37]	*	*	*	*	*	*			6
Henrique et al. [23]	*	*	*	*		*	*	*	7
Fassbinder et al. [7]	*	*	*	*		*	*	*	7
Aoike et al. [16]	*	*	*	*	*	*	*	*	8
Rebored et al. [44]	*	*		*	*	*	*		6
Manfredini et al. [45]	*	*	*	*	*	*	*	*	8
Chan et al. [24]	*	*	*	*		*	*	*	7
Ting et al. [38]	*	*	*	*	*	*			6
Musavian et al. [25]	*	*		*	*	*	*	*	7
Parsons et al. [26]	*	*		*	*	*	*	*	7
Esteve Simo et al. [27]	*	*		*	*	*	*	*	7
Dungey et al. [54]	*		*	*	*	*	*	*	7
Anding et al. [28]	*	*	*	*	*	*	*	*	8
Pomidori et al. [46]	*	*	*	*	*	*	*	*	8
Thompson et al. [47]	*		*	*	*	*	*	*	7
Painter et al. [30]	*	*	*	*	*	*	*	*	8
van Vilsteren et al. [48]	*	*	*	*	*	*	*	*	8
Chang et al. [31]	*	*	*	*	*	*	*		7
Molsted et al. [32]	*	*	*	*	*	*	*	*	8
Cho et al. [33]	*	*	*	*	*	*	*	*	8
Painter et al. [29]	*	*	*	*	*	*	*	*	8
Greenwood et al. [49]	*	*	*	*	*	*	*	*	8
Hadebank et al. [39]	*	*	*	*	*	*			6
Sato et al. [99]	*	*	*	*	*	*			6
Scrutinio et al. [81]	*	*	*	*	*	*	*	*	8
Esteve Simo et al. [36]			*	*	*	*	*	*	6
Peres et al. [43]	*			*	*	*	*	*	6
Tang et al. [51]	*	*	*	*	*	*	*	*	8

Table 1 (continued)

Trial, (year)	Case cohort representative	Selection of non-exposed control	Ascertainment of exposure	Outcome negative at start	Comparability by design	Outcome assessment	Duration of follow-up	Adequacy of follow-up	Total score
Greenwood et al. [50]	*	*	*	*	*	*	*	*	8
Downey et al. [71]	*	*	*	*	*	*			6
Svarsted et al. [15]	*	*	*	*	*	*	*	*	6
Ulubay et al. [41]	*	*	*	*	*	*	*	*	8
Ulubay et al. [40]	*	*	*	*	*	*	*	*	8
Sezer et al. [42]	*	*	*	*	*	*	*	*	8
Faria et al. [66]	*	*	*	*	*	*	*	*	8
Samara et al. [17]	*	*	*	*	*	*	*	*	8

*Stars awarded for each quality item (Newcastle–Ottawa scale). For each domain, either a "star" or "no star" is assigned, with a "star" indicating that study design element was considered adequate and less likely to introduce bias. A study could receive a maximum of nine stars

the majority [16, 27–29, 45, 48, 50, 53], but not in all the studies [30, 47, 53]. Greenwood et al. observed an improvement in this test only in the anaerobic group and not also in the aerobic one, as compared with controls [49].

All the studies that assessed physical function using the timed up and go test showed a significant beneficial effect of training [16, 22, 28, 34]. Two studies found a significant decrease in time to climb [22, 52], while in the study by Molested et al. [32], this time did not change after 12 training.

Exercise and muscle performance

Ten studies evaluated the relationship between exercise and muscle performance [6, 22, 24, 27, 33–35, 47, 50, 53]. Lower body muscle performance was assessed by various tests including leg-press strength [22, 24, 33, 53], one repetition maximum [34, 35, 47], leg extension power [22, 27, 50], maximum peak torque of the knee [6]. Handgrip was used as a surrogate for upper body muscle performance [24, 27, 33, 53].

Leg-press strength is improved following exercise in all the studies [22, 24, 33, 53]. The results for the other tests are more heterogeneous. Thompson et al. [47] did not observe a significant increase in one repetition maximum after training, while the other two studies have found an improvement in this parameter [34, 35]. Similarly, Esteve et al. [27] showed an increase in leg extension power, Greenwood et al. [49] found a similar increase, but only in those that were performing anaerobic, and not aerobic, exercise, while Storer et al. [22] did not find any beneficial effect of training on this test. There was no improvement in knee peak torque after training [6]. Handgrip was improved in only one study [27].

Exercise and cardiopulmonary exercise performance

Cardiopulmonary exercise performance was assessed by measuring maximum oxygen uptake [6, 16, 20, 22, 23, 32, 48–50]. Only five of these studies found an improvement in maximum oxygen uptake following training [20, 22, 32, 49, 50].

Exercise and quality of life

Sixteen studies assessed the effect of training on quality of life [6, 20, 24–30, 32, 45, 47, 48, 51–53] and/or depression [48, 51]. The most frequently used questionnaire was the short form 36 (SF-36) [6, 20, 24–26, 29, 30, 32, 47, 51, 52], which evaluates the changes in eight subscales of quality of life: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Based on these subscales, physical component summary (PCS) and mental component summary (MCS) domain scores could also be calculated. Other questionnaires used were: the Kidney Disease Quality of Life Short Form (KDQOL-SF) [45, 52], the EuroQol-5D (EQ-5D) [20, 27], Short-Form General Health Survey (RAND-36) [48].

The effect of exercise on quality of life differs depending on the study chosen. Among studies that reported on every subscale of SF-36, three studies showed no statistically significant change in any of the domains [6, 20, 26]. While some studies suggested a significant improvement in the PCS [29, 32, 47, 51] and/or MCS [51, 53] with training,

Table 2 Characteristics of the included trials that involve end-stage renal disease patients

Trials	Type	Patients number	Sex (male), (%)	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on CV risk
Bae et al. [6]	Prospective	10 HD patients	40	56.5 ± 4.5	12 weeks	Overall physical function and QoL before and after aerobic training were evaluated by body composition, 6MWT, CPET and questionnaire for QOL	Safe	Benefit on QOL and physical performance
Storer et al. [22]	Prospective	36 HD patients	58	44 ± 9	9 weeks	Endurance training effect on cardiopulmonary fitness	Leg cycling during HD improves cardiopulmonary fitness, physical performance, muscle function	N/A
Moore et al. [37]	Prospective	8 HD patients	75	46.9	N/A	Cardiovascular response to submaximal stationary cycling during a HD is evaluated by cardiac output, stroke volume, MAP (a–v) O_2	Cardiovascular response to exercise is superimposed on the hemodynamic effects of dialysis and that the cardiovascular response to submaximal exercise	Training is recommended for the first 2 h of the dialysis
Henrique et al. [23]	Prospective	14 HD patients	28	47.6 ± 12.7	12 weeks	BP, 6MWT, CPET assess effects of individualized aerobic training on physical capacity	Aerobic exercise during dialysis results with increased physical capacity, better control of hypertension	Contribution to better BP control during dialysis
Reboredo et al. [44]	Randomized	24 HD patients	41	50.7 ± 11	12 weeks	Evaluations of the intradialytic exercise on effectiveness VO_2 peak, 6MWT and Tlim compare constant and incremental work rate tests	Constant work rate test is more sensitive to measure the Tlim, VO_2 peak and effort-related physiologic changes	N/A

Table 2 (continued)

Trials	Type	Patients number	Sex (male), (%)	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on CV risk
Manfredini et al. [45]	Randomized	227 HD patients	66	63 ± 13	6 months	Effects of home-based exercise program on physical capacity and BP, 6MWT, 5STS and evaluate QoL	Walking capacity and quality of social interaction are improved in active arm patients who are performing low-intensity home-based exercise	Improvement of QoL and walking capacity
Chan et al. [24]	Prospective	22 HD patients	59	71 ± 11	12 weeks	To determine the feasibility of a novel PRT device, physical functioning and psychological health status is measured	Intradialytic exercise with this novel device resulted with the improvement in the lower muscle strength and several subscales of HRQoL	Better outcomes in physical functioning and psychological health
Ting et al. [38]	Prospective	160 patients	53	53.3 ± 9.1	N/A	Investigation of the association between decreased VO_2 peak and cardiovascular changes by using VO_2 testing, CPET, echocardiography and pulse wave analysis	VO_2 peak is significantly decreased and LV mass is higher	The maladaptive LV changes as well as blunted chronotropic response are important mechanistic factors resulting in reduced cardiovascular reserve
Musavian et al. [25]	Prospective	16 HD patients	81.2	51.9 ± 1.5	8 months	Comparing the effects of active and passive exercise during HD on QoL	The mean diastolic BP was significantly decreased after the passive intradialytic exercise program	The passive intradialytic exercise had a positive effect on BP
Parsons et al. [26]	Prospective	13 HD patients	61.53	53 ± 18	20 weeks	KDQOL is measured to see the effects of 5-months intradialytic exercise	Overall increase in the clearance of serum urea and better performance on the 6MWT	Improvements in the dialysis efficacy and physical function capacity

Table 2 (continued)

Trials	Type	Patients number	Sex (male), (%)	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on CV risk
Esteve Simo et al. [27]	Prospective	22 patients	48	84 ± 3.96	12 weeks	Muscle strength, 6MWT and QoL values are measured to determine the effects of intra-dialytic exercise in elderly HD patients	A significant increase in 6MWT and muscle strength in exercise group is observed. Better mood is measured via QoL questionnaire in exercise group	Better outcomes in physical capacity and facing with depression
Dungey et al. [54]	Randomized	15 HD patients	60	57.9 ± 10.5	12 weeks	Effects of intra-dialytic exercise on inflammation	Systolic BP has increased, but no significant change is detected in inflammatory markers	Increased BP without markers of the myocardial damage
Anding et al. [28]	Prospective	46 HD patients	52	63.2 ± 16.3	1-year to 5-year follow-up	Effect of physical exercise program on 6MWT, STS60, maximal strength measurement and QoL	The increased scores of 6MWT and STS60 tests showed significant benefit on physical mobility and QoL	Improvement in adherence to individual exercise program and better QoL with increased mobility. Exercise improves physical function significantly
Pomidori et al. [46]	Randomized	42 HD patients	72	63 ± 15	6 months	Assessment of the effects of low-intensity exercise on respiratory muscle function	Significant difference in maximal inspiratory pressure in favor of exercising group	Positive effects on respiratory muscle strength
Thompson et al. [47]	Randomized	31 HD patients	77	57.6 (49–75)	12 weeks	Evaluating the feasibility and the efficacy of exercise during HD on QoL	Strategies to increase acceptability of the intervention for staff include improving workflow. Secondary outcomes were not statistically significant	N/A

Table 2 (continued)

Trials	Type	Patients number	Sex (male), (%)	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on CV risk
Painter et al. [30]	Randomized	194 HD patients	N/A	57.9 ± 14	2 months	Comparing the responses to intervention of HD patients on the PCS on the Medical Outcomes Study	Low functioning HD patients can benefit from exercise counseling in the both objective measures of the physical functioning and self-reported physical functioning	N/A
Van Vilsteren et al. [48]	Randomized	98 HD patients	66	52 ± 15	12 weeks	To determine exercise program could improve behavioral change, physical fitness, physiologic condition and health-related QoL	Participating in a low- to moderate-intensity pre-conditioning exercise program showed beneficial effects on physical fitness and health-related QoL	N/A
Chang et al. [31]	Prospective	71 HD patients	70	51 ± 11	8 weeks	To evaluate the effect of intradialytic leg ergometry exercise for improving fatigue and daily activity levels	Intradialytic leg ergometry is safe exercise that is effective to reduce fatigue and improve physical fitness	N/A
Molsted et al. [32]	Randomized	33 HD patients	47	59 (25–58)	5 months	To determine the effects of 5-month physical exercise of HD patients' physical capacity	Physical exercise twice a week for 5 months increases physical function and aerobic capacity	There was no medical complication related to the exercise program. No significant changes were observed in BP and lipid profile
Cho et al. [33]	Randomized	48 HD patients	60	61 ± 7	8 weeks	To investigate the effects of a virtual reality exercise program on physical fitness and fatigue	VREP improves physical fitness, body composition and fatigue	N/A
Painter et al. [29]	Randomized	286 HD patients	40	56 ± 15	8 weeks	To test the effects of exercise programming on the levels of physical activity and functioning, self-reported health status	The intervention group showed increased participation in physical activity	N/A

Table 2 (continued)

Trials	Type	Patients number	Sex (male), (%)	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on CV risk
Hadebank et al. [39]	Prospective	50 patients	80	46 ± 10	N/A	Evaluating the better characterize vasodilation and exercise capacity	Exercise capacity was relatively preserved, while vasodilative capacity was substantially impaired	Endothelium-derived vasodilative capacity is reduced to extent typically observed in heart failure patients despite better exercise capacity
Ulubay et al. [41]	Prospective	22 HD patients	54	30 ± 8	N/A	Pre-operative evaluation of the pulmonary function with CPET and PFT	CPET and PFT parameters are viable in dialysis patients except TLC and RV since they are negatively affected by the presence of dialysate	N/A CPET and PFT are reliable tests for pulmonary evaluation
Ulubay et al. [40]	Prospective	22 HD patients	54	29.6 ± 8.3	N/A	Investigation of the determining factors of peak VO_2 by CPET, PFT	The only significant data are positive correlation between the peak VO_2 and serum phosphorus level	N/A Sedentary lifestyle is not contributing factor for limiting exercise capacity
Sezer et al. [42]	Prospective	30 HD patients	53	40.2 ± 10.3	N/A	Identification of the contributing factors to exercise capacity by using PFT, MIS and CPET	Malnutrition Inflammation Score is negatively correlated with VO_2 peak. Also, VO_2 peak is negatively correlated with serum ferritin and positively with serum triglyceride level	N/A Chronic malnutrition and inflammation may cause decreased exercise capacity
Greenwood et al. [49]	Randomized	46 Renal transplant patients	65	54 ± 11	12 weeks	To examine the potential of aerobic training or resistance training on vascular health and indexes of cardiovascular risk	Both aerobic training and resistance training interventions appear to be feasible and clinically beneficial	There were no reported adverse events, cardiovascular events or hospitalizations as a result of the intervention

Table 2 (continued)

Trials	Type	Patients number	Sex (male), (%)	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on CV risk
Peres et al. [43]	Prospective	9 HD patients	64.8 ± 1.9	2 weeks	Assessment of the effects of intra-dialytic exercise on acute systemic inflammation	A significant increase of IL-10 is obtained at the end of the HD session accompanied by intradialytic exercise	Improvement in the anti-inflammatory response	Peres et al. (2015) [43]
Esteve Simo et al. [36]	Prospective	40 HD patients	55%	68.4	24 weeks	To examine the beneficial effect of intradialysis endurance training program on muscular strength and functional capacity	Intradialysis training program improved muscular strength and functional capacity	N/A

BP blood pressure, *CKF* chronic kidney failure, *ESRD* end-stage renal disease, *HD* hemodialysis, *HTN* hypertension, *HRQoL* health-related quality of life, *KDQOL* Kidney Disease Quality of Life Short Form, *MAP* mean arterial pressure, *MEP* maximal expiratory pressure, *MIP* maximal inspiratory pressure, *N/A* not applicable, *6MWT*, 6-min walk test, *PCS* Physical Component Scale, *PFT* pulmonary function test, *PRT* progressive resistance training, *STS60* the sit-to-stand test, *TLC* total lung capacity, *Tlim* time to exercise intolerance, *TSL1* sit and stand 1-min test, VO_2 oxygen uptake

others did not [20, 24, 26, 47]. Painter et al. [29] observed an increase in the PCS, but not in the MCS, only in those patients with low baseline PCS values.

Using the KDQOL-SF questionnaire, Manfredini et al. showed that the global score on average changed favorably in the exercise condition compared with the control arm, but the difference largely failed to achieve any statistical significance. When compared with changes in the control arm, only two items—both in the kidney disease component (cognitive function and quality of social interaction)—achieved formal statistical significance [45]. In the other study that used the same questionnaire, the anaerobic training group reported a better quality of life in terms of social support, patient satisfaction and general health, while the aerobic training group described a general well-being related to domains referring to physical functioning, pain, symptoms, sleeping, sexual function and energy/fatigue [52].

There was no improvement in the quality of life when the EQ-5D questionnaire was used [20, 27]. There was an improvement for the RAND-36 components of vitality, general health perception and health change [48].

The effect on depression was assessed separately using the geriatric depression scale [24], the beck depression inventory [27], the self-rating depression scale [48] or the hospital anxiety and depression scale [51]. With the exception of one study [48], all studies mentioned a significant improvement in depression assessments [24, 27, 51].

Discussion

Exercise has favorable effects on various parameters including physical function and muscle function/atrophy. It is known that physical inactivity is associated with increased mortality in CKD patients [55, 56].

It was shown that physical activity is increased in CKD and ESRD patients after exercise programs [18, 22, 23, 26, 29, 31, 34, 45, 57, 58]. Physical work capacity is generally decreased in HD patients due to myopathies, neuropathies, peripheral vascular pathology or anemia [59]. As these pathologies are associated with uremic toxins, it was hypothesized that increased toxin clearance with intradialytic exercise would minimize their effect on various physiologic systems, thereby enhancing cardiovascular and skeletal muscle performance [26]. With regard to muscle wasting, it was shown that both high-intensity and low-intensity training programs improved the muscle strength in HD patients [60–64]. Storer et al. demonstrated that after 8.6 ± 2.3 weeks of endurance exercise performed three times every week significantly increases leg-press strength and fatigability. Similarly, a trend for improved leg extension power has been observed [22]. The finding is somehow contradictive since endurance training has little effect on the development of

Table 3 Characteristics of the included studies that involve chronic kidney disease patients

Trial, (year)	Type	Patients number	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on cardiovascular risk (CV)
Sato et al. [99]	Prospective	505 patients	66.4 ± 11	N/A	Comparison of the prognostic factors of chronic heart failure patients with and without CKD by echocardiography and CPX data	Peak VO_2 is the prognostic factor in CHF patients with CKD	N/A
Scrutinio et al. [81]	Prospective	2938 HF patients	57.9 ± 12.4	3.7 years	Investigation of the correlation between renal function and VO_2 peak value as a prognostic factor	Renal dysfunction is positively correlated with decreased VO_2 peak as a CPET-derived variable	In HF patients with poor renal function peak VO_2 offers limited prognostic information
Tang et al. [51]	Randomized	90 CKD patients	46 ± 15	12 weeks	To examine the effects of a 12-week home-based exercise program on physical function and health-related QoL	Home-based individualized exercise program is an effective and feasible way of improving physical function, psychological stress and QoL	N/A
Greenwood et al. [50]	Randomized	20 CKD patients	54 ± 13	12 months	To examine the effect of moderate-intensity exercise training on kidney function and indexes of cardiovascular risk	The effect of a 1-year exercise intervention on progression of kidney disease is inconclusive	Significant between group mean differences existed in PWV, waist circumference and VO_2 peak
Downey et al. [71]	Randomized	59 CKD patients	57 ± 1	Daily (during maximal exercise test)	BP and endothelial responses during maximal whole body exercise	Low FMD correlates with augmented BP responses during exercise and lower peak VO_2	NO bioavailability may ameliorate exaggerated exercise pressor responses, improve exercise tolerance
Svarsted et al. [15]	Randomized	40 CKD patients	46 ± 3	2 h	Effect of prolonged low-intensity bicycle exercise on hemodynamic variables	The prolonged low-intensity exercise has a substantially greater effect on renal hemodynamics in CKD patients	N/A
Aoike et al. [16]	Randomized	29 CKD patients	55.1 ± 11.6	12 weeks	Impact of home-based exercise on the physical capacity, CPET, VO_2 peak, 6MWT, functional capacity test	Home-based exercise increased oxygen consumption, improvement in physical conditions and better sleep quality	Effective on the cardiopulmonary and functional capacities
Fassbinder et al. [7]	Prospective	54 CKD patients	58.1 ± 10.8	N/A	Physical capacity and QoL are compared in HD patients and pre-dialysis patients by measuring the MIP, MEP, VO_2 peak, 6MWT, TSL1	Functional capacity is decreased in both HD and pre-HD patients	Physical therapy can play key role in CKD patients

Table 3 (continued)

Trial, (year)	Type	Patients number	Age (mean, year)	Follow-up (time)	Outcome measure	General effects of exercise	Effect on cardiovascular risk (CV)
Faria Rde et al. [66]	Prospective	38 CKD patients	51.5 ± 7.5	2–4 weeks	Investigation of the pulmonary function and exercise tolerance with data obtained by CPET, spirometer test, 6MWT	VO_2 peak/maximal tolerance to exercise and 6MWT scores/submaximal exercise tolerance were lower in pre-dialytic CKD patients	Pre-dialytic CKD patients have decreased tolerance to exercise
Samara et al. [17]	Prospective	28 CKD patients	53.5 ± 12.9	N/A	Discovering the association between the QoL and heart rate recovery time following CPET max–submaximal	Cardiopulmonary recovery parameters are correlated with depression and QoL	N/A

BP blood pressure, *CKD* chronic kidney disease, *CrCl* creatinine clearance, *CPX or CPET* cardiopulmonary exercise testing, *HD* hemodialysis, *HF* heart failure, *FMD* flow-mediated dilatation, *LVEF* left ventricular ejection fraction, *MEP* maximal expiratory pressure, *6MWT* 6-min walk test, *N/A* not applicable, *NO* nitric oxide, *PFT* pulmonary function test, *RV* residual volume, *QoL* quality of life, *TLC* total lung capacity, *VO_2* oxygen uptake, *TSL1* sit and stand 1-min test

muscle strength or power in healthy individuals [65]. However, individuals in chronic deconditioned states such as CKD/ESRD are expected to exhibit the greatest initial gain in muscle function with training in conjunction with a large adaptation potential [22]. Thus, endurance exercise training, even at lower intensities, may provide adequate resistance to improve muscle function in CKD patients. Cho et al. demonstrated that a virtual reality exercise program (VREP) for 40 min, 3 times a week for 8 weeks, improved leg muscle mass in HD patients. Back strength (kg), leg strength (kg), balance (second) have all been improved after VREP [33].

Pomidori et al. investigated the effect of two 10-min walking sessions every other day at an intensity below a speed specific to the patient considering the patient's lung function and respiratory muscle strength, evaluated by spirometry and maximal inspiratory pressure, respectively. Minimal dose of structured exercise maintained a stable respiratory muscle function, in contrast to the control group (self-care without exercise program) where it worsened [46].

Exercise training also improves cardiorespiratory function and cardiovascular outcomes. One of the most commonly studied parameters in this respect is the oxygen consumption at peak exercise (VO_2 peak). As a metric that provides an index of exercise capacity, VO_2 peak is indicative of the cardiovascular system's ability to take up, distribute and use oxygen at maximal exercise [38]. Low peak VO_2 in CKD patients can be due to a variety of conditions including anemia, electrolyte imbalance, hyperparathyroidism and respiratory problems [40, 66]. Several previous studies have demonstrated VO_2 peak increase after endurance exercise in HD and CKD patients [22, 67, 68]. However, other studies did not show any improvement in VO_2 peak [23] which may be attributed to prescribing low-intensity exercise [69] or short-duration aerobic training [70].

A very recent study has proposed a lower VO_2 in CKD patients due to endothelial dysfunction. Downey et al. demonstrated that lower FMD values were associated with an upwardly concave systolic BP during exercise in CKD and with poorer exercise capacity measured as VO_2 peak. The authors suggested that exercise intolerance in CKD patients may be due to decreased nitric oxide (NO) bioavailability and endothelial dysfunction causing impaired vasodilation during exercise [71]. On the contrary, Habedank et al. noticed no correlation between endothelial (dys)function and peak VO_2. The authors argue that the lack of association may relate to the physical condition of the cohort investigated which may be rather preserved high peak VO_2 levels (about 24 mL/min/kg) [39].

Arterial stiffness is an important marker of cardiovascular health and is predictive of outcome in HD, CKD and renal transplant patients [72, 73]. Greenwood et al. in a single-blind, randomized, controlled, parallel trial randomly assigned 60 kidney transplant patients to aerobic training

($n = 20$), resistance training ($n = 20$) or usual care ($n = 20$). Aerobic training and resistance training were delivered 3 days per week for a 12-week period. The usual-care group received standard care. Pulse wave velocity, peak VO_2, sit-to-stand 60, isometric quadriceps force and inflammatory biomarkers were assessed at 0 and 12 weeks. After 12 weeks pulse wave velocity decreased significantly in both aerobic training and resistance training groups compared with the control group [49]. As opposed to usual care, both the aerobic training and resistance training interventions demonstrated a significant improvement in average peak VO_2, associated with pulse wave velocity. Toussaint et al. [74] in the HD population suggest a significant decrease in pulse wave velocity as a result of a 12-week intradialytic aerobic exercise training program. Another study by Mihaescu et al. investigated the effect of resistance training in HD patients. The group reported a decline of 1 m/s in pulse wave velocity in the exercise training group, associated with lower systolic BP The control group demonstrated an increase in pulse wave velocity of 1.3 m/s [75]. The beneficial effect of exercise program has also been demonstrated in other studies relating to endothelial function [20, 50, 76].

In continuous ambulatory peritoneal dialysis (CAPD) patients peak VO_2 has been demonstrated to be low. Ulubay et al. investigated factors that influence peak VO_2 in renal transplant candidates receiving CAPD therapy. Cardiopulmonary exercise tests were performed on a cycle ergometer at the same time of the day for all patients, and exercise duration, maximum work rate and peak VO_2 level were analyzed. Peak VO_2 was found to be correlated with serum phosphate levels and no other parameter [40]. The same group also argued that peak VO_2 did not change when the peritoneal cavity was filled with solution (full status) and again when the cavity had been drained (empty status) [41].

Exercise may also have impact on BP. Henrique et al. evaluated 14 HD patients, before and after 12 weeks of aerobic exercise, performed during hemodialysis sessions. There was a significant reduction in both systolic and diastolic BP, from 151 ± 18.4 to 143 ± 14.7 mmHg and from 94 ± 10.5 to 91 ± 9.6 mmHg, respectively. Similarly, average arterial BP declined from 114 ± 13.0 to 109 ± 11.4 mmHg. This beneficial effect of exercise with regard to BP reduction was also confirmed with some [77–79] but not in other studies [32].

The timing of the exercise is an important parameter in HD patients. Exercise elicits immediate cardiovascular responses, with respect to which it is important to consider whether exercise training is performed “on dialysis” (i.e., simultaneously exercising and dialyzing) or “off dialysis” (i.e., exercising and dialyzing at separate times). Simultaneous fluid removal during exercise may limit the exercise tolerance. Moore et al. showed that fluid removal at a rate of 1356 mL/h during dialysis had no significant cardiovascular effects during the first 2 h. However, at 3 h, cardiac output, stroke volume and mean arterial pressure were found to be decreased, limiting exercise tolerance. The hemodynamic instability at 3 h appears to have been due to an inappropriate decrease in heart rate, as in vasodepressor syncope. In this study, however the patient number is low which precludes to investigate independent factors such as autonomic dysfunction related to these findings [37]. On the other hand, Dungey et al. [54] demonstrated that although BP falls during exercise in HD patients, the cause is not cardiac injury as no change was observed in concentrations of cTnI, myoglobin or CK-MB. It is also important to notice that no serious adverse event has been reported after around 28,000 h of intradialytic exercise [80]. One may consider intradialytic exercise safe, given careful selection of the patients.

Cardiovascular outcomes

Exercise has also been associated with undesired outcomes such as cardiovascular events. Manfredini et al. [45] demonstrated that among patients who completed the regular exercise trial, patients in the active group had poorer hospitalization-free survival than the control group. In another study, Scrutinio et al. investigated the correlation of renal function with peak VO_2 consumption in heart failure patients. In total, 2.938 systolic heart failure patients underwent clinical, laboratory, echocardiography and cardiopulmonary exercise testing. The patients were then stratified according to estimated GFR. Mean follow-up was 3.7 years during which the primary outcome was a composite of cardiovascular death and urgent heart transplantation. On multivariable regression, eGFR was predictor of peak VO_2 ($P < 0.0001$). After adjusting for significant covariates, low peak VO_2 has been found to be associated with primary outcome. The strength of this association increased as eGFR decreased [81] (Table 4).

Quality of life, cognitive function and depression

As suggested above, regular exercise has favorable actions on quality of life, cognitive function and depression. The beneficial effect of exercise program with respect to these parameters can be explained by a number of factors including increased muscular strength [24], increased social interaction [45], release of neurotransmitters (e.g., endorphins). The direct effects of exercise on emotional and behavioral aspects range from substitution of negative thoughts and low self-esteem to decreased anxiety and improved attitude toward self. In parallel, group exercise has been shown to promote socialization with participating in a fun, organized activity during HD sessions [18, 27, 37, 82].

Table 4 Evaluation of cardiovascular events and death on the trials

Trials	Baseline groups	Renal transplantation, (*n*)	Cardiovascular events, (*n*)	Cardiovascular death, (*n*)	All death, (*n*)
Reboredo et al. [44]	HD	N/A	7.1%	N/A	N/A
Chan et al. [24]	HD	N/A	0	N/A	N/A
Musavian et al. [25]	HD	N/A	N/A	0	0
Esteve Simo et al. [27]	HD	N/A	0	0	0
Anding et al. [28]	HD	5/46 (11%)	N/A	N/A	28%
Thompson et al. [47]	HD	N/A	N/A	0	0
Greenwood et al. [49]	Renal transplant patients	100%	0	0	N/A
Sato et al. [99]	CKD	N/A	22.8%	4.4%	N/A
Greenwood et al. [50]	CKD	N/A	0	0	N/A
Aoike et al. [16]	CKD	N/A	0	0	N/A

CKD chronic kidney disease, *HD* hemodialysis, *N/A* not applicable

Mechanisms

After all these evidences, this section briefly explains the underlying mechanisms of regular exercise on these positive findings.

Resistance training highly increases the metabolism of protein synthesis, leading to increased cross-sectional volume of muscle fibers. Exercise may increase the levels of growth factors such as insulin-like growth factor-I receptor and decrease the inhibitors of muscle hypertrophy in HD patients [83]. Thus, these factors may be responsible for the beneficial effects on physical function and muscle atrophy.

During intradialytic exercise enhanced blood flow and increased capillary surface area result in a greater flux of urea and other toxins from the tissue to the vascular compartment, hence an increased removal at the dialyzer. This may alleviate symptoms of uremia [25, 26].

Another important contributor may be the presence of heart failure which is commonly seen in CKD and ESRD patients with either reduced or preserved EF [84]. CKD patients have sympathetic hyperactivity [85] which is proportional to decreased kidney function [86]. Petersson et al. demonstrated increased renal norepinephrine spillover to underlie the pathophysiological mechanism in heart failure, in parallel with and independent of cardiac sympathetic drive [87]. Despite chronic sympathetic activation, decreased responsiveness of the failing heart to catecholamines may potentially limit exercise capacity [81]. Sympathetic drive may contribute to skeletal myopathy, further decreasing exercise capacity [88, 89]. It was also demonstrated that CKD and ESRD patients have exaggerated increases in BP during handgrip exercise due, in part, to over-activation of the sympathetic nervous system [90, 91]. Last but not least, reduced nitric oxide bioavailability may also contribute to exaggerated autonomic responses during exercise with the evidence of NO-mediated inhibition of sympathetic nervous system activation under normal conditions [92, 93].

Exercise has also direct actions on myocardial function in CKD. Luiz et al. evaluated the effects of long-term aerobic swimming exercise with overload on renal and cardiac function in rats undergone 5/6 nephrectomy (5/6Nx). Eight Wistar rats were divided into 4 groups: Control (*C*), Control + Exercise (*E*), sedentary 5/6Nx (NxS) and 5/6Nx + Exercise (NxE). The rats were subjected to swimming exercise sessions with overload for 30 min 5 days per week for 5 weeks. Exercise reduced proteinuria, diminished the decline of eGFR and attenuated sclerosis index at the glomerulus. The NxS group had higher LV posterior wall in diastole and systole compared with the E group. The developed isometric tension in Lmax of the heart papillary muscle was lower in the NxS group compared with the *C*, *E* and NxE groups. Sedentary animals with nephrectomy were observed to have disrupted in myocardial contractility [94].

Chronic inflammatory state, which is present in CKD patients, can be another potential factor leading to decreased exercise capacity in these patients. Systemic inflammation may induce proteolysis in skeletal muscle leading to muscle atrophy [95, 96]. Physical exercise on the other hand has direct anti-inflammatory actions [97]. It was shown that intradialytic exercise increased the levels of IL-10, a potent anti-inflammatory cytokine. Similarly, tendency for decreased tumor necrosis alpha levels was observed [43]. Thirty minutes of aerobic exercise in pre-dialysis individuals induced a significant elevation of IL-6 and IL-10, with little effect in the TNF receptors (sTNF-RI and sTNF-RII) in post-exercise period. After 1 h from the exercise session, IL-6 and IL-10 remained in high concentrations and an increase in sTNF-RII was found. These findings support the idea of interaction between immune system and exercise [98].

Controversies and future perspectives

One of the most important issues is the valid judgment regarding the effectiveness of exercise programming. To judge the effectiveness of exercise training in CKD and HD patients, most of the available literature relies on the changes in oxygen uptake (VO_2) at peak incremental work rate (IWR) exercise testing as the main laboratory-based criterion. As previously mentioned, with regard to VO_2, there are contrasting findings, which were previously attributed to prescribing low-intensity [69] or short-duration aerobic training [70]. Other factors are thought to be involved as well. It is possible that training may improve several submaximal responses (e.g., work and ventilatory efficiencies, cardiovascular stress), which are not necessarily translated into higher maximal aerobic capacity measured by VO_2 or 6-min walking test [44]. Thus, simpler but more sensitive tests should be developed to better evaluate the effectiveness of the exercise programs.

Secondly, although various exercise programs have been implemented, how exercise training should be performed is still a matter of debate (intradialysis vs. off dialysis, aerobic vs. anaerobic, endurance resistance or in combination in dialysis center and at home, duration, intensity, etc.) [45]. Although it was observed that exercise during dialysis is more efficient and has less dropout rates [57], other trials show the beneficial effect of home dialysis programs in CKD patients. Manfredini et al. [45] successfully implemented home exercise programs and subsequently argued improved physical function, cognitive function and social interaction.

Another conflicting issue is the type of exercise. Performed studies generally use one type of exercise program—either endurance or resistance exercise. However, a recent study showed that resistance and endurance exercises can be applied in combination even in elderly patients. Anding et al. investigated the effect of a structured physical exercise program (combination of resistance and endurance exercise) in 46 patients with HD. Combination strategy has been proven to improve muscle strength, physical activity (sit-to-stand test and 6-min walk test) physical functioning, role of physical limitations, role of emotional limitations and mental health subscales of SF-36 [28]. Thompson et al. also investigated the effect of combination of cycling and resistance exercise program on quality of life. In this factorial (2 × 2) pilot trial, 31 HD patients were randomized to cycling, resistance, cycling and resistance or an attention control groups. Participants completed the Kidney Disease Quality of Life Short Form 36 (KDQOL-SF 36), and the 6MWT was used as a measure of aerobic capacity. No significant differences between baseline and 12 weeks were found in the PCS or MCS components of the SF-36 or physical performance tests among subgroups [47]. Similarly, the existing literature does not conclude whether passive or active exercise is more important [25].

A single exercise program may not be proper for every patient as some could not be done safely nor satisfactorily by all participants due to risk of muscle injuries and adverse cardiovascular events causing a high number of dropouts [27]. Hence, it needs to be determined whether the exercise program is suitable for the patient. When necessary, the program should be adapted according to individual characteristics together with an exercise counselor providing motivational support to stimulate patients to stay more active [48]. Even the most effective exercise programs would not keep the interest of patients if composed of repetitive routines only. Therefore, careful planning of the content of the exercise programs with the motivation and continued participation of the patients in mind is essential [33, 91]. Innovative ideas such as virtual reality exercise programs have been successfully implemented to pass these barriers [33].

One should also consider making meta-analysis instead of writing a narrative review. However, as previous studies were very heterogeneous regarding the type of exercise performed (type of training and duration) and the type of assessment, we proposed that a narrative review would be better suited to describe the findings. This also brings the issue that while writing the review we could not be certain to suggest firm conclusions. Since this review involves both observational and a few interventional studies, higher quality and strength is needed to make such suggestions. So the mode of presentations both in text and in tables is arranged accordingly and not so stringent.

Conclusion

Exercise training in CKD and ESRD patients has various beneficial effects on various domains such as physical function, muscle atrophy, depression and quality of life. The mechanisms behind these beneficial effects of exercise are not fully elucidated. However, mechanisms such as increased growth factors, increased secretion of endorphins, decreased sympathetic overactivity and decreased inflammation all have been suggested. Since the area is still evolving, there are conflicting issues and unknowns. More research is needed to fully elucidate the beneficial effects of exercise and to investigate whether exercise has also impact on hard outcomes such as mortality.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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