Universidade da Maia

Intradialytic exercise in hemodialysis patients

Implementation and effectiveness on long-term patient outcomes

Pedro Miguel Pereira Martins

Tese de doutoramento em

Ciências do Desporto - Exercício e Saúde

Janeiro/2025

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Janeiro/2025

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A presente dissertação foi elaborada tendo em conta o Código de Conduta Ética da Universidade da Maia e, particularmente, os princípios da honestidade, rigor e transparência na investigação ínsitos no Código Europeu de Conduta para a Integridade na Investigação.

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Provas públicas realizadas em 3/28/25

Esta versão corresponde à aprovada pelo Júri.

O Presidente do Júri,

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Abstract

Hemodialysis (HD) patients have high levels of inactivity that are associated with poor health outcomes. Since 2005, the National Kidney Foundation guidelines (Kidney Disease Outcomes Quality Initiative) recommend chronic kidney disease (CKD) patients to perform aerobic exercise for 30 minutes most, if not all, days per week (1). Apparently, this ambiguous recommendation have not inspired the nephrology community to improve physical activity (PA) levels, since inactivity remains an hallmark of this population (2). This thesis includes a systematic review in which PA was associated with a lower mortality risk in end-stage kidney disease (ESKD) patients. Intradialytic exercise (IDE) could be a strategy to improve PA, since it is convenient for HD patients, being its implementation recommended by the UK Kidney Association (UKKA) (3). Nevertheless, little is known about the implementation and scalability of IDE and about its effectiveness in real-world conditions, including its association with relevant endpoints for this population. Therefore, this thesis investigated the effectiveness and implementation outcomes of a nation-wide IDE program settled as part of routine care and its association with mortality and hospitalization. Moreover, it was examined the effectiveness and implementation of an online exercise program implemented as an alternative to IDE during the COVID outbreak.

IDE demonstrated to be feasible and safe as part of routine care and its effectiveness was sustained in real-world conditions to improve physical function, body composition and hemoglobin (Hb) balance. Nevertheless, despite having a good adherence (75%±20%), the exercise dose achieved through IDE was not enough to meet the current PA recommendations (3, 4). Implementation was also limited by a considerable proportion of non-eligibility (44%), refusals (36.1% among those eligible) and attrition rate (57% at one-year), mostly voluntary (52%). Moreover, 44% of the units did not adopted IDE. Regarding its association with mortality and hospitalization, IDE can be associated with improved outcomes, but this was significant only for a higher exercise dose group (110±16 minutes/week). As such, a considerable exercise dose is required and, for some patients, this could not be achieved only through IDE.

The online exercise program used a videoconferencing platform and was implemented during the COVID outbreak, when the IDE was suspended. Implementation outcomes could have been limited by the pandemic context, but as for IDE, some drawbacks were observed. Some units did not adopt the intervention (33%), a considerable proportion of patients did not accept (73%) and 41% dropped out during the three-month follow up. Such as for IDE, those who completed the intervention had a good adherence rate (73%±19%). The intervention was safe and effective to improve physical function, depressive symptoms, and fatigue. Thus, the online exercise could be applied beyond the pandemic to complement the traditional stand-alone IDE intervention.

Taken together, our findings suggest that IDE is safe, feasible and effective and should be used to improve mortality and hospitalization outcomes in this critically ill population. Nevertheless, IDE alone is not enough to meet the recommended PA levels and some patients do not achieve an effectively protective exercise dose. Thus, the online exercise could be used beyond the pandemic to complement IDE.

Key words: hemodialysis, intradialytic exercise, online exercise, implementation, mortality, hospitalization

Acknowledgments

This PhD would not even have started if a few leaders had not crossed my path. Firstly, Alexandra… my professional mother and the very first believer, whose dedication to our company and patients continues to be an inspiration and an everyday energy boost. Thanks Nuno and António, the ones in charge whose vision led to invest in our PEF. Thanks for your confidence. Without you three, there would be no exercise program and without the exercise program, there would be no PhD.

Thanks João for such a friendly leadership. The one who never gives up and whose passion, determination and power have been decisive. Hope to continue to be challenged by your passionate leadership. Thanks Diogo for your continuous support and advices. Your contributions add so much to this thesis.

I´m also profoundly grateful to everyone that in our units made our exercise program our pride. Without your commitment this program wouldn´t have been possible.

Thanks to everyone in the Exercise in CKD research group, for always welcoming me in the University of Maia.

I am very thankful to all the PEF participants who joined us in this journey. Thanks for your bravery and for all your life histories from which I have learned so much.

Cheers to my entire family who always support me unconditionally. Thanks dad and mom for being the great example I also intend to be for Constança. Thanks Carol for our love and thanks Constança for having such a contagious and energetic smile.

Publications

A journal article and several scientific meeting proceedings were originated from the studies reported on this thesis.

Journal article

Martins, P., Marques, E.A., Leal, D.V. et al. Association between physical activity and mortality in end-stage kidney disease: a systematic review of observational studies. BMC Nephrol 22, 227 (2021). https://doi.org/10.1186/s12882-021-02407-w

Scientific meeting proceedings

Martins P, Leal DV, Ferreira MA, Wilund K, Viana JL (2022). "Intradialytic exercise: a large-scale nationwide implementation study". Abstracts from the 59th European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Congress, Paris, France

Martins P, Leal DV, Ferreira MA, Wilund K, Viana JL (2022). "Intradialytic exercise is associated with lower mortality risk in hemodialysis patients". Abstracts from the ASN Kidney Week 2022 Congress, Orlando, USA

Martins P, Leal DV, Ferreira MA, Wilund K, Viana JL (2022). Association between intradialytic exercise and mortality risk in hemodialysis patients. XXXVI Portuguese Society of Nephrology 2022, Vilamoura, Portugal

Leal DV, **Martins P**, Cardoso DF, Ferreira MA, Wilund K, Viana JL (2022). "Implementation of a nationwide online exercise program in hemodialysis patients". Abstracts from the ASN Kidney Week 2022 Congress, Orlando, USA

Leal DV, **Martins P**, Cardoso DF, Ferreira MA, Wilund K, Viana JL (2022). Online exercise program: a nationwide implementation study. XXXVI Portuguese Society of Nephrology 2022, Vilamoura, Portugal. Best abstract on hemodialysis.

Martins P, Leal DV, Ferreira MA, Wilund K, Viana JL (2023). Association of intradialytic exercise with hospitalization in hemodialysis patients: a cohort study. XXXVII Portuguese Society of Nephrology 2023, Porto, Portugal

Martins P, Leal DV, Ferreira MA, Wilund K, Viana JL (2023). Intradialytic exercise is associated with improved hospitalization outcomes in hemodialysis patients: a cohort study. Time to move: 7th International Transplantoux Symposium. Best abstract award

Andrade FP, **Martins P**, Leal DV, Ferreira A, Wilund K, Viana JL (2024). Impact of hydration status on physical function and body composition in hemodialysis patients. XXXVIII Portuguese Society of Nephrology 2023, Funchal, Portugal

Other awards

Martins P, Leal DV, Ferreira MA, Wilund K, Viana JL (2024). "Association of Intradialytic exercise with mortality and hospitalization". *ANADIAL-SPN award for the best research in nephrology 2024*

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List of abbreviations

AH: antihypertensive

BCM: body composition monitor

BMI: body mass index

BP: blood pressure

CES-D: center of epidemiologic studies depression scale

CI: confidence interval

CIDESD: Research Center in Sports Sciences, Health Sciences and Human Development

CKD: chronic kidney disease

CKD-MBD: chronic kidney disease – mineral bone disorder

CV: cardiovascular

EPO: erythropoietin

ES: effect size

ESKD: end-stage kidney disease

EuCliD: NephroCare European Clinical Database

FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue Scale

FGF-23: fibroblast growth factor-23

GFR: glomerular filtration rate

Hb: hemoglobin

HCP: healthcare professionals

HD: hemodialysis

HDF: hemodiafiltration

HR: hazard ratio

IDE: intradialytic exercise

IQR: interquartile range

KDIGO: Kidney Disease Improving Global Outcomes

KRT: kidney replacement therapy

KTx: kidney transplant

LVH: left ventricular hypertrophy

MSc: Master of Science

OMNI-RES: OMNI Resistance Exercise Scale

PA: physical activity

PD: peritoneal dialysis

PSQI: Pittsburg Sleep Quality Index

RCT: randomized controlled trial

RWMA: regional wall motion abnormalities

SD: standard deviations

SLS: single leg stance

STS: sit-to-stand

UG: up and go

UKKA: UK Kidney Association

VCTE: videoconferencing telehealth exercise

WHO: World Health Organization

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Chapter 1: General Introduction

1.1. Rationale and structure of the thesis

Inactivity is notably high in chronic kidney disease (CKD) patients, particularly those on hemodialysis (HD). This inactivity is associated with poor health outcomes and previous research has demonstrated many health benefits of exercise in this population (e.g., improving physical function, quality of life and immunity). Making use of otherwise sedentary-time, intradialytic exercise (IDE) is believed to be very convenient for this population that inevitably deals with a very time-consuming treatment. Despite there are still few clinical settings where an exercise intervention is available, IDE is the most common exercise option in this population. However, the evidence supporting the benefits of exercise in HD patients is mostly from small randomized controlled trials (RCT), usually investigating the effects of IDE under ideal circumstances. RCT are usually performed in a highly selective HD population and are managed in tightly controlled settings, which limits its external validity (5). Indeed, it is mostly based on these types of studies that the UK Kidney Association (UKKA) guidelines recommend IDE to be available in all HD units (3). However, is still of utmost importance to investigate how this intervention could be widely translated to clinical practice and what is its effectiveness under real-world conditions, including its association with important endpoints as mortality and hospitalization.

To answer these important questions, this thesis was structured in seven chapters. Beyond the present section, Chapter 1 also includes a background that reviews the state-of-the-art evidence that supports this research and the objectives section. Chapter 2 (General Methods) describes the research design and the methods that were shared by the different studies of this thesis. Chapter 3 presents a systematic review investigating the association of PA with mortality and hospitalization in all end-stage kidney disease (ESKD) patients: HD, peritoneal dialysis (PD) and kidney transplant (KTx). Chapters 4 and 5 are the main studies of this thesis and were based on a nation-wide implementation of IDE in Portugal. These chapters provide real-world data on IDE implementation (Chapter 4) and its association with mortality and hospitalization outcomes (Chapter 5). Furthermore, as the recent pandemic led to the suspension of IDE, an alternative nation-wide online exercise program had to be developed. Therefore, this current thesis also presents the detailed description of the developed exercise program designed to be implemented remotely using online platforms during the COVID-19 lockdowns (Chapter 6). Its implementation and health outcomes are thoroughly described in this chapter. Finally, in chapter 7 (General Discussion), a summary of the main findings and their possible implications is provided.

1.2. Background

CKD definition, classification and epidemiology

CKD arises from many heterogeneous disease pathways that harm the kidneys´ function and structure over a period of months or even years (6). Current international guidelines define CKD as a decreased kidney function shown by a glomerular filtration rate (GFR) of less than 60mL/min per 1.73m^2 or markers of kidney damage, or both, of at least three months in duration, regardless of the underlying cause (7). Thus, CKD diagnosis depends on the establishment of a chronic reduction of kidney function and/or structural kidney damage (6).The Kidney Disease Improving Global Outcomes (KDIGO) classification of CKD evolved over time. In the 2002 guidelines, CKD was classified in five stages according to GFR alone (8). Since 2012, the KDIGO guideline included both the GFR and albuminuria for CKD definition criteria and classification (7). The 2024 KDIGO guideline had no significant changes on CKD criteria and classification (9). Table 1.1. summarizes the criteria for CKD diagnosis.

Table 1. 1. *Criteria for CKD diagnosis (present for ≥3 months). Taken from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD (9)*

Markers of kidney damage (one or more)	Albuminuria (ACR ≥30 mg/g [≥3 mg/mmol]) Urine sediment abnormalities Persistent hematuria Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min per 1.73 m2 (GFR categories G3a–G5)

CKD: chronic kidney disease; ACR: albumin-to-creatinine ratio; GFR: glomerular filtration rate

Indeed, GFR is generally accepted as the best index of kidney function and albuminuria as a marker of kidney damage (10). GFR is the first step in urine formation and corresponds to the passive ultrafiltration of plasma from blood into the Bowman space. GFR depends on body size and is indexed relative to an average body surface area of 1.73m^2, expressed as mL/min/1.73m^2. Age influences GFR and the mean value for adults younger than 40 years (≈120-130 mL/min/1.73m^2) declines with age. Values less than 60 mL/min/1.73m^2 are considered a reduction in kidney function for adults of any age (10). GFR is estimated (eGFR) based on equations relative to endogenous filtration markers as creatinine (Chronic Kidney Disease Epidemiology Collaboration) and cystatin C. Despite proteins from kidneys and urinary tract may be detected in urine, the glomerular capillary wall prevents the passage of albumin and other large serum proteins to the Bowman space. A mean value between 5-10mg/day is usual in young adults due to exercise, fever, body size and upright position (10). Values higher than 30mg/day, usually taken in a spot urine sample, indicate structural changes in glomerular capillary wall (10).

The KDIGO 2D matrix (Figure 1.1.) combines levels of albuminuria and GFR to describe the risk of CKD patients to experience adverse outcomes as kidney failure, cardiovascular (CV) disease, hospitalization, acute kidney injury and death (11).

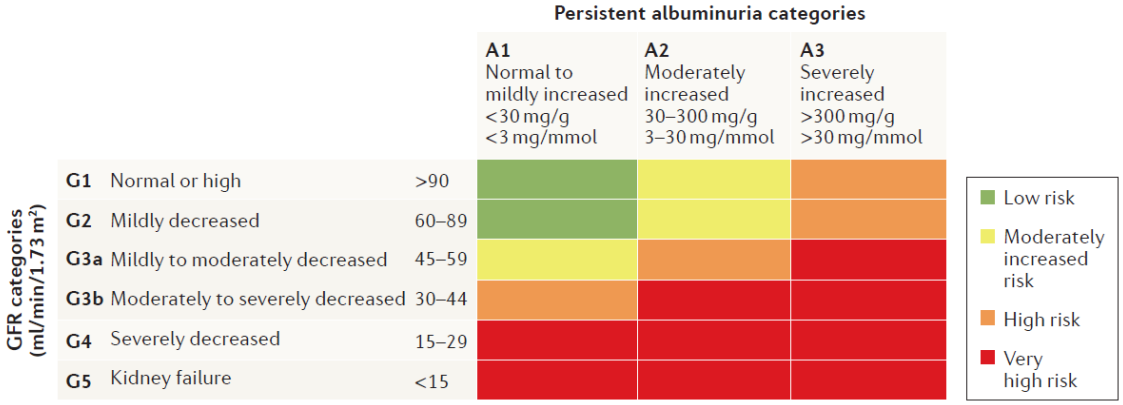

Figure 1. 1. *KDIGO classification of CKD. Taken from the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD (9)*

CKD is part of the worldwide non-communicable disease burden. Hypertension, diabetes and obesity are between the growing non-communicable diseases and are important risk factors for CKD (12). Hypertension affects 26% of the global population (972 million cases) and is projected to increase to 1.56 billion by 2025 (13); worldwide, 285 million adults have diabetes and is expected to rise to 439 million by 2030 (14); prevalence of obesity doubled since 1980 to an extent that is now nearly a third of the world´s population (15). Thus, the already alarming epidemiology of CKD, is expected to get worse in the next decades.

Despite some variations due to methodological differences in epidemiologic studies, worldwide prevalence of CKD is estimated to be 13.4% (16). CKD prevalence exceeds in 5.2% the prevalence of diabetes (16), declared as the biggest 21st century epidemic. Prevalence of CKD is estimated to be 3.5% for stage 1; 3.9% for stage 2; 7.6% for stage 3; 0.4% and 0.1% for stage 4 and 5, respectively (16). Figure 1.2. illustrates how the proportion of patients in the advanced stages of CKD is very low, including those on kidney replacement therapy (KRT). People with CKD are five to ten times more likely to die than they are to progress to kidney failure, contributing to the lower prevalence of stage 4 and stage 5 CKD (6). For those 2% that will progress to kidney failure (GFR <15mL/min/1.73m^2), kidney function cannot sustain life for a long period, and

patients need a KRT: dialysis or KTx. Comprehensive conservative care has emerged as an alternative to KRT for patients with a poor prognosis that would not benefit from KRT (6).

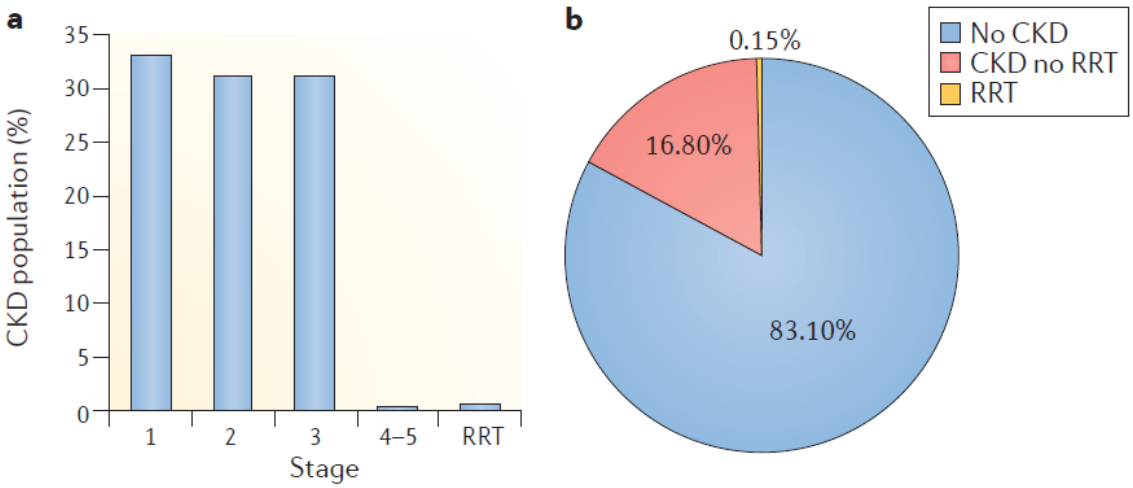

Figure 1. 2. *The burden of CKD; a) Percentage distribution of CKD stages; b) CKD in the global population. Taken from Vanholder et al. (2017) (17)*

Kidney replacement therapies and the relevance of hemodialysis

Options for kidney failure patients are either KRT or comprehensive conservative treatment. The latter emerged from the observation that dialysis may not necessarily prolong or improve the quality of life in the elder patients or in patients with multiple comorbidities and poor physical function (18). In this sense, comprehensive conservative treatment combine strategies to delay CKD progression, to minimize complications and symptoms, and involve planning of care in advance, improved communication, and the provision of psychological and family support to improve quality of life (17). According to a web-based survey, this is an option in 15% of the cases (19).

Prevalence of KRT in Europe (985 pmp) is lower to that observed in the USA (2196 pmp) and in Japan (2599 pmp), and similar to that observed in Australia (966 pmp) (20). In Europe, HD is the most prevalent KRT (502 pmp), followed by KTx (430 pmp) and PD (52 pmp) (20) (missing values or rounding off prevent the sum to making up the total). Worldwide, the need of KRT is notably high and is expected to grow from 9.7 million in 2010 to 14.5 million in 2030 (Figure 1.3.) (21), but it is estimated that only 37% of the patients will actually receive a KRT. Among the European countries, Portugal has the highest prevalence of overall KRT (1906 pmp) and the highest prevalence of HD (1143 pmp), while PD prevalence is the 6th (70 pmp) and KTx prevalence is the 2nd highest in Europe (693 pmp) (20). In the last years, the prevalence of patients on dialysis continuous to grow in Portugal, reaching in 2022 1330 pmp (Figure 1.4.) (22).

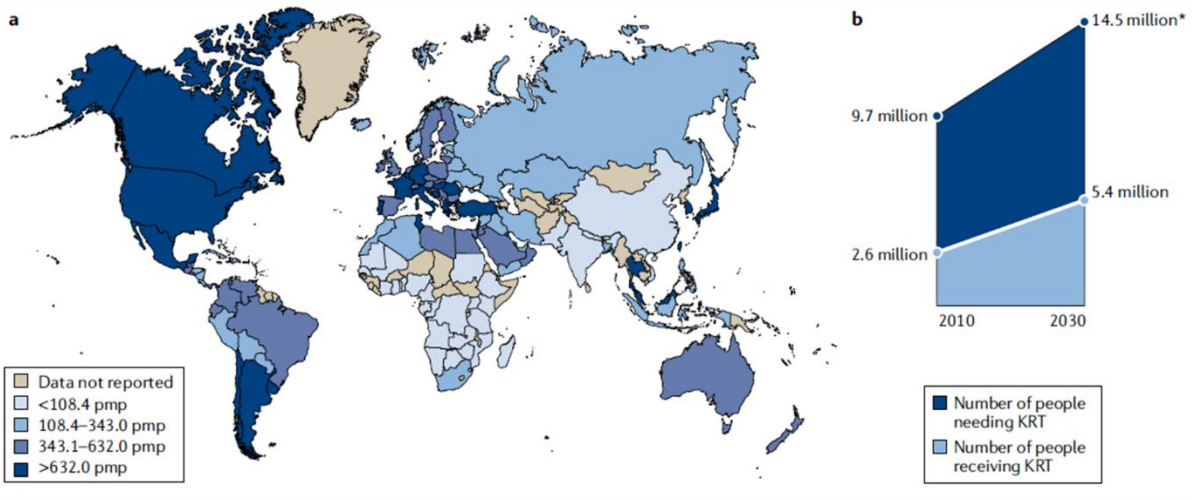

Figure 1. 3. *Current and projected prevalence of kidney failure requiring a KRT. Taken from Himmelfarb et al. (2020) (21)*

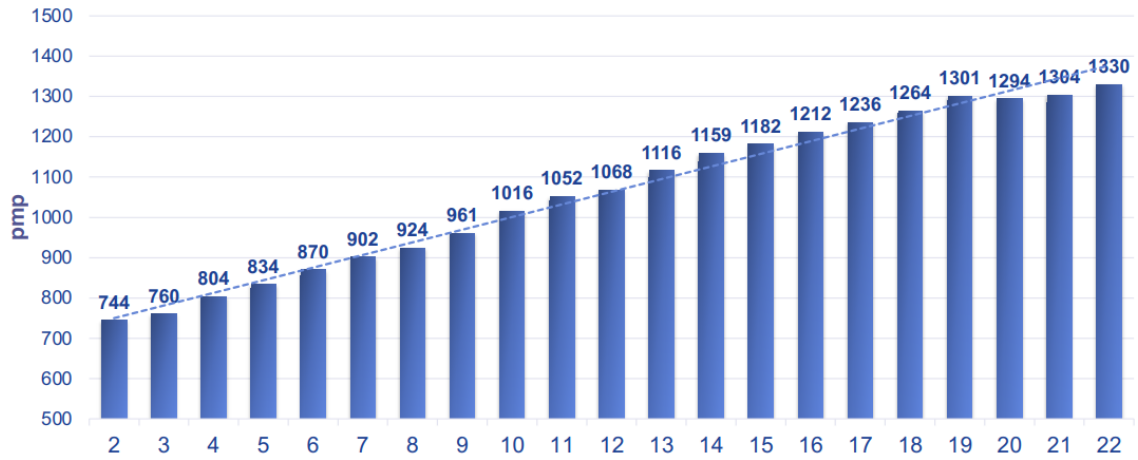

Figure 1. 4. *Prevalent patients on dialysis (HD and PD) from 2002 to 2022. Taken from the Portuguese Registry of KRT (22)*

HD uses pumps, membranes, and dialysates to clear uremic toxins from the blood (11) and is usually performed three times per week. The efficient solute removal provided by a single HD session over 4h should be extrapolated to the full interdialytic interval of 48-72h, by comparison with the kidney removal capacity. As such, HD allows an anuric patient to have a kidney-equivalent filtration of only 5-10 mL/min, still resulting in high concentrations of uremic toxins (23). While solute removal in conventional HD relies only in diffusion, in hemodiafiltration (HDF) convective transport enhances the elimination of middle-sized molecules, as β_2-microglobuline and fibroblast growth factor-23 (FGF-23) (23). Nevertheless, β_2-microglobuline per single HDF session is far from normal removal rates when averaged for 48-72h (23).

PD uses the peritoneal membrane as an exchange interface to clear uremic toxins from the blood. This is possible with a transcutaneous catheter implanted into the peritoneal cavity that can be drained daily and used to refill dialysate fluid. After hours reaching a balance between uremic blood and fresh dialysate, each exchange is expected to drain excess fluid and uremic toxins (11). HD and PD provide equivalent survival among incident dialysis patients (24), with a 5-year survival estimated to range between 40-50% (11). However, in most countries, the cost of HD is between 1.25 and 2.35 times greater than PD (25). Regional variations are evident in the proportion of patients treated with PD, ranging between 66% in Mexico, 18% in Canada and 7% in the USA (25). Thus, assuming similar health outcomes for patients that are eligible for both PD and HD, and the lower cost of PD, this treatment might be underused in most countries (26).

Combining prolonged survival, improved quality of life and reduced costs, KTx is by far the most cost-effective treatment for kidney failure (17). Yet, in 2004, only 23% of the KRT population had a functioning KTx, representing over 50% of the patients only in very few European countries (27). Comorbidities as cancer, chronic infection, cardiac or peripheral vascular disease, and the risk of medical noncompliance are carefully evaluated, and the waiting time can vary from a few months (in Belgium and Austria) to many years (in Germany) (11). Approximately, 56% of people on dialysis are actively waiting for a KTx, but demand exceeds availability, and only 25% receive a KTx , whereas, each year, 6% die while expecting for a transplant (6). Hence, to improve availability, there is a pressing need to implement KTx procedures as a whole: deceased plus living donation (17). The last is known to have even better outcomes (better graft and patient survival) (11, 23), reason why the minimal preemptive transplantation prevalence (2.8% in USA and 4% in Europe), should be improved (20).

KDIGO guidelines recommend dialysis to be initiated when ≥1 of the following is present: signs/ symptoms of kidney failure, inability to control volume status or blood pressure (BP), a progressive deterioration in nutritional status refractory to dietary interventions, or cognitive impairment (typically when GFR ranges between 5-10 mL/min/1.73m^2). Also, a living donor preemptive KTx should be considered when GFR is <20 mL/min/1.73m^2 and there is evidence of progressive and irreversible CKD over a period of 6-12 months (7).

The financial impact of CKD

The escalating prevalence and progression of CKD result in a high economic burden to patients, caregivers, and to the society. CKD patients incur 85% higher healthcare costs and 50% higher government subsidies than the general population (28). In developed countries, about 2-3% of the total health-care expenditure is allocated only to kidney failure patients, who represent only 0.1-0.2% of the total population (12). This disproportionate allocation of resources may arise disconcerting ethical dilemmas.

In fact, direct and indirect costs are elevated and increase further throughout the disease progression. Medicare per-person annually spending is $20.162 for CKD (all stages) (29). The cost per person gradually increases: $17.969 for stages 1-2; $19.392 for stage 3; and $25.623 for stages 4-5. However, considering only kidney failure patients, the cost drastically increases to $65.142 per year. HD is the most expensive ($85.000 per patient-year), followed by PD ($69.000

per patient-year) and KTx ($30.000 per patient-year) (29). Cost attributable to CKD are largely driven by KRT, but are also associated with renal primary care (antihypertensive prescribing, tests and consultations, anemia and bone mineral disease treatment), excess non-renal care attributable to CKD (excess myocardial infarction, excess stroke and excess hospital length of stay) and renal secondary care (renal admissions and nephrology consultations) (30). Indirect costs reflect productivity losses related to illness or death, which typically are considered in terms of absenteeism and presenteeism. In the late stages of CKD, paid employment decreases, while disability payments increase (29). A demonstrative example is the 71% unemployment rate of kidney failure patients, against 10% of the US general population (31). Depressive symptoms and inactivity are predictors of unemployment and should be addressed to prevent reduced occupational activity in dialysis patients (31).

At a societal level, contrarily to what was explained at an individual level, CKD is costlier in the early and moderate stages, because there are much fewer patients in the advanced stages of CKD (29). However, as kidney care and patient survival improves, more and more patients will progress to cost-intensive CKD stages, increasing even more the current financial impact of CKD. Thus, primary and secondary prevention of CKD are increasingly important and PA promotion in the general population (32) and in early stages of CKD (33) could be a relevant contribute.

Uremic syndrome

CKD is recognized as a complex and systemic disease disrupting energy balance, innate immunity and neuroendocrine signaling (34). The so called uremic syndrome is a complex myriad of accelerated ageing and organ dysfunction, that will develop with CKD progression (23). This syndrome results from the toxic effects of the uremic toxins, the deterioration of renal endocrine function (production of erythropoietin – EPO, active vitamin D and renin), the deregulation of kidney electrolyte homeostasis, and functional alterations from CKD itself and its causes (e.g. diabetes, autoimmune disorders) (23).

Among others, uremic syndrome involves CV disease, metabolic bone disease, malnutrition and protein-energy wasting, anemia, neurological and endocrine dysfunction.

Several causes contribute to CV disease in CKD. Klotho deficiency of CKD contributes to premature arterial ageing, making calcification and stiffening typical features of CKD arteriosclerosis (35). Aortic stiffness results in high aortic pressure causing left ventricular afterload, decreased coronary perfusion and microvascular rarefaction (27). Both, left ventricular afterload and left ventricular preload (overhydration, anemia, arteriovenous fistula) are contributors to left ventricular hypertrophy (LVH) (27). Atherosclerosis is not a specific consequence of CKD but is highly prevalent in CKD patients (27). Also, CV disease is aggravated by non-traditional risk factors as low-grade inflammation, oxidative stress, nitric oxide inhibitors and high sympathetic reactivity (23).

CKD-mineral bone disorder (CKD-MBD) is mainly triggered by elevated concentrations of phosphate, resulting in several compensatory mechanisms to maintain serum phosphate concentration, such as FGF-23 and parathyroid hormone, at the cost of loss of bone structure

and function (23). These dysregulations cause abnormalities in bone turnover, mineralization, volume, linear growth or strength and vascular or other soft-tissue calcifications, collectively defined as CKD-MBD (36). This is an umbrella term that includes renal osteodystrophy and its other manifestations, as detailed in Table 1.2. CKD-MBD is substantially associated with poor health outcomes, including mortality, CV disease and bone fractures (37). Patients with advanced CKD-MBD might also have bone pain, difficulty walking and skeletal deformities (11).

Table 1. 2. *KDIGO classification of CKD-MBD and renal osteodystrophy. Taken from Moe et al. (36)*

Definition of CKD-MBD
Systematic disorder of mineral and bone metabolism caused by CKD manifested by either one or a combination of the following: • Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism • Abnormalities in bone turnover, mineralization, volume, linear growth, or strength • Vascular or other soft-tissue calcification
Definition of renal osteodystrophy
• Renal osteodystrophy is an alteration of bone morphology in patients with CKD • It is one measure of the skeletal component of the systematic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy

KDIGO: kidney disease improving global outcomes; CKD: chronic kidney disease; MBD: mineral bone disorder; PTH: parathormone

Malnutrition is multifactorial and caused by loss of appetite, reduced intestinal motility and absorption capacity, inflammation, depression, and loss of amino acids via dialysis. Loss of appetite may be caused by retention products as the cytokines leptin, ghrelin and neuropeptide Y (23). Beyond malnutrition, other highly prevalent factors contribute to protein-energy wasting syndrome in CKD: uremia-induced alterations such as increased energy expenditure, persistent inflammation, acidosis, and multiple endocrine disorders that render a state of hypermetabolism leading to excess catabolism of muscle and fat. Additionally, inactivity and the dialysis treatment *per se*, further contribute to protein-energy wasting (38).

Causes of anemia include reduced renal EPO production, reduced lifespan of blood cells, impaired intestinal iron absorption mediated by hepcidin (a key regulator of iron circulation), and repetitive blood losses in patients on HD. Accordingly, CKD-related anemia is usually normocytic (with normally sized red blood cells) and normochromic (with normal hemoglobin levels inside red blood cells) (11).

Neurological dysfunction may also occur with a high prevalence of cerebrovascular disease (stroke, white matter lesions and intracerebral bleeds) and cognitive disorders that may be associated with vascular and/or degenerative abnormalities (23). Beyond the traditional CV risk factors, non-traditional risk factors (oxidative stress, chronic inflammation, endothelial dysfunction, vascular calcification, HD-related hemodynamic instability) increase the risk of stroke in CKD patients (39). Cognitive impairment is also frequent and may be explained by several interlinked factors such as hyperhomocysteinemia, hemostatic abnormalities or hypercoagulable states, inflammation, and oxidative stress. Non-vascular risk factors could also contribute to cognitive impairment as anemia, multiple medications, sleep disturbances and the retention of uremic toxins as β_2-microglobuline (23, 40). Several endocrine dysfunctions may

progress with CKD. Abnormalities in gonadal hormones as testosterone can result in reduced fertility, sexual problems in men and women, and may aggravate the typical anabolic resistance of CKD patients (11, 38). Consequences of uremic syndrome are summarized in Table 1.3. A vicious cycle makes this amalgam of symptoms to contribute and to be aggravated by the inactivity of HD patients.

Table 1. 3. *Consequences of uremic syndrome. Adapted from Vanholder et al. (2016) (23)*

Cardiovascular	Hypertension, fluid overload, cardiac decompensation, endothelial dysfunction and stiffness, cardiovascular events, pericarditis
Hematological	Anemia, erythrocyte fragility, immune dysfunction, inflammation, hypercoagulability, bleeding
Endocrine	Hyperparathyroidism, insulin resistance, impotence, infertility, thyroid dysfunction, hyperaldosteronism, growth disturbance, adipokine imbalance, klotho deficiency and FGF-23 excess, active vitamin D deficiency
Osteoarticular	Osteomalacia, osteodystrophy, adynamic bone disease, β_2-microglobuline amyloidosis, muscle weakness, fractures, bone pain, calciphylaxis and cardiovascular calcification
Neurological	Polyneuropathy, coordination disturbances, tremor, cognitive dysfunction, decreased attention span, coma
Gastrointestinal	Anorexia, gastroparesis, nausea, vomiting
Dermatological	Skin atrophy, pruritus, calciphylaxis
Stomatological	Periodontitis, stomatitis
Nephrological	Renal tubular damage, progression to kidney failure
Other	Malnutrition, changes in drug protein binding, changes in metabolism, hyperkalemia, metabolic acidosis

FGF-23: fibroblast growth factor-23

Benefits of physical activity or exercise in chronic kidney disease patients

PA is one of the modifiable lifestyle factors that have been consistently associated with a reduced incidence of CKD (18%) and, once CKD is established, with a limited CKD progression in both GFR decline and albuminuria (41). Thus, PA promotion should be a cornerstone of the primary prevention of CKD, reducing its high financial impact that was previously discussed in this section. Besides its benefits in CKD primary and secondary prevention, PA and exercise have also advantages for those with established CKD and ESKD. Several mechanisms may explain these benefits, including improved chronic inflammation, cardiovascular health, sarcopenia and bone health.

In HD patients, chronic inflammation is multifactorial (uremic milieu, lifestyle and epigenetic influences, infectious and thrombotic events, dialysis procedure and dysbiosis) and highly contribute to the poor health outcomes observed in this population (higher mortality and CV events, sarcopenia, cognitive impairment, bone disease, anemia and insulin resistance) (42). Exercise may improve systemic inflammation biomarkers in HD patients (43) by altering the circulation of pro-inflammatory (e.g., interleukin-6) and anti-inflammatory cytokines (e.g. interleukin-10). This could be driven by an increase of the activity of the nuclear factor erythroid-2 related factor 2 (NRF2) pathway in peripheral blood mononuclear cells (PBMCs) that impedes nuclear-factor Kappa B signaling and subsequent pro-inflammatory cytokine synthesis (44); a reduced activation of monocytes (determined by HLA-DR expression) and T cells (determined by CD69 expression) (45); a reduction in the proportion of the pro-inflammatory intermediate monocyte subset and an increase in the number of regulatory T (T_{reg}) cells (46); and a reduced

expression of chemokine receptor CCR5 by monocytes and T cells, that may reduce immune cell infiltration into adipose, cardiac, muscle and vasculature tissue sites (47).

As detailed latter in this section, CV disease is highly prevalent in dialysis patients, being the main cause of death in this population (48). Exercise may improve CV health by reducing arterial stiffness (49) in consequence of improved endothelial function and vasodilation, due to an increased nitric oxide bioavailability (50). Moreover, resistance training may improve anemia by improving iron status, and reducing ferritin and hepcidin (51). Ultimately, all these benefits may explain why exercise improves LVH, as was previously demonstrated in the CYCLE-HD trial (52).

Traits of sarcopenia (low muscle strength, low muscle mass and low physical performance) are very common and are associated with poor health outcomes in HD patients (53). Several factors contribute to sarcopenia and could be related to CKD itself, the HD procedure and the low-grade chronic inflammation. These factors increase protein degradation and decrease protein synthesis, leading to a negative protein balance (54). Resistance exercise is known to improve sarcopenia traits in CKD patients (55). Repetitive resistance exercise sessions stimulate net protein synthesis through the activation of mammalian target of rapamycin (mTOR) signaling pathway, and increasing anabolic hormone production such as testosterone, growth hormones, and insulin-like growth factor 1 (IGF-1) (55). The effectiveness of IDE to improve sarcopenia traits will be investigated along this thesis in Chapter 4 and Chapter 6.

Despite evidence is very limited in CKD populations, PA and exercise promote bone health and might counteract CKD-MBD (47), typical comorbidity in HD patients that was previously explained in this section. Exercise-related improvements in bone mineral density and reduced bone loss may be mediated via a decrease in sclerostin release from bone either directly and/or via a reduction in skeletal muscle myostatin mRNA expression. Exercise-mediated reductions in the release of FGF-23 and increments in klotho release in bone might also contribute to improved bone mineral density and reduced bone loss (47). Nevertheless, to improve bone health, not all exercise modalities are equally osteogenic (e.g. swimming, cycling and walking do not provide a notable stimulus to bone) (56). Thus, current evidence indicates that the effects of exercise on bone are modality-, dose-, and intensity-dependent (56) and should be dynamic not static (i.e., cyclic not continuous), induce bone strains (deformations), and should be applied rapidly (56). Finally, as bone will adapt to customary patterns of loading (e.g. running), diversification of loading (e.g. multidirectional movements) is required to stimulate an adaptive skeletal response (57).

Having all these physiological benefits, exercise is known to ultimately improve several predictors of mortality as physical function (58), cardiorespiratory fitness (59) and body composition (60), and thus has the potential to promote better clinical endpoints in this vulnerable and at-risk population.

Inactivity of hemodialysis patients and the potential role of intradialytic exercise

The symptom burden of uremic syndrome gets worse as CKD progresses and is associated with a progressive reduction in PA. The lowest PA levels are found in dialysis, with 94% of HD and

92% of PD patients considered insufficiently active (2, 61). This inactivity worsens the catabolic state of CKD reducing neuromuscular functioning and exercise tolerance. Over time, these catabolic adaptations might result in functional impairment that contribute to further inactivity, reducing, by other hand, the anabolic stimuli to the muscles (62). Thus, CKD patients are trapped in a vicious cycle of inactivity that is associated with poor health outcomes (63, 64).

In a Canadian survey with HD and PD patients, 74% of the participants recognized the benefits of exercise and 57% reported that they would exercise if advised to do so by their physician. In other hand, only 25% of the patients mentioned no difficulty with exercise, whereas 29% and 37% reported a desire to exercise but either had difficulty or were unable to exercise, respectively (65). These data suggest that dialysis patients are receptive to exercise, but in some way, they need to be supported to do so. Many barriers to exercise have been described in this population and may be grouped in capability (physical or psychological skills), opportunity (physical or social influences), and motivation (that may be reflective or automatic) (Table 1.4.) (66). Thus, barriers to exercise are complex and diverse. In an integrative review, fatigue was the most commonly reported patient perceived barrier (12 of the 14 studies), followed by perceived co-morbid health conditions (8 of the 14 studies) (67). Barriers to exercise are reported by 92% of HD patients and 18% report more than 10 barriers (68). Curiously, patient barriers are not consistent with those most commonly reported by the healthcare professionals (HCP): patient disinterest and lack of motivation (67). Thus, not surprisingly, many of the patient perceived barriers described in Table 1.4., may be linked with the lack of interest and support from HCP. Dialysis staff barriers are described in Table 1.5. and include the lack of equipment and knowledge to promote exercise, the nonexistence of a unit exercise protocol, including guidelines for physical performance assessments, the lack of time, the belief that exercise is not a priority compared to other medical issues, and also concerns about exercise safety (needle dislodgement, BP stability, and infiltration) (66). In a survey with nephrologists around the globe, all respondents agreed that exercise was beneficial, however 40% were concerned about the risk of exercise, and more than half believed that dialysis patients would not exercise if advised to do so. Both beliefs were associated with decreased exercise counseling among nephrologists (69). This persistent conservative and pessimistic attitude may have been limiting an effective PA promotion in standard clinical care.

Table 1. 4. *Patients´ barriers and motivators to engage in PA and exercise. Taken from Clarke and Jhamb (2019) (66)*

Barriers and motivators	Capability		Opportunity		Motivation	
	Physical	Psychological	Social	Physical	Reflective	Automatic
Physical function	X				X	
Dialysis related symptoms (e.g., fatigue)	X					
Episodic changes in health	X				X	
Time constraints				X	X	
Perception of medical conditions	X				X	
Motivation to exercise					X	
Helplessness and sadness						X
Knowledge of exercise recommendations		X				
Treatment restrictions				X		
Support of friends and family			X			
Peer or group support			X			
Support of HCP			X			
Exercise culture			X			
Exercise counseling				X		
Relationship with doctor			X			
Concerns over safety						X
Disrupting dialysis routine						X
Desire to be a "good patient"					X	
Perception of exercise (value/boring)					X	
Benefits of exercise					X	
Exercise programme or plan				X	X	
Feeling able to cycle	X					X
Staff workload					X	
Travel and transport access				X		
Seeing others exercise			X			
Cleared as fit to exercise			X			
Access to facilities				X		

HCP: health care professionals

Table 1. 5. *Health care professionals´ barriers and motivators for exercise in dialysis patients. Taken from Clarke and Jhamb (2019) (66)*

Barriers and motivators	Capability		Opportunity		Motivation	
	Physical	Psychological	Social	Physical	Reflective	Automatic
Skills to motivate patients		X				
Skills to use exercise equipment		X				
Perceived patient interest					X	
Responsibility and workload					X	
Accessing patient in an emergency						X
Exercise not a priority					X	
Negative previous experiences					X	
Patient preference for advice from exercise professional					X	
Dedicated professional role			X			
Management support			X			
Observing change in patients					X	
Resources to support exercise				X		
Lack of unit exercise protocol				X		
Cost of equipment				X		
Space availability				X		
Personal and patient safety						X

HD patients expect exercise to increase their energy, strength, independence and transplant candidacy (65). These are very appealing expectations that demonstrate the great potential of exercise in patient´s perspective (70).

IDE has the major advantage to be convenient for patients, making use of otherwise sedentary time, thus increasing patient acceptance and adherence (71). IDE has also the advantage to allow for supervision and support from the dialysis staff. In other hand, IDE promotes reduced

CV adaptations compared to inter-dialytic programs due the limited exercise intensity and limited diversity of exercises. Moreover, IDE may not be suitable for patients at high risk of cramps and intradialytic hypotension. Alternatively, inter-dialytic exercise induces superior CV adaptations and has the potential to undertake a greater range of exercise interventions. However, is conducted in otherwise "free time" on non-dialysis days, causing higher drop-out rates and lower exercise adherence (71). A third option is the home-based exercise intervention that is the preferred option for 73% of the patients (65) and may have similar efficacy to that of IDE (72, 73).

Several systematic reviews demonstrate the efficacy of IDE to improve cardiorespiratory fitness (59), physical function (74), depressive symptoms (75), physical component dimension of SF-36 (76) and to increase phosphate removal during dialysis (77). Yet, IDE is still not commonly used in clinical settings (78).

Challenges to the implementation of intradialytic exercise

Seminal studies analyzing the benefits of exercise in HD patients are from the early 80´s (79-85). The first published study focusing on IDE is from 1986, and demonstrated a higher compliance to exercise sessions with promising results on aerobic capacity and BP control (79). Since then, mounting evidence has proven its benefits and IDE has been constantly advocated for HD patients (86-89), including a guideline from the UKKA recommending its implementation in every HD units (3). However, this knowledge has not yet been translated into clinical practice and IDE is not the standard care for HD patients. Despite some encouraging initiatives of sustained exercise programs (90) and the efforts of the kidney care community, many more must be done to increase PA in this population (91).

IDE fits the definition of a complex intervention (92) and numerous implementation barriers are described and may preclude IDE dissemination. For patients, barriers may outweigh the theoretical knowledge of the advantages of IDE and their wish to exercise (93). Barriers may include discomfort (59%), concerns regarding safety (e.g., vascular access) (37%) and disinterest (27%) (94). However, these patient perceived barriers are not only to the patient himself, but also concerns for the work situation of the dialysis staff, who must accommodate exercise-related tasks to the already existing HD-related tasks (93, 95, 96). Some motivators are also described and should be considered when motivating patients to perform IDE, including improvements in quality of life (98%), will to be healthier (98%) and to improve physical function (95%) (94). Support from family, friends and HCP are also important motivators (95). For HCP, the most common perceived barriers are lack of professional guidance from specialists (93%), lack of exercise knowledge (86%), and lack of exercise special equipment (86%) (94).

Many barriers to IDE implementation are modifiable and may become motivators if properly addressed (97). For instance, the lack of support from the dialysis staff is perceived by patients as a barrier. However, a strong support is viewed as a motivator. As such, IDE should be regarded as a unique opportunity for the nephrology community to implement clinical exercise programs due its potential to facilitate adherence using a "captive time" in which patients are already there for their treatment (87). This may explain why 63.3% of HD patients are willing to initiate

an IDE program (94). However, despite its proved cost-effectiveness (98), the scarce existing data confirms that IDE is rarely offered to HD patients. Data published in 2002 from Texas (USA) have shown that 21% of the HD units had some kind of exercise intervention, but there is no specification if it was IDE or inter-dialytic exercise (99). A report of the Dialysis Outcomes and Practice Patterns Study from 2005-06 have shown that none of the units in France offered IDE and it was rare in other developed countries. The exceptions were Germany and Sweden where IDE was offered in 57% and 64% of the dialysis centers, respectively (78). In 2012, data from Ontario (Canada), demonstrated that only 4% of the HD clinics offered IDE (100). Recently, in Brazil, IDE was offered in 16% of the HD units. However, this result may be overrated because more than half of the HD units did not answer the survey. It is estimated that only 4% of the HD patients in Brazil have access to IDE (101). No data is available in Portugal.

Since 2005, the KDOQI guideline recommend HD patients to exercise at a moderate intensity for 30 minutes most, if not all, days per week (1). This ambitious objective will hardly be achieved ignoring the large amount of time spent in HD. The recently published guideline of the UKKA recommend that HD patients should aim for 150 min of moderate intensity a week (or 75 min of vigorous activity) or a mixture of both and this goal may include a combination of exercise outside of dialysis and IDE. Furthermore, these guidelines recommend IDE to be available in all HD units (3). Thus, a higher dissemination of IDE is needed to improve the poor health outcomes of HD patients (102).

Increased mortality and hospitalization in hemodialysis patients

According to the 2015 Global Burden of Disease Study, CKD has a growing burden on worldwide mortality (103). In 1990, CKD was the 25th leading cause of death, rising to 21st in 2005 and to 17th in 2015. Between 2005 and 2015, total mortality increased by 31.7%, from 937.7 to 1234.9 thousand deaths (103). Mortality increases with decreasing GFR and increasing albuminuria reaching a peak in dialysis patients (104). CKD patients are 5 to 10 times more likely to die than to progress to kidney failure (6). Yearly mortality in dialysis is around 5-27% in developed countries (27). For patients aged 65-74 years (the most common age group), life expectancy is only five years, which is 50% lower to that observed for the general population (27).

All-cause mortality is about 16 times higher in dialysis patients than in the general population (105). CV and non-CV mortality contribute equally to this excess in mortality risk (105). Compared to the general population, the increased risk in dialysis patients is 8.8 times higher for CV mortality and 8.1 times higher for non-CV mortality (105). CV mortality accounts for 44% and non-CV mortality for 56% of all deaths in dialysis patients (105). Main cause of CV mortality is sudden cardiac death accounting for 25% of all deaths in HD patients. Risk of sudden cardiac death is 59 times higher than in the general population, occurring most frequently near the end of the long 72-hour weekend interval between dialysis sessions and in the 12 hours immediately after a HD treatment (106, 107). Non-CV mortality is commonly due to infections (15%) and malignancies (8%) (105). Compared to the general population, dialysis patients have an elevated risk of death from infectious diseases (10 to 100-fold higher) and cancer (2.6-fold higher) (108,

109). Taken together, CV and infectious diseases account for up to 70% of all deaths in CKD (110), while cancer death accounts for 6% (109).

Likewise, hospitalization risk also increases in a graded fashion across the spectrum of CKD progression, and peaks in dialysis, especially in the months surrounding the initiation of dialysis therapy (111, 112).

Hospitalization is 15 times higher in CKD patients than in the general population (113), resulting in an annual hospitalization rate of 923 hospitalizations per 1000 patients. For dialysis patients, this number raises to 1469 hospitalizations per 1000 patients (114). Hospital readmissions contributes to this alarming data, with nearly one quarter of hospitalizations resulting in unplanned readmission within 30 days, sometimes with fatal outcomes (115). Even when compared with other important diseases as cancer, chronic obstructive pulmonary disease, depression, diabetes and heart failure, CKD has the highest inpatient days (113). Main causes of hospitalization in HD patients are CV (21%) and infections (17%). CV admissions are mainly due to hypertension (4%) and myocardial infarction (3%), while infection admissions are mostly related to pneumonia (5%) and sepsis (5%) (116). As previously mentioned in this Chapter, increased hospitalization contributes to the high financial impact of CKD, with the excess length of stay representing an annual cost of £46m to the UK National Health Service (30).

High CV morbidity is because 1) CKD is associated with increased prevalence of traditional and non-traditional CV risk factors; 2) CKD is an independent risk factor for CV disease; 3) many CV disease risk factors are also risk factors for progression of CKD; and 4) the presence of CV disease may be a risk factor for CKD. This interplay between CV disease and CKD, with each contributing for the pathogenesis of the other, leads to a vicious cycle of CV and kidney disease progression (117).

CV diseases in CKD are generally classified as those affecting myocardium and those affecting blood vessels, with an interrelated pathophysiology (117).

The myocardium is affected by fibrosis (collagen deposition between capillaries and cardiomyocytes) and by cardiac hypertrophy. LVH is explained by three main mechanisms: 1) afterload-related factors, 2) preload-related factors, as well as 3) nonafterload, nonpreload-related factors. Afterload-related factors include abnormal arterial stiffness, increased systemic arterial resistance, and systolic hypertension, leading to an initial concentric LVH. Continuous left ventricular overload subsequently leads to maladaptive changes and cardiomyocyte death, which in turns result in an eccentric hypertrophy and subsequent left ventricular dilation, systolic dysfunction, and reduced ejection fraction. Pre-load related factors comprise the expansion of intravascular volume leading to volume overload, length extension of myocardial cells, and eccentric or asymmetrical left ventricular remodeling. Non-afterload, non-preload related factors include intracellular mediators and pathways (107).

Blood vessels may be affected by the hemodynamic and metabolic milieu of CKD, resulting in structural abnormalities of arterial lumen and of components of the vessel wall. Arterial lumen is mainly affected by atherosclerotic plaques and subsequent development of coronary artery disease and ischemic heart disease. Arterial wall abnormalities are due to increased collagen, calcification and extracellular matrix, resulting in arteriosclerosis and arterial stiffening (117).

Table 1.6. illustrates traditional and non-traditional risk factors associated with each manifestation of CV disease in CKD. Traditional risk factors are those defined in the Framingham Heart Study and used to predict coronary heart disease in the general population (117). Some traditional risk factors should present a reverse epidemiology pattern in which patients at both extremes have the poorer outcomes (U or J curve), suggesting a paradoxical link between the risk factor (e.g. obesity and hypercholesterolemia) and mortality (118). This is explained by the poor prognostic of patients in the lower extremes due to inflammation and malnutrition. Those are short-term killers and studies with a short follow-up would be extremely sensitive to these patients ignoring the harm for patients in the upper extremities (27, 118). Non-traditional risk factors are those that are not used in the Framingham risk equations and whose prevalence increases with CKD progression, including albuminuria, anemia, abnormalities in bone and mineral metabolism leading to vascular calcification, and increased circulation of inflammatory and prothrombotic mediators (119).

Taken together, traditional and non-traditional risk factors contributes to the high prevalence of CV disease in kidney failure patients: coronary artery disease (38%), angina pectoris (19%), cardiac failure (31%), dysrhythmia (7%), peripheral vascular disease (8%) and LVH (74%) (120, 121).

Immune dysfunction increases the susceptibility of CKD patients to infectious diseases. Gut-microbiota dysbiosis and the accumulation of protein-bound uremic retention solutes affect both innate and adaptive immune systems (108). These uremic solutes impair endothelial cells function and induce chronic low-grade activation of innate immune effectors (monocytes and neutrophils). This toxic loop is responsible for accelerated atherosclerosis. Despite chronic activation, the antibacterial capacity of neutrophils is impaired. Adaptive immune system is also affected with defective dendritic cells, premature aging of T cells and impaired cellular and humoral responses, which in turn leads to an increased risk for malignancies and viral infections (108). Besides intestinal dysbiosis and chronic low-grade inflammation, other factors contribute to immune dysfunction in CKD: oxidative stress, premature immunological ageing, metabolic kidney disease, reduced vitamin D synthesis, hypocalcemia, modification of parathyroid hormone and FGF-23 concentration, and altered function of the renin-angiotensin system (110). In HD patients, immune dysfunction is further aggravated by HD therapy itself through the mechanical stimulation from blood pumping, the pollution of dialysate by bacterial metabolites, and the limited biocompatibility of the dialysis membrane (108).

Table 1. 6. *Manifestations of CV disease in CKD and putative traditional and non-traditional risk factors. Taken from Menon et al. (2005) (117)*

Pathology	Traditional risk factors	Nontraditional risk factors
Cardiomyopathy	Older age Hypertension Valvular disease Dyslipidemia Smoking Diabetes	Albuminuria Reduced GFR Anemia Inflammation Arteriosclerosis Extracellular fluid volume overload Abnormal calcium/phosphate metabolism
Atherosclerosis	Older age Male gender Hypertension Diabetes Dyslipidemia Smoking Physical inactivity LVH	Albuminuria Reduced GFR Anemia Inflammation Oxidative stress Endothelial dysfunction Homocysteine Lipoprotein(a) Malnutrition Thrombogenic factors Sympathetic activity Insulin resistance/metabolic syndrome
Arteriosclerosis	Older age Male gender Smoking Hypertension Diabetes Dyslipidemia	Albuminuria Reduced GFR Endothelial dysfunction Abnormal calcium/phosphate metabolism Metabolic syndrome

CV: cardiovascular; LVH: left ventricular hypertrophy; GFR: glomerular filtration rate.

CKD and cancer are connected in both directions: cancer can cause CKD (either directly or indirectly through the adverse effects of therapies), while CKD may conversely be a risk factor for cancer, and both may be associated because they share common risk factors, often toxins (122). Cancer mortality risk increases with CKD progression (18% increase for every 10mL/min/1,73m^2 reduction in GFR) (123). KTx patients are those at higher risk of cancer (three to four-fold increase in overall cancer risk), mainly caused by viral agents (122). Among dialysis patients there is also an excess risk of cancers of the urinary tract and endocrine cancers, and an excess risk of death from digestive tract cancers, but a reduced risk of prostate cancers (124). Immune dysfunction may explain the higher incidence of viral carcinogenesis. Different types of uremic toxins may impair the anti-tumor activity of certain immune cell types such as natural killer and dendritic cells, promote angiogenesis and enhance accelerated growth of aggressive tumors (124).

CV, infection and cancer mortality are all interconnected as CKD induces a chronic inflammation state that is a non-traditional risk factor for CV disease, and is associated with the inability to mount an efficient immune response, increasing the risk of infection and also the risk of cancers caused by viral agents (108).

For kidney failure patients, KTx is a major opportunity to improve relevant clinical outcomes (125). Thus, eligibility to this gold standard treatment is of great importance for HD patients. However, functional decline may preclude patients to be eligible for KTx, limiting their access to the best KRT (126).

As previously detailed in this Chapter, compelling evidence on the benefits of exercise suggest that it should be used to improve clinical outcomes in HD patients (47). Potential mechanisms were described and could be related with exercise-mediated benefits on chronic inflammation (alterations in circulating pro-inflammatory and anti-inflammatory cytokines) that may improve CV and infection morbidity and mortality (47). Moreover, exercise may have a direct benefit on CV outcomes reducing LVH (52) and myocardial stunning (127, 128) that are known predictors of mortality in HD patients (129, 130). Regular exercise is also known to increase the elimination of immunogenic cancer cells, contributing to contain cancers in a "precancerous" equilibrium state, thus reducing clinically diagnosed cancers and their subsequent mortality (131).

Is intradialytic exercise a realistic strategy to reduce mortality and hospitalization?

Despite the high convenience of IDE, many barriers have precluded a wider implementation in renal care. Thus, to be a realistic strategy to improve relevant clinical outcomes in HD patients, IDE should satisfy two major conditions: 1) successful large-scale clinical implementation in real-world conditions, and 2) effectiveness to improve important endpoints such as mortality and hospitalization.

Some attempts to report implementation outcomes of IDE have been made and are exposed in Table 1.7. For uniformization purposes, implementation outcomes were extracted from each study and adapted to the RE-AIM framework dimensions (132): reach, effectiveness, adoption, implementation and maintenance (explained in detail in Chapter 2, Section 2.1). Studies exposed in Table 1.7. were not specifically developed to be implementation studies, that examine the questions related to implementation (the action of developing an intention to effect which can be health policies, programs, or individual practices) (133). Consequently, these studies have important limitations: 1) low sample sizes (maximum n=46); 2) no scalability assessment (included only one HD unit); 3) no use of a specific framework to systematize data on implementation outcomes (e.g., RE-AIM), and 4) most of the studies are developed in controlled, rather than in real-world conditions. Thus, a research-to-practice gap remains and may have prevented efficacy findings of IDE to be effectively translated in a public health impact. Real-world, large-scale IDE implementation studies are missing and could be informative for stakeholders (e.g., dialysis providers) to support and finance an extensive IDE implementation.

Despite the growing evidence demonstrating the association of PA with mortality (Chapter 3) (63), the association of IDE with the survival of HD patients was only addressed in very few studies (134-136) (Table 1.8). The PEDAL trial (134) was a RCT with a 6-month follow-up period, in which 243 HD patients were randomized to an IDE group (n=127) and to a control group (n=116). No significant differences were observed for all-cause mortality, while numbers were too small to analyze CV mortality. Several limitations precluded a reliable survival analysis in this study. The authors state that this study was underpowered to investigate mortality, and that mortality outcomes were reported just to allow a balance of benefits and harms to be evaluated. Moreover, the short follow-up period (6 months) precluded more events to be included in the analysis. An important finding was the low adherence (only 47% of the exercise sessions), resulting in a very low exercise dose that might precluded the expected benefits of exercise.

Tabibi et al. (135) also performed a RCT founding that an IDE improved survival of HD patients. However, these findings are limited by a low sample size (n=74) and a short observation period (one year) with a low occurrence of events (n=11) that led to an imprecise effect estimation. Moreover, aerobic exercise was not performed in the most typical way (cycling) but in the form of repetitive specified movements. Recently, the DIATT trial (136) published the results from a large multicentric RCT (n=917) and no improvements were found in the exercise group. Nevertheless, the IDE was interrupted during the COVID outbreak (between 11 to 32 weeks) which could have biased the results. Moreover, the follow-up lasted only the intervention period, thus no data is available after 12 months. Accordingly, a low mortality rate was observed (8%), which could have limited survival analysis.

Studies analyzing the effect of IDE on hospitalization outcomes are also scarce (Table 1.8). Parker et al. (137) performed a cohort study comparing hospitalization outcomes in two different periods: six months before and six months during IDE participation. A non-significant reduction was found in hospitalization rate for the entire sample. However, a significant reduction was found in a sub-analysis restricted to incident patients (HD ≤ 3months). Hospital length of stay was significantly reduced for the entire sample. A major limitation of this study is the non-existence of a control group, being likely that the reductions observed for incident patients in the six months of IDE may have been due to HD stability itself rather than a true benefit of exercise. Moreover, exercise dose (4.5 sessions/month) was probably too low to elicit protective mechanisms to effectively prevent hospitalization. The PEDAL trial (134) also analyzed the effects of IDE with hospitalization and, likewise for mortality, non-significant results were found (Table 1.8.). Limitations pointed for mortality outcomes may also justify the non-significant results found for hospitalization. The DIATT trial (136) also reported data on hospitalization outcomes and positive results were found both for hospitalizations/patient and for hospitalization days/patient.

Previous systematic reviews reported the lack of evidence on the effect of IDE on relevant endpoints as mortality and hospitalization (138, 139). These are critically important outcomes for the different HD stakeholders (patients, caregivers and health professionals) (140) and are research priorities for exercise in CKD (141). Thus, evidence of a protective role of IDE on such relevant outcomes could promote a wider translation into clinical practice.

Table 1. 7. *Studies reporting implementation outcomes of IDE*

Study	Country	n patients	n HD units	Follow-up	Exercise protocol	Implementation outcomes
Kouidi et al. (2004) (142)	Greece	24	1	4 y	3 times/wk AE + RE	**Maintenance:** 79%; **Effectiveness:** PF, QoL
Henson et al. (2010) (143)	Australia	13	1	16 w	3 times/wk AE	**Reach:** 11%; **Implementation (adherence):** 73%; **Implementation (duration/ex session):** 29 min; **Maintenance:** 85%; **Effectiveness:** fatigue, QoL, PF
Nonoyama et al. (2010) (144)	Canada	9 (≥55 years)	1	12 w	3 times/wk AE + RE*	**Reach:** 9%; **Implementation (adherence):** 89%; **Maintenance:** 67%; **Effectiveness:** QoL, PF
Reboredo et al. (2011) (145)	Brazil	34	1	5 y	3 times/wk AE	**Implementation (adherence):** 65%; **Effectiveness:** safety
Anding et al. (2015) (146)	Germany	46	1	5 y	2 times/wk AE + RE	**Maintenance:** 80%; **Effectiveness:** QoL, PF, Strength, Ex capacity
Thompson et al. (2016) (147)	Canada	31	1	12 w	3 times/wk AE or RE or both	**Reach:** 31%; **Implementation (adherence)**: 87%; **Maintenance:** 84%; **Effectiveness:** QoL, PF, strength, safety
Kaminska et al. (2021) (148)	Canada	9	1	12 w	3 times/week AE	**Reach:** 64% (of those eligible); **Implementation (adherence):** 67% ≥ 50%; **Effectiveness:** QoL
Imamura et al. (2022) (149)	Japan	39 (≥60 years)	1	2 y	3 times/week RE	**Reach:** 46%; **Maintenance:** 72%; **Effectiveness:** PF, PA
Jhamb et al. (2023) (150)	USA	17	1	12 w	Video based AE + RE	**Reach:** 42.5%; **Implementation (adherence)**: 88%; **Maintenance:** 76%; **Effectiveness:** safety, PF, fatigue, depressive symptoms

IDE: intradialytic exercise; W: weeks; y: years; QoL: quality of life; PF: physical function; AE: aerobic exercise; RE: resistance exercise; Ex: exercise; PA: physical activity; *home exercise running at the same time

Table 1. 8. *Studies reporting the association between IDE and mortality or hospitalization in HD patients*

Study	Design	Sample (n)	Type of exercise	Duration	Adherence	Follow-up	Hospitalization outcomes	Mortality outcomes
Parker et al. (2015) (137)	Cohort	102	Aerobic	6M	37.5% (mean)[1]	12M (6 before + 6 during IDE)	NS ↓ in hospitalization rate for the entire sample Significant ↓ in hospitalization rate for incident patients Significant ↓ in hospital LOS	----
March et al. (2021) (98)	Retrospective analysis of a RCT	Ex: 53 Con: 56	Aerobic	6M		12M (6 during and 6 after IDE)	Number of hospitalizations per patient: Ex: 75; Con: 105	----
Greenwood et al. (2021) (134)	RCT	Ex: 127 Con: 116	Aerobic and resistance	6M	47% (median)	6M during IDE	IRR=1.39 (0.93-2.08), p=0.109	**All-cause mortality** HR=1.19 (0.48-2.94), p=0.71
Tabibi et al. (2023) (135)	RCT	Ex: 37 Con: 37	Aerobic and resistance	6M	81%±6%	12M	---	**All-cause mortality:** Ex: 6%; Con: 27% (p=0.01)
Anding-Rost et al. (2023) (136)	RCT	Ex: 446 Con: 471	Aerobic and resistance	12M[2]	88.1%	12M during IDE	**Number of hospitalizations per patient** Ex: 1.1±1.5; Con: 1.3±1.6 (p=0.024) **Hospitalization days per patient** Ex: 10.8±18.9; Con: 12.8±20.9 (p=0.036)	**All-cause mortality** Ex: 9%; Con: 7.6% (NS)

HD: hemodialysis; RCT: randomized controlled trial; M: months; IDE: intradialytic exercise; NS: non-significant; LOS: length of stay; Ex: exercise; Con: control; IRR: incident rate ratio; HR: hazard ratio; [1]data computed based on the mean number of exercise sessions/month; [2]interrupted for between 11 to 32 weeks

COVID-19 pandemic: impact on hemodialysis patients

The novel coronavirus was first identified in late 2019 in China and was responsible for a high number of infections and consequent deaths throughout the world. Considering its threat to public health, the World Health Organization (WHO) has declared the COVID-19 outbreak a global pandemic on March 11, 2020 (151).

For HD patients, COVID-19 pandemic was particularly distressing. Physical distancing measures were not possible for this population. As a lifesaving treatment, HD could not be interrupted, exposing patients to an increased infection risk, not only during the treatment, but also during shared transportation to and from HD units. This may explain the high infection rate in this population (152). Besides being at increased risk for infection, CKD is one of the strongest risk factors for severe COVID (153). Removing CKD as a risk factor would have decreased the global population at increased risk of severe COVID-19 from 22% to 17% (154). In Europe, 28-day mortality in COVID-19 dialysis patients was about 20%, that is two times higher than non-KRT patients of similar age (155). Moreover, COVID-19 may further exacerbate CV disease (156), hospitalization risk (60% of dialysis patients with COVID-19 were hospitalized) (157), with an high prevalence of long-COVID symptoms (e.g. fatigue) (158). Risk factors for poor outcomes in HD patients included older age, male sex, high comorbidity index, obesity, diabetic nephropathy, coronary heart disease, cerebrovascular accident, and lower neutrophil and lymphocyte counts (155, 158, 159). With all these threats in mind, anxiety and depression of HD patients was further intensified during the pandemic (160-162).

COVID-19 social distancing restrictions caused a reduction in global PA (163), likely due to a decrease in incidental PA because of a reduced participation in community activities such as shopping and socializing, and a reduction in participation of formal exercise, such as attendance to exercise classes, gyms, golf, bowls, and other group activities (164). Hence, COVID-19 pandemic added an extra burden to an already existing inactivity pandemic (165). In HD patients, the combination of mandatory lockdowns and the fear of COVID-19 infection may have further aggravated inactivity of this vulnerable population (166). Moreover, COVID-19 pandemic has put unprecedent pressures on HD units that had to rapidly adopt infection control procedures to safeguard patients and staff while still supporting the continuation of dialysis services (167). Consequently, most HD units suspended their IDE programs, which patients perceived as a negative consequence of the pandemic (160).

Is online exercise a new possibility for hemodialysis patients?

The COVID-19 pandemic exposed areas in healthcare where readiness for disruptive events was fragile. This is the case of IDE programs that are commonly implemented with the existing dialysis staff, without hiring dedicated exercise professionals, which may compromise its sustainability (168). Thus, in consequence of the unprecedent challenges imposed by the COVID-19 pandemic for the dialysis staff (167), many IDE programs were suspended, as detailed in this section.

Staying home, while a safe measure, may have unintended negative consequences as increasing inactivity. Maintaining a regular PA in a safe home environment was an important strategy for healthy living during the coronavirus crisis (169). Thus, rather than waiting for a functional decline to occur, the renal care community had to proactively search for strategies to increase PA in this at-risk population. The need for urgent and innovative strategies for exercise in HD patients during the pandemic, turned the COVID-19 challenge into an opportunity for progress in the existing exercise interventions delivered to HD patients. Telehealth exercise programs were recommended by the WHO Regional Office for Europe (170) and the Centers for Disease Control and Prevention (171). There is considerable evidence of its application in older adults (172), cardiac and pulmonary rehabilitation (173, 174), and in cancer patients (175). Therefore, telehealth exercise interventions may indeed be a potential strategy for HD patients as 1) home is their preferred location to exercise (65); 2) presents no infection risk; and 3) is time flexible in a population where time constraints are a barrier to exercise (66). Thus, telehealth exercise combines advantages of inter-dialytic exercise (higher exercise intensity and potential to undertake a greater range of exercises) and intradialytic exercise (higher convenience) (71). Moreover, using a supervised telehealth exercise intervention, may have a more robust effectiveness than usual home-based exercise without supervision (176). Thus, its applicability may subsist beyond the pandemic and be used to complement IDE, the latter probably insufficient on its own to fulfill the UKKA PA recommendations for HD patients (3) (Chapter 4). However, readiness, proficiency, and motivation to use mobile health technology may be an implementation barrier in this population (177). Thus, research is needed to examine implementation and scalability of telehealth exercise programs in HD settings.

1.3. Objectives

The main objectives of this thesis are:

1. To analyze the association of overall PA with mortality and hospitalization outcomes in kidney failure patients;
2. To examine the implementation of a large-scale IDE program in real-world conditions, including its effectiveness on safety, physical function, body composition, BP, Hb (hemoglobin) and phosphate control;
3. To analyze the association of IDE with important clinical endpoints: mortality and hospitalization;
4. To examine the implementation of an online exercise program implemented during the COVID pandemic for HD patients, including its effectiveness on safety, physical function, body composition, sleep quality, depressive symptoms, and fatigue.

Chapter 2: General Methods

2.1. Research design

The studies included in this thesis are the result of a collaboration between the Research Center in Sports Sciences, Health Sciences and Human Development (CIDESD) and the NephroCare Portugal (Fresenius Medical Care) and received prior approval by the NephroCare Health Ethics Committee (04/2021).

Initially, the research project included 1) a systematic review on the association of PA with mortality and hospitalization; 2) a 1-year in duration implementation study on IDE; and 3) a cohort study to investigate its association with mortality, hospitalization and KTx eligibility. However, data inaccuracy on KTx eligibility precluded this analysis. COVID outbreak did not affect our research project since the data collection of the 1-year implementation study was already performed. Nevertheless, during the initial period of the pandemic, the NephroCare ongoing IDE program was suspended, and an alternative online exercise program was implemented. Therefore, an additional study was added to this thesis to examine the implementation of an online exercise intervention for HD patients during the COVID pandemic.

Thus, this research is mainly based on a retrospective analysis of a nation-wide implementation of IDE in Portugal that is explained below and originated the studies described in Chapters 4 and Chapter 5.

Context of the implementation of the intradialytic exercise program

In Portugal, public-private partnerships between the government and private dialysis providers deliver most of the HD treatments. Access to KRT is free and no insurance is needed. Portugal has an integrated management of kidney failure that includes dialysis services and products (HD treatments, medications, laboratory services, vascular access care, blood transfusions and complementary tests) (178), with no inclusion of any exercise intervention. Thus, the IDE program was fully funded by NephroCare and free of charge for patients. In each unit, the program was conducted with the existing staff and no extra human resources were hired. Interdisciplinary dialysis teams included nurses, physicians, pharmacists, nutritionists, social workers, and healthcare assistants.

NephroCare Portugal is part of the Fresenius Medical Care group and is the larger hemodialysis provider in Portugal. Currently, this company has 42 clinics, representing a 43% of the market share in Portugal.

Targeted sites and participants of intradialytic exercise

At the time of IDE implementation (September 2016), the NephroCare Portugal group had 36 HD units that were all targeted for implementation. Inclusion and exclusion criteria were defined in collaboration with the NephroCare Portugal medical board. Inclusion criteria were 1) physical/cognitive capacity (ability to cycle), 2) HD vintage ≥2 months. Patients were excluded if

1) vascular access in the lower limb, 2) high risk of vascular access hematoma, 3) CV risk, 4) Hb <8.5g/dL and 5) systemic infection.

Description of the intradialytic exercise implementation strategy

The IDE was implemented after a pilot experience in a single dialysis unit (September 2014) that was part of the author of this thesis' Master of Science (MSc) research project, with the main outcomes demonstrating improvements in patients´ physical function, with no adverse events and without affecting dialysis adequacy. These results were well received by the NephroCare Portugal medical and executive boards who decided to expand the program to a national level using a top-down approach. A national IDE coordinator was nominated and all NephroCare Portugal dialysis units (n=36) were invited to join in. A guide to IDE implementation was developed and disseminated to all HD units. In each dialysis unit, the decision to integrate the program was made by consensus of the medical director and the head nurse who designate two members of the medical and nursing staff to be the local IDE coordinators. These players had a critical role for IDE success selecting participants, supervising exercise sessions, performing physical function assessments every three months, keeping data records up to date, training all local staff involved, and reporting to IDE national coordinator. On the initial screening visit, all patients who met the inclusion criteria received an explanation of the purpose, risks and procedures of IDE and patients were invited to sign an informed consent. Every three months, local coordinators had two full days set aside to fully dedicate to IDE patients, without any HD-related tasks. In these days, new patients were recruited, and physical function assessments were taken for all IDE patients. Renal nutritionists were asked to motivate patients and a specific nutritional appointment was developed for IDE patients.

A partnership between NephroCare Portugal and the CIDESD, a consortium of higher education institutions spread across the country, allowed that some dialysis units received yearly master's exercise physiology students' internships that supported IDE implementation. Nevertheless, the program runs independently of having students involved, as only some clinics are in the vicinity of one of these universities, and the internships run only during one academic year (i.e., October to July). A digital platform was developed to monitor IDE implementation. This platform was implemented in every IDE unit and comprises data on patient screening with reasons for exclusion and identification of patients who rejected IDE; exercise prescription (aerobic and resistance exercise); exercise adherence indicating its performance or not in each exercise session (including reasons for not performing IDE); and IDE withdrawal and its reasons. All nurses were trained by the local coordinators to use this digital platform.

Methods and techniques used in our implementation strategy are described in Table 2.1. and were based on the Proctor et al. framework (179).

Table 2. 1. *Methods and techniques used in the IDE implementation strategy.*

	Pilot experience	**Development of IDE implementation guide**	**Meetings with head nurses and medical directors**	**Educational meeting with local coordinators**	**Dissemination of IDE implementation guide to all units**	**University partnership protocols**
Actors	Investigators and dialysis staff of a HD unit	National coordinator	National coordinator	National coordinator	Local coordinators	National coordinator, local coordinators, master students, and their advisors
Actions	Pre-implementation in a single dialysis unit and shared results with medical and executive board	Development of a guide explaining all the procedures related to IDE	Presentation of the implementation guide to local decision makers	Visit to the pilot experience HD unit. Presentation and discussion of the implementation guide to the local coordinators	Presentation of IDE implementation guide to the dialysis staff.	Internships in HD units with IDE
Targets	Raise awareness in the medical and executive board	Uniformize IDE implementation	Influence the head nurse and the medical director to accept IDE implementation	Discussion of implementation strategies with all local coordinators	Acceptance of IDE by the dialysis staff	More individualized intervention
Temporality dose	Pre-implementation	Pre-implementation	Pre-implementation	Pre-implementation	Pre-implementation	Academic year
Implementation outcomes affected	Reach, Effectiveness, Adoption, Implementation, Maintenance (at a smaller scale in a single HD unit)	Reach, Effectiveness, Adoption, Implementation, Maintenance	Adoption	Reach, Effectiveness, Implementation, Maintenance	Reach, Effectiveness, Implementation, Maintenance	Reach, Effectiveness, Implementation, Maintenance
Justification	Demystify barriers to IDE implementation (ex. risks associated with IDE)		Discuss the possibility to implement IDE as proposed in the implementation guide		Demystify dialysis staff-related barriers to IDE implementation	Dedicated and skilled staff for a more individualized intervention with better outcomes

HD: hemodialysis; IDE: intradialytic exercise

Description of the intradialytic exercise intervention

Participants were instructed to perform a simple exercise protocol that was designed to be easily implemented by the existing dialysis staff with low supervision requirements in every HD session. Exercise sessions started at least 30 minutes into dialysis and were completed within 90 minutes of the end of the session. This was considered a safe period to exercise, avoiding an initial period at HD beginning for patient assessment and treatment stabilization and a final period more prone to adverse events as hypotension and cramps. Target intensity was moderate (12-15) and measured by the 6-20 rating of perceived exertion Borg scale (180). After three months of IDE, patients were encouraged to begin strength exercise (performed after aerobic training) that consisted of up to four sets (12 repetitions) of the following exercises: handgrip exercise using squeeze balls, isometric foot extension (plantar flexion) and leg extension (performed against the dialysis chair), isotonic knee extension, knee flexion, hip abduction and hip flexion (performed using ankle weights). Despite strength exercise was not mandatory, all patients were encouraged to engage. Table 2.2. illustrates the exercise protocol.

Table 2. 2. *IDE protocol*

Aerobic training Cycle ergometer	**Warm-up:** 5 minutes; low load **Aerobic component:** up to 60 minutes (12-15 on the 6-20 Borg scale); 50-70 rpm; increased load **Cool-down:** 5 minutes; low load
Strength training 3 months later After aerobic training	**Upper limbs exercise** Handgrip (squeeze balls with different resistance) **Lower limbs exercises** Against dialysis chair – isometric: plantar flexion, leg extension Ankle weights – isotonic: knee extension, knee flexion, hip abduction, hip flexion

rpm: rotations per minute

All patients were encouraged to increase the exercise volume progressively. Therefore, for the aerobic component, exercise duration increased 10 minutes every two weeks (up to a maximum 60 minutes). For strength exercises, firstly the number of sets increased from one up to four, followed by weight increases up to 4.5 Kg. In its most complete version, an exercise session could last about 80 minutes.

The RE-AIM framework

Implementation research intends to facilitate integration of research into practice and study the process by which this occurs (181). More than 150 models, theories, frameworks have been used to guide implementation science (182). The RE-AIM framework was designed in the late 1990s to help evaluate interventions and public health programs, to produce a more balanced approach to internal and external validity (the degree to which the results would also occur in a broader population or in different contexts), and to address key issues that are important for dissemination and generalization (132). This tool was indeed reported to be one of the most frequently used implementation science frameworks in research grant proposals (183) and has also been used to evaluate the health impact of PA interventions (184).

The RE-AIM framework was used in this thesis to analyze the implementation of an IDE program and an online exercise program (Chapters 4 and 6, respectively). All the dimensions were considered following a logical sequence starting with adoption and reach, followed by maintenance, implementation, and effectiveness.

Adoption is the absolute number, proportion and representativeness of settings and intervention agents who are willing to initiate the intervention (e.g., proportion of settings who joined the intervention) (132).

Reach refers to the absolute number, proportion and representativeness of patients who decided to participate (e.g., proportion of patients who joined an exercise program and its comparison with the entire sample) (132).

Maintenance is the extent to which a program or policy becomes institutionalized or part of the routine organizational practices and policies. At an individual level, maintenance refers to the long-term effects of a program (≥6 months) and long-term attrition and differential rates by patients' characteristics (132) (e.g. proportion of patients who withdrew the intervention and its reasons).

Implementation is the intervention agents´ fidelity to the various elements of an intervention´s protocol (132) and refers to fidelity (whether the intervention is delivered as intended) and dose (amount of an intervention that is administered and successfully implemented) (185).

Effectiveness is the impact of an intervention on health outcomes, including negative impacts (132) (e.g. benefits and adverse events associated with an exercise program).

Metrics for each dimension of the RE-AIM framework were adapted for the specific cases of IDE (as detailed in Chapter 4) and the online exercise (Chapter 6).

Physical function and body composition measures

Physical function refers to the ability to carry out the basic actions that are essential to perform more complex activities and to maintain independence. It includes physiological impairment (at organ or system level) and functional limitations (at whole body or person level) (186). Physical function outcomes were examined in Chapters 4 and 6, and included the following physical function tests:

- 30 seconds sit to stand test (STS): number of STS cycles within 30 seconds
- Handgrip strength taken in the non-vascular access arm
- 5 times STS: time needed to complete five STS maneuvers
- 8-foot up and go (UG): the total time a patient needs to rise from a chair, walk 2.44m, turn around, return, and sit down again
- Single Leg Stance (SLS): time that a person can statically stand unassisted on one leg(maximum 45 seconds; 3 attempts).

All the physical function measures were taken before a second or third weekly HD session.

Body composition was determined by multifrequency bioimpedance using the body composition monitor (BCM) device (BCM, Fresenius Medical Care, Bad Homburg, Germany). The BCM is based on a three-compartment model, providing excess fluid mass, lean tissue mass and adipose tissue mass (187) and has been validated against reference methods for assessment of fluid status and body composition in HD patients (188). Body composition outcomes were used in Chapters 4 and 6 and included body mass index (BMI – Kg/m^2), adipose and fat mass outcomes (adipose tissue mass – Kg, fat mass – Kg, fat tissue index – Kg/m^2), and lean mass outcomes (lean tissue mass – Kg, lean tissue index – Kg/m^2, body cell mass – Kg). Body composition measures were taken before an HD treatment.

Systematic review: association of physical activity with mortality and hospitalization in end-stage kidney disease (Chapter 3)

In this systematic review, evidence on the association of PA with mortality and hospitalization in adult end-stage kidney disease patients on KRT (HD, PD, KTx) was examined. Electronic databases (EBSCO, Scopus and Web of Science) and hand search were performed until March 2020, investigating for observational studies addressing the association of PA with mortality or hospitalization. Methodological quality of the included studies (n=11) was assessed using the Quality in Prognosis Studies tool. The review protocol was registered in PROSPERO (CRD42020155591). Methodological heterogeneity among the studies precluded meta-analysis.

Implementation study on intradialytic exercise (Chapter 4)

Hybrid type III implementation study that analyzed the success of the implementation strategy and its health impact. Using the RE-AIM framework, a retrospective analysis was performed to analyze the first year of IDE clinical implementation at a nation-wide level in Portugal.

Cohort study: intradialytic exercise association with mortality and hospitalization (Chapter 5)

Multicentric prospective cohort study that was based on the IDE program previously described in this Chapter. IDE exposure was measured during the first year and then patients were followed for more three years for the events of death and hospitalization. IDE participation was measured based on aerobic exercise dose in minutes/week and three categories were created: a non-exercise (patients eligible but who refused IDE), a low exercise (<87min/week) and a high exercise group (≥87min/week). Also, a subanalysis restricted to IDE participants and considering exposure as a continuous variable was performed. Outcomes included time to all-cause mortality and hospitalization, and number and days of hospitalization/year.

Implementation study on online exercise (Chapter 6)

Hybrid type II implementation study examining implementation and effectiveness of a 12-week online exercise intervention implemented at a nation-wide level. A retrospective analysis was performed using the RE-AIM framework.

2.2. Statistical analysis

Statistical analysis was performed using the IBM® SPSS® statistics version 23 (IBM® Corporation, Armonk, NY, USA).

Descriptive data was presented as mean values ± standard deviation (SD) or as median and interquartile range (IQR). All data were checked for normality using Kolmogorov-Smirnov tests. If non-normally distributed, a logarithmic transformation to base 10 was performed, and normality was rechecked. Comparison between groups was performed using Mann-Whitney U test (non-normally distributed variables) and independent samples t-test (normally distributed variables). The chi-squared test was used for categorical variables.

For every procedure, statistical significance was accepted at $p<0.005$. Further specific statistical procedures are described in each chapter.

Chapter 3: Association of physical activity with mortality and hospitalization in end-stage kidney disease: a systematic review of observational studies

3.1. Abstract

Background: ESKD patients have a high mortality and hospitalization risk. The association of these outcomes with PA was described in the general population and in other chronic diseases. However, few studies examining this association have been completed in ESKD, raising the need to systematically review the evidence on the association of PA with mortality and hospitalization in this population.

Methods: Electronic databases (EBSCO, Scopus and Web of Science) and hand search were performed until March 2020 for observational studies reporting the association of PA with mortality or hospitalization in adult ESKD patients on KRT (HD, PD and KTx). Methodological quality of the included studies was assessed using the Quality in Prognosis Studies tool. The review protocol was registered in PROSPERO (CRD42020155591).

Results: Eleven studies were included: six in HD, three in KTx, and two in HD and PD patients. PA was self-reported, except in one study that used accelerometers. All-cause mortality was addressed in all studies and CV mortality in three studies. Nine studies reported a significant reduction in all-cause mortality with increased PA levels. Evidence of a dose-response relationship was found. For CV mortality, a significant reduction was observed in two of the three studies. Only one study investigated the association of PA with hospitalization.

Conclusions: Higher PA was associated with reduced mortality in ESKD patients. Future studies using objective PA measures could strengthen these findings. The association of PA with hospitalization should be explored in future investigations.

Keywords: CKD; HD; Survival; Hospitalization; PA.

3.2. Background

Progression of CKD is a major concern as survival of ESKD patients depends on a KRT: HD, PD and KTx (for a more detailed explanation see Chapter 1, Section 1.2.). Each year, about 440.000 patients worldwide start a KRT (27), with HD being the most common. However, KTx is the most cost-effective, promoting a better survival and quality of life with reduced costs (26). ESKD patients, particularly those on HD and PD, have an increased mortality and hospitalization (189), with these being important outcomes that are a priority for patients, caregivers and HCP (140, 190).

PA defined as any bodily movement produced by the contraction of skeletal muscles that increases energy expenditure above basal levels (4), is associated with a reduced mortality in the general population (191). However, a relationship between PA and mortality in ESKD has not been thoroughly established. As explained in detail in Chapter 1, Section 1.2., ESKD patients have a high prevalence of traditional CV risk factors, as well as nontraditional CV risk factors, (e.g., microalbuminuria, anemia, oxidative stress, inflammation and hyperphosphatemia) (119). Moreover, this population has an increased risk for other specific causes of death (e.g., infection) (192). Thus, findings related to PA and mortality in the general population cannot be extrapolated to CKD patients (193). Inactivity in CKD patients was previously debated in Chapter 1, Section 1.2. Several factors contribute to a vicious cycle of reduced PA in ESKD: behavioral (e.g. depression), pathophysiological (e.g. anemia, HD related fatigue) and logistical (e.g., time spent on dialysis) (62). Therefore, inactivity (an insufficient PA level to meet the WHO recommendations (4) is common in ESKD patients and is associated with important predictors of mortality, such as inflammation, body composition, physical function and cardiorespiratory fitness (62). A systematic review found an inverse association between PA and mortality in CKD (64). However, this study was restricted to non-dialysis patients, which have lower mortality and hospitalization rates compared to ESKD patients (189). No previous systematic reviews combined the evidence on the association of PA with mortality and hospitalization in the high-risk ESKD population.

This systematic review aims to examine whether higher PA levels are associated with lower mortality and hospitalization in adult patients with ESKD on KRT. Our summarized evidence should impact the kidney care community by raising awareness for the need to increase PA in this highly inactive population.

3.3. Methods

Protocol and registration

The protocol of this study was registered on the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020155591) and can be assessed at https://www.crd.york.ac.uk/PROSPERO/. This report followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (194).

Criteria for considering studies for this review

The inclusion criteria for this review were: (1) observational studies; (2) reported associations between PA as an exposure variable with all-cause or CV mortality and/or hospitalization; (3) reported effect estimates with 95% confidence interval (CI); and (4) adult (age ≥ 18 years old) community dwelling KRT patients. Abstracts, conference papers and studies published in non-English-language journals were excluded.

An inclusive approach was used regarding PA measures. Thus, any of the following were considered: (1) any type of PA measurement, including self-reports, devices and direct observation; (2) any of the PA dimensions: frequency, intensity, time and type (195); (3) any PA domain: leisure-time, occupational, household and transport-related (196); (4) PA instruments reporting energy expenditure, and (5) summarized PA-related measures by devices (e.g., number of steps) (197).

Physical fitness and PA are two different constructs (198). Thus, studies using physical fitness measures and reporting them as PA were excluded.

Search strategy for identification of studies

The EBSCO, Scopus, and Web of Science electronic databases were searched from their date of establishment to 16 of March 2020. Text words used were: (exercise OR “physical activity”) AND (mortality OR hospital* OR “length of stay” OR “cardiovascular event”) AND
(“Chronic Kidney Insufficiency” OR “chronic kidney diseases” OR “Chronic Renal Diseases” OR “Chronic Renal Insufficiency” OR “Renal dialysis” OR “Hemodialysis” OR “HD” OR “Haemodialysis” OR “Kidney Transplantation” OR “Renal Transplantation” OR
“Kidney Grafting”). An additional hand search was performed to screen for other potential eligible studies including the reference lists from the included studies. Citations were managed using the software EndNote X7.3.1 (Clarivate Analytics, USA). The search strategy was conducted by one reviewer. An example of a full electronic search strategy (EBSCO) can be found in Table 3.1.

Table 3. 1. *Full electronic search strategy*

Physical activity	"exercise" [All Fields] OR "physical activity" [All Fields]
Mortality	"mortality" [All Fields] OR "cardiovascular event" [All Fields]
Hospitalization	"hospital*" [All Fields] OR "length of stay" [All Fields]
End-stage renal disease	"Chronic Kidney Insufficiency" [All Fields] OR "chronic kidney diseases" [All Fields] OR "Chronic Renal Diseases" [All Fields] OR "Chronic Renal Insufficiency" [All Fields] OR "Renal dialysis" [All Fields] OR "Hemodialysis" [All Fields] OR "HD" [All Fields] OR "Haemodialysis" [All Fields] OR "Kidney Transplantation" [All Fields] OR "Renal Transplantation" [All Fields] OR "Kidney Grafting" [All Fields]

Data extraction and quality assessment

Results from the overall electronic search were reviewed by two authors based on the title and abstract. Articles deemed potentially relevant were retrieved for full-text review and inspected to avoid multiple publication bias. In cases of suspected duplication, corresponding authors were contacted and, if confirmed, preference was given to the studies with a longer follow-up. Any disagreements were resolved via joint consensus.

A data extraction form was used to capture relevant information from the included studies. The following information was recorded: authors' name, publication year, country, follow-up length, sample size, type of KRT, participants' mean age, sex distribution, PA measurement, PA domains, PA output, outcome measures, adjustment variables, technique for handling the missing data, and overall main findings. The exposure variable was PA and outcomes of interest were all-cause, CV or cause-specific mortality/hospitalization. Measures of association were reported in reference to the least physically active group. When needed, authors were contacted to provide the missing data.

The methodological quality of the studies was evaluated using the Quality in Prognosis Studies tool (199). This instrument includes six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The original classification grades each domain in three categories (high, moderate or low risk of bias). We added an additional "unclear" category that was applied when a judgement is not possible due to insufficient information. This modified Quality in Prognosis Studies tool is described in Table 3.2.

Two authors assessed the risk of bias of all included studies. Discrepancies in scoring were settled by agreement.

Table 3. 2. *Adapted Quality in Prognosis Studies tool*

Domains	Prompting items for Consideration (Yes, No, N/A)	Rating (Low, Moderate, High, Unclear)
Study participation	Adequate participation in the study by eligible persons Description of the source population or population of interest Description of the baseline study sample Adequate description of the sampling frame and recruitment Adequate description of the period and place of recruitment Adequate description of inclusion and exclusion criteria	**High bias:** The relationship between the PF and outcome is very likely to be different for participants and eligible nonparticipants **Moderate bias**: The relationship between the PF and outcome may be different for participants and eligible nonparticipants **Low bias**: The relationship between the PF and outcome is unlikely to be different for participants and eligible nonparticipants **Unclear**: insufficient information
Study attrition	Adequate response rate for study participants Description of attempts to collect information on participants who dropped out Reasons for loss to follow-up are provided Adequate description of participants lost to follow-up There are no important differences between participants who completed the study and those who did not	**High bias**: The relationship between the PF and outcome is very likely to be different for completing and non-completing participants **Moderate bias**: The relationship between the PF and outcome may be different for completing and non-completing participants **Low bias**: The relationship between the PF and outcome is unlikely to be different for completing and non-completing participants **Unclear**: insufficient information
Prognostic Factor Measure	A clear definition or description of the PF is provided Method of PF measurement is adequately valid and reliable Continuous variables are reported or appropriate cut points are used The method and setting of measurement of PF is the same for all study participants Adequate proportion of the study sample has complete data for the PF Appropriate methods of imputation are used for missing PF data	**High bias**: The measurement of the PF is very likely to be different for different levels of the outcome of interest **Moderate bias**: The measurement of the PF may be different for different levels of the outcome of interest **Low bias**: The measurement of the PF is unlikely to be different for different levels of the outcome of interest **Unclear**: insufficient information
Outcome measurement	A clear definition of the outcome is provided Method of outcome measurement used is adequately valid and reliable The method and setting of outcome measurement are the same for all study participants	**High bias**: The measurement of the outcome is very likely to be different related to the baseline level of the PF **Moderate bias**: The measurement of the outcome may be different related to the baseline level of the PF **Low bias**: The measurement of the outcome is unlikely to be different related to the baseline level of the PF **Unclear**: insufficient information
Study confounding	All-important confounders are measured Clear definitions of the important confounders measured are provided Measurement of all-important confounders is adequately valid and reliable The method and setting of confounding measurement are the same for all study participants Appropriate methods are used if imputation is used for missing confounder data Important potential confounders are accounted for in the study design Important potential confounders are accounted for in the analysis	**High bias:** The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome **Moderate bias:** The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome **Low bias:** The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome **Unclear**: insufficient information
Statistical Analysis and Reporting	Sufficient presentation of data to assess the adequacy of the analytic strategy Strategy for model building is appropriate and is based on a conceptual framework or model The selected statistical model is adequate for the design of the study There is no selective reporting of results	**High bias**: The reported results are very likely to be spurious or biased related to analysis or reporting **Moderate bias**: The reported results may be spurious or biased related to analysis or reporting **Low bias**: The reported results are unlikely to be spurious or biased related to analysis or reporting **Unclear**: insufficient information

3.4. Results

Search results

Electronic search retrieved 2766 records and one additional study was added through hand search (200). After removing duplicates (n=725), 2042 titles were screened. Whenever needed, abstracts were also analyzed. Of the 48 full-text articles screened, eleven fulfilled the eligibility criteria and were included. The flow diagram of the study selection process is presented in Figure 3.1., and the PRISMA checklist is presented in the Appendix 1.

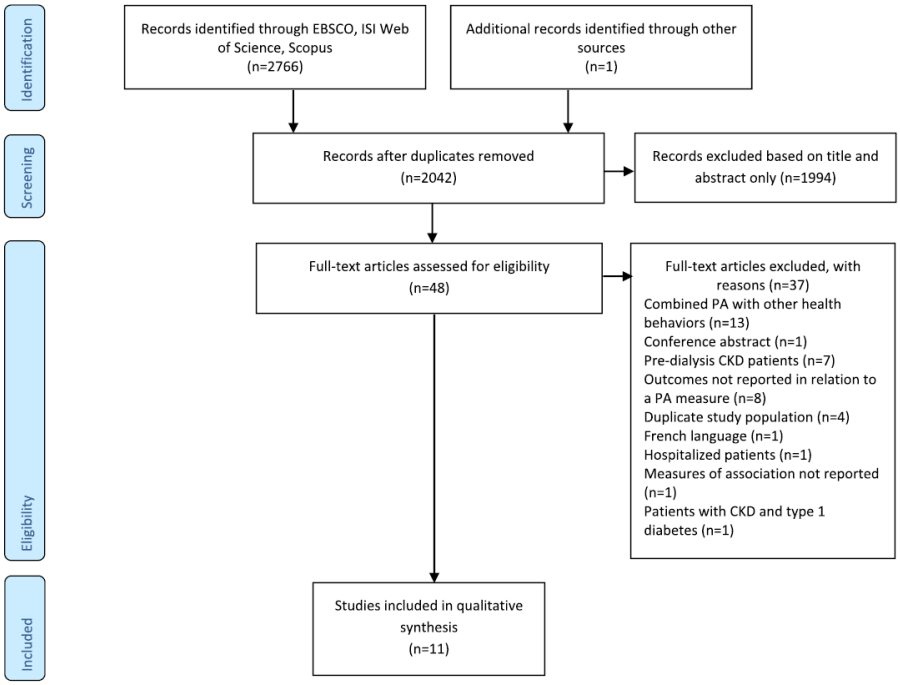

Figure 3. 1. *Flowchart of study selection*

Study characteristics

The characteristics of the included studies are summarized in Table 3.3. Four studies were from USA (201-204) , two from Europe (200, 205), two from Asia (206, 207) and one from Canada (208). The other two studies pooled data from several countries (78, 209). The number of participants ranged from 109 patients (208) to 20920 patients (78), and mean age from 48 (204) to 65 years (207). Six studies were in HD (78, 201, 202, 206, 207, 209), three in KTx (200, 204, 205), and two included both HD and PD patients (203, 208). None of the studies addressed PD patients alone. The mean/median length of follow-up ranged from 1.5 years (206) to 8.4 years (204). In eight studies, PA was measured using a validated self-report questionnaire (200-202, 204-206, 208, 209), two used a single question

on exercise frequency (78, 203), and one study used accelerometry (207). All the reports measured, at least, the leisure-time PA domain; one study also included the transport-related PA (200); and three studies reported an overall score that combined all PA domains (205, 207, 209). Zhang et al. (206) and Byambasukh et al. (200) reported outcomes in relation to specific PA intensities, namely light PA and moderate to vigorous PA, respectively.

All studies investigated the association of PA with all-cause mortality, and, of those, three studies also investigated CV mortality (200, 203, 205). No studies were found for other specific causes of mortality. The association between PA and hospitalization was explored only in one study (78).

Table 3. 3. *Characteristics of the included studies*

Study; Country	Type of RRT; Sample size; Age (yrs); % female	Follow-up length[3] (yrs)	PA assessment method; instrument	PA measured domains	PA (exposure) measurement scale	Outcome(s)
Tentori et al. 2010; Several countries[1] (78)	HD; n=20920; 60.7±14.8; 41.8	1.75	Self-reported: Single question	Leisure time	**Categorical:** never or <1 time/wk; 1 time/wk; 2-3 times/wk; 4-5 times/wk; 6-7 times/wk (daily) **Dichotomous:** 'regular exercise' (≥1 time/wk) versus 'non-regular exercise' (never or <1 time/wk)	All-cause mortality, All-cause hospitalization, cause-specific hospitalization
Lopes et al. 2014; Several countries[1] (209)	HD; n=5763; 63.4±14.5; 38.3	1.6	Self-reported: RAPA	Total	**Categorical:** Never/rarely active (rarely or never do any PA); infrequently active (some light or moderate PA, not every wk); sometimes active (light PA, every wk); often active (moderate PA: < 30min, 5 days/wk or vigorous PA: < 20min, 3 days/wk); very active (moderate PA: > 30min, 5days/wk or vigorous PA: > 20min, 3days/wk)	All-cause mortality
Kutner et al. 2016; USA (201)	HD, n=755; 57.3±14.0[2]; 40.4	2.0	Self-reported: MLTAQ	Leisure time, household	**Dichotomous:** Inactive (<500 Kcal/wk) or Active (≥500 Kcal/wk)	All-cause mortality
Zhang et al. 2017; China (206)	HD; n=317; 60.2±13.7; 45.4	1.5 (mean)	Self-reported: Stanford 7-PARQ	Leisure time, occupational	**Continuous:** each point increase in light PA time (hours/wk) and total PA score (kcal/kg/day)	All-cause mortality
Matsuzawa et al. 2018; Japan (207)	HD; n=282; 64.8±10.6; 45.0	4.7	Device: Accelerometer	Total	**Dichotomous:** <4000 steps/non-HD day or ≥4000 steps/non-HD day **Continuous:** each 1000 steps/non-HD	All-cause mortality
Johansen et al. 2019; USA; HD (202)	HD; n=727; 57.2±14.3; 40.8	3.8	Self-reported: Modified MLTAQ	Leisure time, household	**Dichotomous:** Inactive (<383 kcal/wk; women, <270 kcal/wk) or Active (≥383 kcal/wk; women, ≥270 kcal/wk)	All-cause mortality
Stack et al. 2005; USA (203)	HD/PD; n=2386; 57±16; 47.0	3.6 (mean)	Self-reported: Single question	Leisure time	**Categorical:** ≤1 times/wk, 2-3 times/wk, 4-5 times/wk, Daily/almost daily	All-cause mortality, CV mortality
Brar er al. 2019; Canada (208)	HD/PD; n=109; 57.5[2]; 33.0	3.3	Self-reported PASE	Leisure time, occupational, household	**Dichotomous:** Inactive (men: <383 kcal/wk; women: <270 kcal/wk) or Active (men: ≥383 kcal/wk; women: ≥270 kcal/wk)	All-cause mortality
Zelle et al. 2011; The Netherlands (205)	KT; n=540; 51±12; 46%	5.3	Self-reported: MLTAQ and TOAQ	Total	**Continuous:** log-MET-min/day	All-cause mortality, CV mortality
Rosas et al. 2012; USA (204)	KT; n=507; 47.8±12.8; 39%	8.4	Self-reported: PASE	Leisure time, occupational, household	**Categorical**: inactive, moderate, active[4] **Continuous:** PASE score	All-cause mortality
Byambasukh et al. 2020; The Netherlands (200)	KT; n=650; 51.8±13.2; 43.7%	5.7	Self-reported: SQUASH	Leisure time, household, transportation[5]	**Categorical:** inactive (no MVPA); less active (median 120min/wk of MVPA); active (median 360 min/wk)	All-cause mortality, CV mortality

Age is presented as mean±SD; [1]Australia, Belgium, Canada, France, Germany, Italy, Japan, New Zealand, Spain, Sweden, UK, USA; [2]Pooled mean based on the mean age reported for each group; [3]median values are reported, otherwise mean values are presented as listed; [4]Cutoffs not reported; [5]Authors intentionally excluded occupational of the total reported PA measure. HD = hemodialysis; RAPA = Rapid Assessment of physical activity; PA = physical activity; MLTAQ = Minnesota Leisure Time Activity Questionnaire; PARQ = Physical Activity Recall Questionnaire; PD = peritoneal dialysis; CV = cardiovascular; PASE = Physical Activity Scale for the Elderly; KT = kidney transplant; TOAQ = Tecumseh Occupational Activity Questionnaire; SQUASH = Short questionnaire to assess health-enhancing physical activity; MVPA = moderate-to-vigorous PA;

Risk of bias

Risk of bias was evaluated using the Quality in Prognosis Studies tool (Table 3.4.). Across-studies, most domains showed low risk of bias. Thus, results were unlikely altered by methodological flaws. However, due to poor reporting of loss to follow up, the 'study attrition' domain was categorized as unclear in most studies. Potential bias in 'prognostic factor measurement' was related with the simplistic assessment of PA, mostly capturing only the frequency component (78, 203).

Table 3. 4. *Risk of bias summary of the included studies using the QUIPS tool*

Study	Study participation	Study attrition	Prognostic Factor Measurement	Outcome measurement	Study confounding	Statistical Analysis and Reporting
Tentori et al. 2010 (78)	Low	Low	High	Low	Low	Low
Lopes et al., 2014 (209)	Low	Unclear	Low	Low	Low	Low
Kutner et al., 2016 (201)	Low	Unclear	Low	Low	Low	Low
Zhang et al., 2017 (206)	Moderate	Low	Low	Low	Moderate	Low
Matsuzawa et al., 2018 (207)	Moderate	Unclear	Low	Low	Low	Low
Johansen et al., 2019 (202)	Low	Unclear	Low	Low	Low	Low
Stack et al., 2005 (203)	Moderate	Low	High	Low	Low	Low
Brar et al., 2019 (208)	Moderate	Low	Low	Low	Low	Low
Zelle et al., 2011 (205)	Low	Unclear	Low	Low	Low	Low
Rosas et al., 2012 (204)	Low	Unclear	Moderate	Low	Low	Low
Byambasukh et al., 2020 (200)	Low	Low	Low	Low	Low	Low

QUIPS: quality in prognostic studies

Physical Activity and Mortality outcomes

Overall, the results showed that higher PA was associated with reduced mortality rates. Heterogeneity among the studies (statistically, clinically, and methodologically) precluded quantitative synthesis (meta-analysis). Hazard ratio (HR) or relative risk were reported in all studies (summarized in Table 3.5.). For all-cause mortality, the association was statistically significant in nine studies (78, 200-202, 204-207, 209). Comparing the lowest and the highest physically active groups, HR ranged from 0.42 [95% CI: 0.22-0.82] (207) to 0.70 [95% CI: 0.53-0.93] (202) (Figure 3.2.). These results were independent of the exposure measure, levels for PA categorization, and adjustment for confounders. Thus, studies in HD (78, 201, 202, 206, 207, 209) and KTx (200, 204, 205) all supported a significant inverse association between PA and all-cause mortality. The two studies that included patients under HD or PD (203, 208) reported no evidence of significant association between mortality and PA (208), or no association only in the group of patients exercising more than 2-3 times/week (203).

Based on frequency alone (78, 203) or combining frequency, duration, and intensity (200, 204, 209), five studies grouped patients in three or more PA levels, allowing for a dose-response

analysis. In four of these studies, a graduated dose-response was observed (78, 200, 204, 209). The exception was Stack and colleagues (203) study in which the protective benefit of PA was reduced for patients exercising more than 2–3 times/week.

All studies exploring PA as a continuous variable, demonstrated that PA increments (one hour/week of light PA (206), 1000 steps/non-HD day (207), 1 MET-min/day (205), or 10-unit increase in the Physical Activity Scale for the Elderly (204)) have an inverse significant association with all-cause mortality.

The association of PA with CV mortality was addressed in three studies (200, 203, 205). Of those, two studies found an inverse significant association between PA and CV mortality with a similar magnitude to results reported for all-cause mortality (200, 205). The other study found no evidence of association between PA and CV mortality (203).

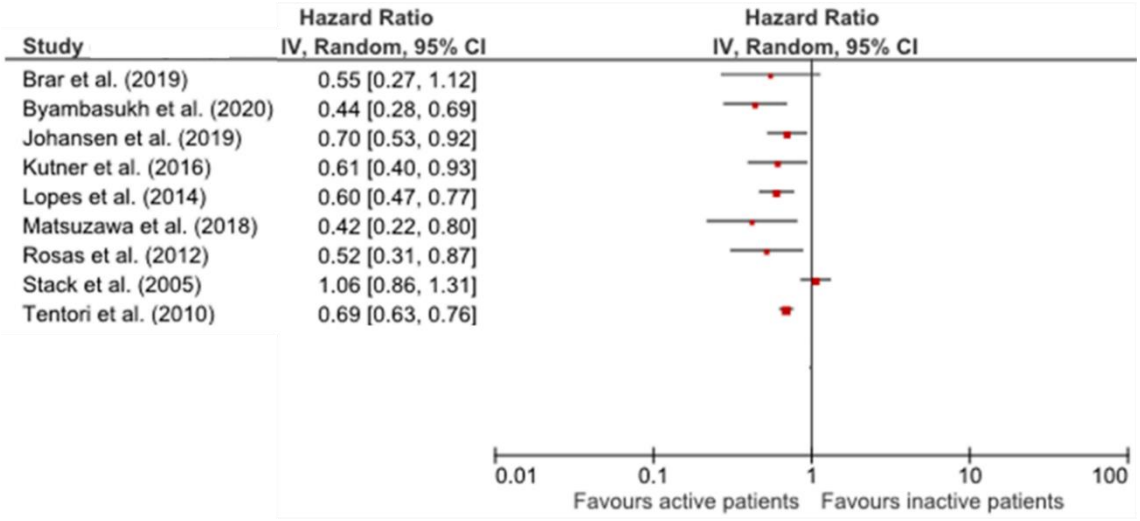

Figure 3. 2. *Results of the included studies comparing all-cause mortality between the most active and the most inactive groups*

Table 3. 5. *Summary of findings: association of PA with mortality outcomes*

Study	RRT	Confounders	Main findings	Deaths n (%)	Adjusted All-cause mortality HR or RR [95% CI]	Adjusted CV mortality HR [95% CI]
Tentori et al. (2010) (78)	HD	Age, sex, black (Y/N), ESRD duration, BMI, 14 comorbid conditions (Y/N)[2], albumin, phosphorus, calcium, creatinine, Hgb, catheter use (Y/N), smoker (Y/N), some college education (Y/N), employed (Y/N), private insurance (Y/N), lives alone (Y/N) and able to walk (Y/N)	All-cause mortality risk ↓ with ↑ PA (exercise frequency)	4143 (19.8)[9]	Reference: non-regular exercise (n=10999) Regular exercise (≥1 time/wk) (n=9921): **0.73 [0.69-0.78]** Reference: <1time/wk (n=10999) 1 time/wk (n=2205): **0.82 [0.73-0.91]** 2-3 times/wk (n=3558): **0.72 [0.66-0.79]** 4-5 times/wk (n=1201): **0.73 [0.62-0.86]** 6-7 times/wk (n=2957): **0.69 [0.63-0.76]**	
Lopes et al. (2014) (209)	HD	Region[3], age, sex, black (Y/N), smoker (Y/N), employed (Y/N), some college education (Y/N), lives alone (Y/N), assistance with walking (Y/N), time on HD, strength/flexibility activities (Y/N), BMI, 14 comorbid conditions[2], catheter use (Y/N), Hgb, Kt/V, creatinine, albumin, calcium, systolic BP< 120mmHg (Y/N), systolic BP >160mmHg (Y/N) phosphorus, PTH and nPCR	All-cause mortality risk ↓ with ↑PA	Never/rarely active: 427 (25.9) Infrequently active: 93 (15.5) Sometimes active: 143 (14.8) Often active: 191 (13.9) Very active: 119 (10.1)	Reference: never/rarely active (n=1649) Infrequently active (n=599): 0.89 [0.72-1.10] Sometimes active (n=969): 0.84 [0.67-1.05] Often active (n=1373): **0.81 [0.68-0.96]** Very active (n=1173): **0.60 [0.47-0.77]**	
Kutner et al. (2016) (201)	HD	Age, sex, race (White, Black, other), college education (Y/N), current smoker (Y/N), participant clinic, BMI, diabetes (Y/N), CV comorbidity (Y/N)[4], lupus/rheumatoid arthritis (Y/N), COPD (Y/N), cancer (Y/N), ESRD duration, catheter use (Y/N), hours wk/HD treatment	All-cause mortality risk ↓ in active patients	Inactive: 67 (18.4) Active: 43 (11.0)	Reference: inactive (n=364) Active (n=391): **0.61 [0.40-0.93]**	
Zhang et al. (2017) (206)	HD	Age	All-cause mortality risk ↓ with ↑ light and overall PA	133 (42.0)[9]	Every hour/wk increase of light PA: **0.69 [0.49-0.98]** Every Kcal/kg/day increase of overall PA: **0.66 [0.45-0.95]**	

Matsuzawa et al. (2018) (207)	HD	Age, sex, time on HD, BMI, diabetes (Y/N), peripheral vascular disease (Y/N), CBV accident/transient ischemic attack (Y/N), geriatric nutritional risk index, and comorbidity score	All-cause mortality risk ↓ with ↑steps/day	<4000 steps/day: 61 (39.9) ≥4000 steps/day: 17 (13.0)	Reference: <4000 steps/day (n=153) ≥4000 steps/day (n=129): **0.42 [0.22-0.82]** Every increase of 1000 steps/day: **0.84 [0.74-0.96]**	
Johansen et al. (2019) (202)	HD	Age, sex, race (Black, White, Asian, other), Hispanic (Y/N), BMI, time on HD, diabetes (Y/N), atherosclerotic heart disease (Y/N), heart failure (Y/N), catheter use (Y/N), albumin	All-cause mortality risk is related with all frailty components All-cause mortality risk ↓ in active patients	204 (28.1)[9]	Reference: inactive (n=297) Active (n=430): **0.70 [0.53-0.93]**	
Stack et al. (2005) (203)	HD+PD	Age, sex, race (White, Black, Asian), cause of ESRD (glomerulonephritis, diabetes, hypertension), congestive heart failure (Y/N), coronary artery disease (Y/N), peripheral vascular disease (Y/N), left ventricular hypertrophy (Y/N), undernourished (Y/N, caregiver subjective opinion), albumin, phosphorus and hematocrit	All-cause mortality risk ↓ for patients exercising 2-3 times/wk. No significant results for 4-5 times/wk and daily exercise. No significant results for CV mortality.	1366 (57.3)[9]	Reference: ≤1time/wk (n=1333) 2-3times/wk (n=437): **0.74 [0.58-0.95]** 4-5times/wk (n=134): 0.70 [0.47-1.04] Daily (n=482): 1.06 [0.86- 1.30]	2-3times/wk: 0.80 [0.58-1.08][1] (Reference: ≤1time/wk)
Brar et al. 2019 (208)	HD+PD	Age, sex, albumin, hemoglobin and number of comorbidities	No significant reduction in all-cause mortality risk for active patients	38 (34.9)[9]	Reference: inactive Active: 0.55 [0.27-1.13]	
Zelle et al. (2011) (205)	KTx	Age, sex, history of CV events[5] (Y/N), insulin concentration, systolic BP, waist circumference, triglycerides, smoker (Y/N), CRP, Framingham risk score, creatinine clearance, urinary protein excretion, 24-h urinary creatinine	All-cause and CV mortality risk ↓ with ↑PA	81 (15.0)[9]	Every increase of 1 MET-min/day: **0.75 [0.60-0.94]**	Every increase of 1 MET-min/day: **0.62 [0.45-0.86]**
Rosas et al. (2012) (204)	KTx	Recipient and donor age, African American (Y/N), sex, diabetes (Y/N), dialysis duration, ever smoked (Y/N), BMI, delayed graft function[6] (Y/N)	All-cause mortality risk ↓ with ↑PA at the time of kidney transplantation	Inactive: 61 (36.3) Moderate: 39 (23.3) Active 28 (16.3)	Reference: inactive (n=169) Moderate (n=166): 0.87 [0.56-1.35] Active (n=172): **0.52 [0.31-0.87]** Every 10-unit increase in PASE score: **0.96 [0.92-0.99]**	

Byambasukh et al. (2020) (200)	KTx	Age, sex, eGFR, urinary protein excretion, time between transplantation and baseline, primary renal disease[7], acute rejection (Y/N), pre-emptive transplantation (Y/N), living donor (Y/N), current smoker (Y/N), total alcohol consumption, total energy intake, immunosuppressive medication (Y/N) [8], systolic BP, use of antihypertensive drugs (Y/N), triglycerides, HDL-C, BMI, waist circumference, 24-h creatinine excretion	All-cause and CV mortality risk ↓ with ↑PA	129 (19.8)[9]	Reference: inactive (n=246) Less active (n=201): **0.45 [0.29-0.70]** Active (n=203): **0.44 [0.28-0.69]**	Less active: 0.55 [0.26-1.16] Active: **0.44 [0.19-0.99]** (Reference: inactive)

[1]Data not reported for other PA categories: 4-5times/wk and daily PA (results were not significant); [2]diabetes, hypertension, coronary artery disease, congestive heart failure, other cardiovascular disease, peripheral vascular disease, cerebrovascular disease, recurrent cellulitis, GI bleed, lung disease, neurologic disorder, depression, other psychiatric disorders, cancer other than skin, HIV; [3]Europe, Australia/New Zealand, Japan or North America; [4]congestive heart failure, coronary artery disease, cerebrovascular accident, peripheral vascular disease, other cardiac diseases; [5]myocardial infarction or transient ischemic attack/CBV accident; [6]need for dialysis during the 1st week after transplantation; [7]glomerulosclerosis, glomerulonephritis, tubulointerstitial nephritis, polycystic kidney disease, renal hypodysplasia, renavascular diseases, diabetes, others; [8]calcineurin inhibitors, prednisolone; [9]data not provided for each PA group; HR: hazard ratio; RR: relative risk; CI: confidence interval; CV: cardiovascular; ESRD: end-stage renal disease; BMI: body mass index; BP: blood pressure; PTH: parathyroid hormone; nPCR: normalized protein catabolic rate; PA: physical activity; COPD: chronic obstructive pulmonary disease; HD: hemodialysis; CBV: cerebrovascular; CRP: C-reactive protein; MET: metabolic equivalents; KTx: kidney transplant; PD: peritoneal dialysis

Physical Activity and Hospitalization outcomes

This review includes only one study addressing the association between PA and the hospitalization risk (78), which reported that patients exercising ≥1time/week, compared to patients exercising <1time/week, had a similar risk of hospitalization for all-cause (HR = 1.00 [95% CI: 0.96–1.04]), cardiac events (HR = 0.97 [95% CI: 0.91–1.03]), and amputations (HR = 0.98, [95% CI: 0.83–1.17]). However, patients exercising ≥1time/week had a significant lower fracture-related hospitalization risk (HR = 0.76 [95 % CI: 0.61–0.94]).

3.5. Discussion

Summary of main findings

This systematic review found evidence of a significant and consistent association between higher PA levels and reduced mortality in ESKD patients. This finding is sustained by studies addressing all-cause mortality. Results are less robust for CV mortality as this outcome was only addressed in three studies (200, 203, 205). The association between PA and hospitalization was only reported in one study (78), therefore no conclusions can be drawn. Nevertheless, this study demonstrated that physically active patients have a lower hospitalization risk due to fractures (78).

Results for HD and KTx patients are consistent in favor of a protective effect of PA on all-cause mortality. PD patients were only investigated in combination with HD patients, and results are somewhat conflicting (203, 208). Brar et al. (208) found a non-significant reduction in all-cause mortality. However, this is the study with the smallest sample (n=109), possibly underpowered to find a significant association. Stack et al. (203) observed a significant lower mortality risk for patients exercising 2–3 times/week. However, unexpectedly, this benefit was reduced for patients exercising more than 2–3 times/week. Nevertheless, the large proportion of patients in the higher exercise frequency groups (e.g., 20% of patients exercising daily) seems unrealistic for dialysis patients and it is indicative of some potential bias (e.g., physiotherapy) that might have led to this intriguing result. These discrepant findings suggest more research is needed, preferably with more accurate PA measures, to evaluate the dose-response association between PA and mortality.

In line with findings for the general population (191), we observed a dose-response association between PA and all-cause mortality, demonstrated in studies with three or more PA volume categories (78, 200, 204, 209), with the exception of the study from Stack et al. (203). The evidence of a dose-response association is a relevant finding, especially for deconditioned ESKD patients since the benefits of PA were observed even with modest PA amounts.

Some methodological drawbacks can be caused by the categorization of continuous variables, particularly if data-dependent quantiles are used to form categories. Therefore, more robust findings are obtained when the exposure is analyzed as a continuous variable (210). In the present review, four studies reported results based on continuous PA data and found reductions in all-cause mortality with increments in PA (204-207). These results strengthen the evidence of an inverse association between PA and all-cause mortality in ESKD.

The association of PA with CV mortality is paramount as CV complications are the main cause of death in ESKD (27) (explained in detail in Chapter 1, Section 1.2.). Although only three studies addressed this outcome (200, 203, 205), two of them found a protective role of PA that was similar for all-cause and CV mortality. This finding is in agreement to those for the general population (211). Because in ESKD, non-CV and CV mortality share common risk factors, such as infections and inflammation (212), it is impossible to differentiate the mechanisms exclusively affecting CV from those supporting non-CV mortality. Nevertheless, several mechanisms related to PA may decrease CV mortality in ESKD. Specifically, it is known that an increase in PA may reduce the progression of atherosclerosis and even reduce the atherosclerotic burden (213), it

improves endothelial function by increasing the laminar sheer stress rising nitric oxide bioavailability (50), and reduces arterial stiffness by improving vasodilation due to elevated nitric oxide levels and preventing the connective tissue building-up in the arteries (213). PA may also exert anti-inflammatory effects (45), and has been observed to be associated with reduced oxidative stress (i.e., increase in antioxidants resulting in less accumulation of reactive oxygen species) (213). Furthermore, higher PA levels improve CV risk profile (BP control and blood lipid profile) (213), with anti-ischemic effects of PA being potentially related to an enhanced coronary blood flow reserve (213). Moreover, PA may activate antiarrhythmic protective mechanisms due to a reduction in sympathetic and increase in parasympathetic/vagal stimulation of the myocardium, improving the electrical stability of the heart (213). PA has also been observed to elicit antithrombotic effects creating an environment that favours fibrinolysis over thrombosis (213). All these mechanisms may explain the reduced CV mortality in active patients. The prevention of muscle wasting and functional decline, important predictors of mortality in ESKD, may also explain why PA decreases all-cause mortality in this population (62).

This review provided empirical evidence that PA is associated with a reduced mortality risk in this population. Because KRT are fundamentally used to sustain life, strategies that improve survival should be combined with this treatment. Thus, interventions to promote PA should be implemented in clinical settings (e.g., IDE). In HD patients, the most popular form of PA promotion is through IDE. Nevertheless, whether this intervention is associated with a reduced mortality remains poorly studied. This association is examined in Chapter 5.

Strengths and limitations

Regarding the type of KRT, none of the included studies provided data on PD patients alone, which limited our conclusions for this specific population.

Evidence shows that self-reported measures tend to underestimate the association between PA and mortality (211). This is possibly explained by their overestimation of PA (195). If so, we might have underestimated the protective role of PA. Also, some studies only assessed leisure-time PA, which fails to capture the overall PA behavior. However, the resulting bias may have been minimal as this is the predominant PA domain in developed countries (214).

Another potential bias is related to the observed underreported study attrition. Thus, there may be unknown reasons for loss to follow-up that could have influenced the outcomes (e.g., discontinuation of HD treatment can precede mortality).

Additionally, reverse causality may have overestimated our results. Usually, most ill patients have reduced PA levels. Thus, the observed association between PA and mortality could also have been driven by the poor health status, rather than the PA exposure *per se* (215). Some of the included studies have a short follow-up period and are, consequently, at an increased risk of reverse causality. Nevertheless, most studies performed an analysis adjusted for baseline comorbidities that may have minimized this bias.

Finally, confounding bias could have also influenced our results. Nevertheless, most studies performed a comprehensive adjusted analysis. Even so, we cannot rule out a residual confounding from non-controlled variables.

Agreements and disagreements with other studies and reviews

The influence of PA on hard clinical endpoints (e.g., mortality) was already demonstrated in previous systematic reviews in the general population (191), and in patients with diabetes (216), which is a common comorbidity in ESKD patients. There are comparable findings to the present review. Firstly, the dose-response association between PA and all-cause mortality is supported by other reviews (191, 216). Secondly, when inactive patients were compared with the most active patients, our observed risk reduction for all-cause mortality ranged from 30% (202) to 58% (207), which is comparable to that observed for diabetic patients (40%) in the same activity-pattern groups (i.e., inactive versus active patients) (216). Also, evidence suggests that PA may equally decrease mortality in healthy and in chronic disease patients (217). However, a higher protective effect of PA (73% reduction in all-cause mortality) has been reported for the general population (191) compared with our findings. That review only included accelerometer-based studies, which may explain the differences in the reported HR.

The mineral and bone disorders of CKD causes bone fragility resulting in a higher risk of fractures and, consequently, an increase in hospitalization and mortality rates (218). Thus, strategies to reduce bone fractures in this population are needed. PA should be considered as a key element in these strategies, as it acts favorably in two key risk factors: bone characteristics (such as mineral density) (219) and the prevention of falls (220). Despite in this systematic review only one study investigated the association between PA and hospitalization, a potential for a reduction in fracture-related hospitalizations is assumed (78). This result agrees with the findings from a previous umbrella review in older adults (221).

3.6. Conclusion

The present systematic review found evidence of a dose-response reduction in all-cause mortality associated with increased PA. Moreover, greater PA was associated with a reduction in CV mortality; however, the lack of studies exploring the link between PA and CV mortality, as well as hospitalization, limited the strength of our conclusions.

Implications for practice and future research

Despite the well-accepted wide-range health benefits attributed to PA, there is still a lack of efficient strategies in renal care targeting the low levels of PA in these patients (222), which may be in part because PA is a complex behavior and its promotion is a challenge in healthcare settings (223). Thus, to successfully change PA behavior, approaches must be grounded in relevant theories and target both, the individual and their environment (224). Such a comprehensive intervention is not common in ESKD patients but is popular in other populations (e.g., pulmonary, and cardiac rehabilitation). Nevertheless, some successful approaches of sustainable exercise programs are also known for ESKD patients, including IDE, home-based exercise, inter-dialytic exercise, prehabilitation for transplant candidates, rehabilitation post-transplant and education programs (90). The present findings should inform policy makers and other stakeholders for the need to address inactivity in this population.

We identified several issues that must be a priority in future studies design, specifically (1) targeting all different KRT (particularly PD patients), (2) collecting data on the specific causes of mortality (e.g., CV, infection, or cancer) and in hospitalization outcomes, and (3) using accelerometry to objectively measure PA. This would provide more reliable PA data and the opportunity to explore the role of each PA components (frequency, intensity, and duration), and sedentary behavior. Collecting PA data at different timepoints could also inform the clinical significance of PA variations over time. Moreover, few investigated whether the protective association of PA with mortality and hospitalization could be achieved through IDE in HD patients. This issue will be debated in detail in Chapter 5.

Chapter 4: Intradialytic exercise: a controlled nation-wide effectiveness-implementation study

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4.1. Abstract

Background: as previously discussed in Chapter 1, section 1.2., despite its convenience for HD patients, many barriers preclude dissemination of IDE. To date, evidence on IDE benefits is mostly sustained on efficacy studies, rather than real-world and broadly generalizable effectiveness trials. Thus, the aim of this study is to evaluate a nation-wide implementation of an IDE program settled as part of the routine practice, provided by the existing dialysis staff. Simultaneously were studied implementation outcomes and its effectiveness on safety, physical function, body composition and fluid status, BP, Hb and phosphate control.

Design, setting, participants and measurements: hybrid type III study analyzing implementation and effectiveness of an IDE program implemented at a nation-wide level. Retrospective analysis of the first year of implementation using the RE-AIM framework (*Reach, Effectiveness, Adoption, Implementation and Maintenance*) adapted to IDE. Implementation outcomes across the different HD units were compared. For effectiveness outcomes, participants were followed for 1 year and compared with patients who refused IDE. For physical function, a pre-post design and a subsequent analysis comparing higher and lower exercise participation groups were performed.

Results: *Adoption*: 20 HD units adopted the intervention (55.6%). *Reach*: 1270 patients were eligible (55.8%). Main reason for non-eligibility was physical/cognitive incapacity (50.8%). Non-eligibility across HD units had no correlation with intradialytic adverse events (p=0.141). Of those eligible (n=1270), 36.1% refused the intervention. Compared to refusals, IDE participants were in a better health condition. *Maintenance:* all HD units continued the intervention. At a patient level, attrition rate was 57.2%, being voluntary withdrawal the main reason for drop-out (52.4%), especially during the first 6 months. *Implementation*: adherence (%) was 75.0±19.7. Main reason for non-performed exercise sessions was voluntary (61.5%). Patients performed 2.2±0.6 aerobic exercise sessions/week, completing 86.3±29.0 min/week. Strength exercise had a lower implementation. There was a wide variation between units for implementation outcomes. *Effectiveness*: exercise (n=347) and non-exercise (n=394) patients were compared. There was a significant lower incidence of cramps in the exercise group (p<0.001) and no significant differences for other HD-related adverse events. For physical function, the pre-post analysis showed a significant improvement in all physical function tests, except for handgrip strength. However, a dose-response was found when a lower exercise group was compared to a higher exercise group. Significant differences in the variation of body composition favorable to the exercise group were found for lean tissue mass (p=0.045), lean tissue index (p=0.013) and for body cell mass (p<0.001). No significant differences were observed for BP. However, antihypertensive (AH) drugs prescription increased slightly in the exercise and not in the non-exercise group. No significant differences were observed for Hb variation. Nonetheless, non-exercise group increased EPO dose, while the exercise group decreased (p=0.008). No significant differences between groups were observed for phosphate control.

Conclusion: IDE is a realistic and safe intervention in routine practice. High variability on implementation outcomes across HD units suggests room for improvement. Firstly, raising awareness for the importance of IDE might influence medical and executive boards to adopt IDE in their HD units. Reach dimension could be improved using a more flexible approach for patient

screening and reducing patients who rejected IDE. Maintenance dimension may be improved with strategies to prevent voluntary withdrawal. Moreover, improving the approach of the dialysis staff to IDE patients may further increase patient's adherence. Despite a substantial implementation dose, IDE was not enough to achieve the recommended PA levels. Effectiveness was sustained in real-world conditions. However, higher exercise doses could have further health benefits. Hence, more personalized approaches including PA as a component of a comprehensive behavior change, would complement IDE, helping HD patients to meet the current PA recommendations with higher health impacts.

Keywords: CKD; HD; PA; exercise; implementation.

4.2. Background

Despite the association of an active lifestyle with better health outcomes in HD patients (63, 209), 94% of the patients remains insufficiently active (2). The catabolic state of CKD worsens neuromuscular functioning and exercise tolerance. Over time, these catabolic effects of CKD might lead to functional impairment that contribute to further inactivity and consequent reduction in anabolic stimuli to the muscles (62). This vicious cycle of inactivity makes PA promotion a tough challenge in HD patients. Barriers to PA and exercise are reported by 92% of HD patients (68) and were previously discussed in Chapter 1, Section 1.2. Nevertheless, most patients recognize the benefits of exercise, notwithstanding the need for support to do so (65). IDE is an opportunity for HCP to support HD patients to exercise while on dialysis and is also very convenient for patients, making use of otherwise sedentary-time (71). Several systematic reviews demonstrate its efficacy to improve cardiorespiratory fitness (59), physical function (74), depressive symptoms (75), and physical component of health-related quality of life (76). Current guidelines recommend that HD patients should aim for 150 min per week of moderate intensity aerobic exercise (3). This objective will hardly be achieved ignoring the large amount of time spent in HD. Yet, despite the UKKA recommendation for its implementation in every HD units (3), no data is available on implementation outcomes at a large-scale nation-wide level, factor that may contribute to the scarce existence of IDE in clinical settings (78, 100, 101). IDE programs satisfy the criteria for a complex intervention (92) and many barriers preclude its implementation (Chapter 1, Section 1.2.).

Time lag between research discovery and routine clinical uptake is inflated by the preponderance of research designs with an exclusive emphasis on efficacy studies, instead of more broadly generalizable effectiveness trials (225). Thus, implementation studies are needed to inform how to successfully implement IDE in clinical settings and to investigate the effectiveness of IDE in real-world conditions. The aim of this study is to evaluate a nation-wide implementation of IDE settled as an integral part of the care of HD patients in routine practice provided by the existing dialysis staff. This report simultaneously examined implementation outcomes and its effectiveness on safety, physical function, body composition and fluid status, and on BP, Hb and phosphate control.

4.3. Methods

This article follows the recommendation of the Standards for Reporting Implementation Studies statements (226) and checklists are available in Appendix 2. This study was approved by the NephroCare Portugal Ethics Committee (04/2021).

Study design

This is an implementation study that follows a hybrid research design focusing on both the success of the implementation strategy to enhance the use of IDE, and the health impact of this evidence-based practice. Precisely, this is a hybrid type III study that is used when the effectiveness of an intervention is well established, but it is unclear how robust the effects are likely to be under implementation conditions (225). This study is based on a retrospectively analysis of the implementation of an IDE program at a nation-wide level in the HD units of the larger dialysis provider in Portugal (NephroCare). We used the RE-AIM framework (*Reach, Effectiveness, Adoption, Implementation and Maintenance*) that was earlier explained in Chapter 2, Section 2.1. All units that joined the program during the first year of its implementation (from September 2016 to September 2017) were analyzed and patients were followed during 1 year for effectiveness outcomes (safety, physical function, body composition and fluid status, BP control, Hb control and phosphate control). For each effectiveness outcome, IDE patients (exercise group) was compared with a non-exercise group of patients that refused IDE. However, physical function measures were only performed in the exercise group, thus a pre-post design was used. Additionally, a subsequent analysis was performed dividing the exercise group (median number of exercise sessions). Accordingly, a lower exercise group (<124 exercise sessions) was compared with a higher exercise group (≥124 exercise sessions).

For every effectiveness outcome, patients were considered if they completed the 1-year follow-up in the exercise or in the non-exercise group.

Context

In Portugal, public-private partnerships between the government and private dialysis providers deliver most of the HD treatments. The context in which the nation-wide IDE program was implemented was already debated in General Methods (Chapter 2, Section 2.1.).

Targeted sites and participants

Our intervention targeted 36 NephroCare Portugal units. Inclusion and exclusion criteria were defined in collaboration with the medical board. Inclusion criteria were 1) physical/cognitive capacity (ability to cycle), 2) HD vintage ≥2 months. Patients were excluded if 1) vascular access in the lower limb, 2) high risk of vascular access hematoma, 3) CV risk, 4) Hb <8.5g/dL and 5) systemic infection.

Description of the implementation strategy

Implementation strategies are of utmost importance for implementation science, as they explain how to change healthcare practice. Comprising the means or methods for adopting and sustaining interventions, implementation strategies are necessary for realizing the public health benefits of evidence-based care (179). Our implementation strategy was described in detail in General Methods (Chapter 2, Section 2.1.).

Description of the intervention

A simple exercise protocol was designed to be easily applied by the dialysis staff with low supervision requirements. It is performed in every dialysis session between the first 30 minutes and the last 90 minutes of HD treatment. The exercise protocol was described in detail in General Methods (Chapter 2, Section 2.1.).

Implementation and Effectiveness Outcomes

Defined implementation and effectiveness outcomes are described in Table 4.1.

Table 4. 1. *Implementation and effectiveness outcomes (RE-AIM dimensions)*

Dimension	Measures
Adoption	Proportion of HD units who accepted IDE
Reach	Proportion of non-eligible patients with reasons Comparison of eligible and non-eligible patients Prevalence of non-eligibility across HD units Proportion of patients refusing the intervention Comparison of refusals with patients that accepted IDE Prevalence of patients refusing IDE across HD units
Maintenance (setting level)	Proportion of HD units who continued the intervention
Maintenance (patient level)	Attrition rate with reasons and timing Comparison of voluntary withdrawals with completers Prevalence of voluntary withdrawals across HD units
Implementation (fidelity)[1]	Adherence (exercise sessions among total HD sessions), number and proportion of fully, partially, and non-performed exercise sessions with reasons Mean adherence levels to IDE across HD units
Implementation (dose)[1]	Weekly exercise dose: aerobic (sessions/week, duration/week) and strength (sessions/week, workload/week) Exercise dose per exercise session[2]: aerobic (duration) and strength (weight, sets, workload)
Effectiveness[1]	Safety, physical function, body composition and fluid status, BP, Hb, and phosphate

[1]outcomes studied in patients who completed the 1-year follow-up period; [2]outcome used to calculate the total exercise dose that can be achieved through IDE in a perfect scenario of patients that performed all exercise sessions (theoretical potential of IDE); HD: hemodialysis; IDE: intradialytic exercise; BP: blood pressure; Hb: hemoglobin.

Safety was studied examining incidence of all reported intradialytic adverse events in every HD session during the study period. Adverse events included cramps, headache, needle displacement/dislodgement, dyspnea, dysrhythmia, abdominal pain, chest pain, fatigue, hypertension, hypotension, hypoglycemia in diabetics, nausea/vomiting, and syncope. A composite outcome was computed summing all adverse events. Incidence of adverse events is rare and more interpretable findings are generated multiplying per 1000 HD sessions (number of adverse events/1000 HD sessions). Moreover, we used aggregated data of each HD unit to study the correlation of the proportion of non-eligible patients with the incidence of adverse events.

Body composition, BP control, Hb balance and phosphate control measures were taken at baseline and at 1 year in both the non-exercise and in the exercise group. Physical function measures were only measured in the exercise group.

Physical function tests included 8-foot UG (agility and dynamic balance), 30 seconds STS (muscle resistance), 5 times STS (muscle power), SLS (static balance), and hand dynamometer (handgrip strength). Methodological instructions for each test were previously defined and described in the IDE implementation guide.

Body composition and fluid status were determined by multifrequency bioimpedance using the BCM, developed by Fresenius Medical Care, Bad Homburg, Germany (previously explained in Chapter 2, Section 2.1.)

BP outcomes included systolic and diastolic BP (mmHg) before the HD treatment (weekly average), as well as AH drugs. BP was measured using the Blood Pressure Module of the 5008 HD system (Fresenius Medical Care, Bad Homburg, Germany). All possible AH medications prescribed were considered: calcium channel blockers (amlodipine, diltiazem, lercanidipine, nifedipine), beta blockers (atenolol, bisoprolol, carvedilol, propranolol), angiotensin-converting enzyme inhibitors (captopril, enalapril, lisinopril, perindopril, ramipril), angiotensin receptor blockers (irbesartan, losartan) and other AH drugs (clonidine, minoxidil, rilmenidine). For each medication group, number and dose was computed summing all the prescribed drugs. An overall outcome was also performed summing the number and dose of all prescribed AH drugs. Proportion of patients taking AH drugs at baseline and at 1-year was also studied.

Hb balance was studied based on Hb (g/dL) using sodium lauryl sulfate spectrophotometry (Sysmex XN 1000), and EPO dose requirement (units per week). In addition, proportion of patients requiring EPO at baseline and at 1-year was analyzed.

Phosphate control outcomes investigated were serum phosphorus (mg/dL) determined by molybdate UV (Siemens Atellica CH), and phosphate binder´s prescription. All available phosphate binders were considered: calcium acetate, calcium acetate/magnesium carbonate, lanthanum carbonate, sevelamer carbonate and aluminum hydroxide. Both the number and dose of phosphate binders were examined. Proportion of patients taking phosphate binders at baseline and at 1-year was also examined.

Data collection and analysis

Data relative to IDE participation was extracted from the IDE digital platform (patient recruitment, exercise prescriptions, withdrawals, and adherence to exercise sessions). Patient descriptive and clinical data was extracted from the European Clinical Database (EuCliD) (227). Except physical function, all effectiveness measures were already part of routine care and were extracted from EuCliD. Thus, physical function data was also extracted from the specific IDE digital platform.

Descriptive data is presented as mean values and ± SD or as median and IQR. Data was checked for normality using Kolmogorov-Smirnov test. If non-normally distributed, a logarithmic transformation to base 10 was performed, and normality was rechecked. Comparison between groups at baseline (non-eligible vs. eligible, refusals vs. participants, voluntary withdrawal vs. completers, non-exercise vs. exercise) was performed using Mann-Whitney U test (non-normally distributed variables) and independent samples t-test (normally distributed variables). Chi-squared test was used for categorical variables. Aggregated data for each HD unit was used to analyze the prevalence of non-eligibility, refusals, and voluntary withdrawals; and to analyze the adherence and the incidence of adverse events across the different HD units.

Safety outcomes (incidence of adverse events during the study period) were compared between groups using Mann-Whitney U test (unadjusted analysis) and Quade´s ANCOVA (adjustment for confounders). Pearson correlation was used to analyze the correlation between the prevalence of non-eligibility in each unit and the mean incidence of adverse events (aggregated data). Wilcoxon Signed Rank test was used to compare physical function measures at baseline and at 1-year. For other effectiveness measures, variations from baseline to 1-year were computed. Normally distributed variations were compared using independent samples t-test (unadjusted analysis) and ANCOVA (adjusted for baseline values). Non-normally distributed variations were compared using Mann-Whitney U test (unadjusted analysis) and Quade´s ANCOVA (adjusted for baseline values). Categorical outcomes (patients taking AH drugs, EPO and phosphate binders) were studied comparing groups at baseline and at 1-year (Chi-square test). Effect sizes (ES) were calculated by hand, dividing the difference between the means of the groups by the pooled SD (228). Statistical significance was accepted at $p<0.005$.

4.4. Results

RE-AIM dimension: Adoption

Proportion of HD units who accepted IDE

All NephroCare Portugal dialysis units (n=36) were invited to participate and, during the first year, 20 (55.6%) accepted to initiate the program.

RE-AIM dimension: Reach

Proportion of non-eligible patients with reasons

Of those assessed for eligibility (n=2278), 1008 (44.2%) patients were excluded (Figure 4.1.). Main reasons for exclusion were physical/cognitive incapacity (50.8%) and CV risk (34.6%) (Table 4.2.).

Table 4. 2. *Reasons for exclusion from IDE*

Reason	n	%
Hemoglobin <8.5g/dL	3	0.3
Vascular access in the lower limb	24	2.4
Risk of vascular access hematoma	39	3.9
Cardiovascular risk	349	34.6
Physical/cognitive incapacity	512	50.8
Other/unknown	81	8
Total	**1008**	**100**

Comparison of eligible and non-eligible patients

Non-eligible and eligible patients are compared in Table 4.3. Non-eligible patients had a poorest general health status (older age, higher prevalence of central venous catheter, less patients performing HDF, higher comorbidity burden with a higher Charlson Comorbidity Index and a higher prevalence of diabetes and CV disease), a poorest body composition (higher fat tissue index, lower lean tissue index and higher overhydration), and a lower phosphate and Hb levels. Also, the proportion of females was higher in the non-eligible group. Patients eligible had a higher interdialytic weight gain, systolic and diastolic BP and a higher prevalence of AH drugs prescription.

Table 4. 3. *Comparison of eligible and non-eligible patients*

	non-Eligible (n=1008)	Eligible (n=1270)	p
Age (y)	73.3±12.3	62.4±14.6	**<0.001**[1]
Female, n (%)	457 (45.3)	465 (36.6)	**<0.001**[2]
Dialysis vintage (months)	68.9±63.5	72.8±80.2	0.187[1]
Interdialytic Weight Gain (L)	2.7±1.1	2.8±1.0	**0.007**[1]
Vascular access			
Arteriovenous fistula, n (%)	636 (62.5)	1020 (80.3)	**<0.001**[2]
Arteriovenous graft, n (%)	156 (15.5)	131 (10.3)	
Central Venous Catheter, n (%)	216 (21.4)	119 (9.4)	
Treatment modality			
Hemodiafiltration, n (%)	898 (83.1)	1193 (91.5)	**<0.001**[2]
Hemodialysis, n (%)	110 (10.9)	77 (6.1)	
Blood pressure			
Systolic BP (mmHg)	138.9±24.8	141.0±20.3	**0.013**[1]
Diastolic BP (mmHg)	62.0±14.2	68.6±13.5	**<0.001**[1]
Patients taking AH drugs, n (%)	554 (55.0)	765 (60.2)	**0.011**[2]
Age-adjusted Charlson Comorbidity Index	7.5±2.3	5.5±2.4	**<0.001**[1]
Diabetes Mellitus, n (%)	467 (46.3)	335 (26.4)	**<0.001**[2]
CV Disease			
Prevalence of CV disease, n (%)	853 (84.6)	1022 (80.5)	**0.010**[2]
No. of CV diseases	2.3±1.8	1.8±1.6	**<0.001**[1]
Body Composition			
Body Mass Index (Kg/m^2)	26.4±5.4	26.4±4.8	0.416[1]
Lean Tissue Index (Kg/m^2)	11.4±2.6	13.3±3.0	**<0.001**[3]
Fat Tissue Index (Kg/m^2)	14.1±6.0	12.4±5.4	**<0.001**[1]
Overhydration (%)	9.9±8.8	7.6±8.3	**<0.001**[1]
Phosphate (mg/dL)	4.0±1.3	4.5±1.3	**<0.001**[1]
Hemoglobin (g/dL)	11.0±1.3	11.3±1.1	**0.001**[1]

Data are mean±SD; [1]Mann-Whitney U test; [2]Chi-square test; [3]Independent Samples T-test; BP: blood pressure; AH: antihypertensive; CV: cardiovascular

Prevalence of non-eligibility across HD units

Non-eligibility to IDE in each unit ranged from 16.7% to 74.2% (Table 4.4.).

Table 4. 4. *Results across HD units: non-eligibility, refusals, voluntary withdrawal, adherence and adverse events*

	Non-eligible (%)	Refusals (%)[1]	Vol. withdrawal (%)[2]	Mean adherence (%)[3]	Adverse events/1000 HD sessions[4]
Clinic 1	20	11.1	18.8	74.5	12,00
Clinic 2	28.2	44.4	15.4	75.1	1,50
Clinic 3	36.9	59.6	35.0	79.6	7,00
Clinic 4	21.3	20.6	8.0	70.0	12,80
Clinic 5	34.6	32.9	31.9	87.0	5,80
Clinic 6	57.5	39.2	51.6	63.6	9,30
Clinic 7	25.9	60.7	63.0	63.0	1,60
Clinic 8	47.5	12.5	14.3	69.1	9,90
Clinic 9	50.8	10.9	31.6	75.2	11,70
Clinic 10	61.8	6.9	25.9	92.0	9,00
Clinic 11	38.7	36.8	0.0	66.3	9,10
Clinic 12	74.2	8.3	18.2	87.2	19,30
Clinic 13	64.4	29.0	25.0	79.4	14,90
Clinic 14	53.6	26.8	21.2	72.8	7,20
Clinic 15	53.2	53.2	54.9	60.6	2,90
Clinic 16	53.1	28.9	40.7	71.9	10,50
Clinic 17	16.7	16.7	24.0	82.0	9,60
Clinic 18	67.1	15.4	13.6	73.3	5,50
Clinic 19	53.3	0.0	0.0	67.9	14,40
Clinic 20	59.6	30.6	28.0	79.0	10,00

[1]Calculated among eligible patients; [2]Calculated among participants; [3]Mean adherence of patients completing the 1-year follow-up; [4]Calculated among patients who completed the 1-year intervention period; HD: hemodialysis

Proportion of patients refusing the intervention

Of those eligible (n=1270), 36.1% (n=459) refused and 63.9% (n=811) accepted the intervention (Figure 4.1.).

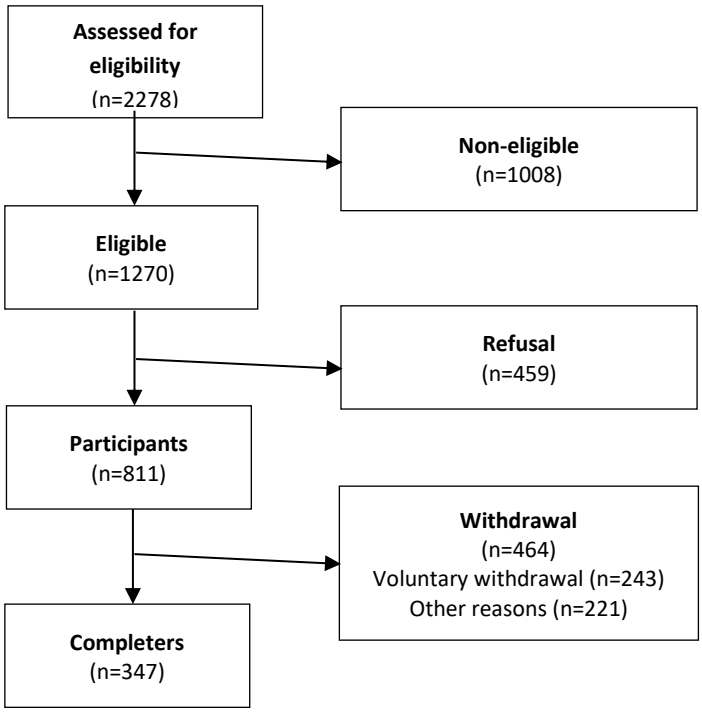


Figure 4. 1. *Enrollment flowchart for IDE*

Comparison of refusals with patients that accepted IDE

Table 4.5. compares refusals and participants in IDE. Both groups had criteria for IDE, however refusals were older, had a higher dialysis vintage, a higher prevalence of central venous catheter, a higher comorbidity burden (higher Charlson comorbidity index and higher prevalence of CV disease), a poorer body composition (lower lean tissue index), a higher overhydration and a lower Hb, suggesting that patients refusing IDE were in a poorer health condition.

Table 4. 5. *Comparison of refusals with IDE participants*

	Refusals (n=459)	**Participants (n=811)**	**p**
Age (y)	64.4±14.6	61.3±14.6	**<0.001[1]**
Female, n (%)	162 (35.3)	303 (37.4)	0.463[2]
Dialysis vintage (months)	84.6±88.1	66.1±74.6	**<0.001[1]**
Interdialytic Weight Gain (L)	2.8±1.1	2.8±1.0	0.096[1]
Vascular access			
Arteriovenous fistula, n (%)	344 (74.9)	676 (83.4)	**<0.001[2]**
Arteriovenous graft, n (%)	47 (10.2)	84 (10.4)	
Central Venous Catheter, n (%)	68 (14.8)	51 (6.3)	
Treatment modality			
Hemodiafiltration, n (%)	429 (93.5)	764 (94.2)	0.436[2]
Hemodialysis, n (%)	30 (6.5)	47 (5.8)	
Blood pressure			
Systolic BP (mmHg)	140.5±21.3	141.3±19.7	0.492[3]
Diastolic BP (mmHg)	68.0±13.9	68.9±13.3	0.225[1]
Patients taking AH drugs, n (%)	270 (58.8)	495 (61.0)	0.439[2]
Age-adjusted Charlson Comorbidity Index	5.9±2.5	5.3±2.4	**<0.001[1]**
Diabetes Mellitus, n (%)	114 (24.8)	221 (27.3)	0.348[2]
CV Disease			
CV disease, n (%)	392 (85.4)	630 (77.7)	**0.001[2]**
No. of CV diseases	2.0±1.8	1.6±1.5	**<0.001[1]**
Body Composition			
Body Mass Index (Kg/m^2)	26.2±4.9	26.6±4.7	0.105[1]
Lean Tissue Index (Kg/m^2)	13.1±3.0	13.5±3.0	**0.015[3]**
Fat Tissue Index (Kg/m^2)	12.3±5.4	12.4±5.4	0.637[1]
Overhydration (%)	9.1±9.4	6.8±7.4	**<0.001[1]**
Phosphate (mg/dL)	4.6±1.4	4.5±1.3	0.291[1]
Hemoglobin (g/dL)	11.2±1.3	11.3±1.1	**0.024[1]**

Data are mean±SD; [1]Mann-Whitney U test; [2]Chi-square test; [3]Independent Samples T-test; BP: blood pressure; AH: antihypertensive; CV: cardiovascular; IDE: intradialytic exercise

Prevalence of patients refusing IDE across HD units

In each unit, prevalence of patients refusing to participate in IDE ranged from 0.0% to 60.7% of all eligible patients (Table 4.4.).

RE-AIM dimension: Maintenance

Proportion of HD units who continued the intervention

After 1 year, all 20 dialysis units continued the IDE program.

Attrition rate with reasons and timing

Attrition rate was 57.2% (n=464) and voluntary withdrawal was the main reason accounting for 52.4% of the attrition rate (Table 4.6.).

Table 4. 6. *Reasons for attrition*

Reason	n	%
Nocturnal HD	1	0.2
Dialysis unit transfer	9	1.9
Death	13	2.8
Incapacity	19	4.1
Kidney Transplant	53	11.4
Clinical reason	126	27.2
Voluntary withdrawal	243	52.4
Total	**464**	**100**

Attrition with reasons over time is illustrated in Figure 4.2. During the first six months, 70.8% (n=172) of all voluntary withdrawals already occurred. A deceleration was observed in the last 6 months (accounting only for 29.2% of the overall incidence).

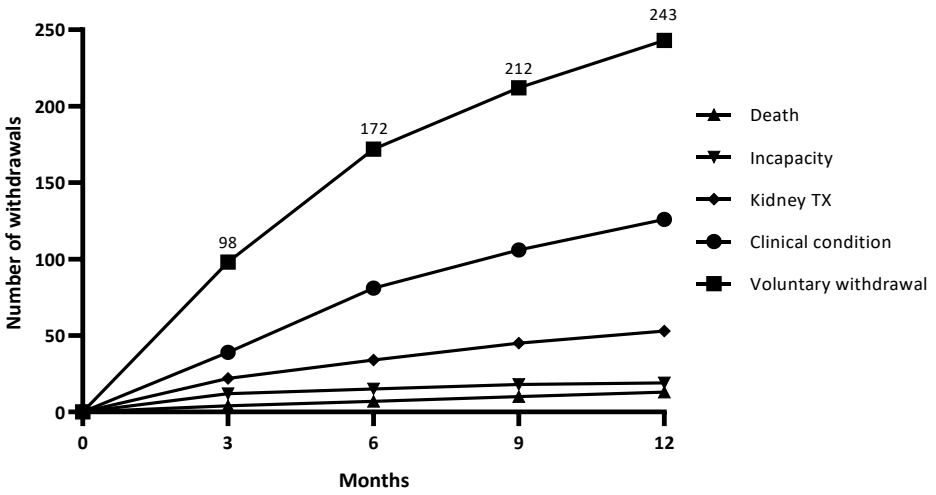


Figure 4. 2. *Reasons for attrition over time*

Comparison of voluntary withdrawals with completers

Table 4.7. compares voluntary withdrawals with patients that completed the 1-year intervention period. Completers group have a significant higher proportion of females, a lower dialysis vintage and a lower systolic BP. No significant differences were found for other variables. Taken together, this data suggests a similar health condition between voluntary withdrawals and completers.

Table 4. 7. *Comparison of voluntary withdrawals with completers*

	Vol. withdrawal (n=243)	Completers (n=347)	p
Age (y)	60.1±16.0	61.5±13.9	0.398[1]
Female, n (%)	115 (47.3)	233 (67.1)	**<0.001[2]**
Dialysis vintage (months)	71.9±78.8	61.3±76.8	**0.007[1]**
Interdialytic Weight Gain (L)	5.2±2.4	5.4±2.4	0.868[1]
Vascular access			
Arteriovenous fistula, n (%)	202 (83.1)	294 (84.7)	0.357[2]
Arteriovenous graft, n (%)	30 (12.4)	32 (9.2)	
Central Venous Catheter, n (%)	11 (4.5)	21 (6.1)	
Treatment modality			
Hemodiafiltration, n (%)	227 (93.4)	327 (94.2)	0.642[2]
Hemodialysis, n (%)	16 (6.6)	20 (5.8)	
Blood pressure			
Systolic BP (mmHg)	142.8±18.6	139.0±19.5	**0.018[3]**
Diastolic BP (mmHg)	70.3±13.7	68.2±13.0	0.056[3]
Patients taking AH drugs, n (%)	145 (59.7)	212 (61.1)	0.869[3]
Age-adjusted Charlson Comorbidity Index	5.2±2.4	5.4±2.4	0.235[1]
Diabetes Mellitus, n (%)	55 (22.6)	100 (28.8)	0.111[2]
CV Disease			
CV disease, n (%)	187 (77.0)	266 (76.7)	0.721[2]
No. of CV diseases	1.6±1.5	1.6±1.4	0.876[1]
Body Composition			
Body Mass Index (Kg/m^2)	26.6±4.7	26.5±4.5	0.889[1]
Lean Tissue Index (Kg/m^2)	13.4±2.8	13.7±3.1	0.356[3]
Fat Tissue Index (Kg/m^2)	12.5±5.2	12.2±5.4	0.509[3]
Overhydration (%)	6.2±7.7	6.8±7.1	0.377[3]
Phosphate (mg/dL)	4.5±1.3	4.4±1.3	0.371[1]
Hemoglobin (g/dL)	11.3±1.0	11.3±1.1	0.996[1]

Data are mean±SD; [1]Mann-Whitney U test; [2]Chi-square test; [3]Independent Samples T-test; BP: blood pressure; AH: antihypertensive; CV: cardiovascular

Prevalence of voluntary withdrawals across HD units

In each unit, prevalence of voluntary withdrawal ranged from 0.0% to 63.0% (Table 4.4.).

RE-AIM dimension: Implementation

Implementation fidelity: adherence, number and proportion of fully, partially and non-performed exercise sessions with reasons

Adherence (%) to IDE sessions was 75.0±19.7. Of all HD sessions (n=50356), 77.4% were fully performed, 3.2% partially performed and 19.4% were non-performed exercise sessions (Figure 4.3.). Main reason for non-performed and for partially performed exercise sessions was voluntary (61.5% and 74.4%, respectively) (Tables 4.8. and 4.9.).

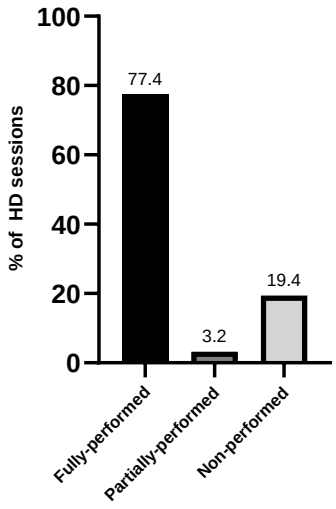


Figure 4. 3. *Proportion of fully, partially, and non-performed exercise sessions*

Table 4. 8. *Reasons for non-performed exercise sessions*

Reason	n	%
Arrhythmia/tachycardia	8	0.1
Dizziness	10	0.1
Chest pain	15	0.2
Glycemia <100 or >300 mg/dL	34	0.3
Cramps	35	0.4
Dyspnea	37	0.4
Fever	51	0.5
Anemia	57	0.6
Nausea	72	0.7
Hypertension	88	0.9
Hypotension	104	1.1
Headache	114	1.2
Wound	146	1.5
Hypervolemia	294	3.0
Fatigue	300	3.1
Vascular access hematoma (or risk of)	448	4.6
Pain	825	8.4
Voluntary	6011	61.5
Other/unknown	1119	11.5
Total	**9768**	**100**

Table 4. 9. *Reasons for partially performed exercise sessions*

Reason	n	%
Chest Pain	1	0.1
Tachycardia	1	0.1
Dizziness	1	0.1
Needle dislodgement	2	0.1
Glycemia <100 or >300 mg/dL	4	0.2
Headache	5	0.3
Vascular access hematoma	6	0.4
Nausea	7	0.4
Dyspnea	13	0.8
Hypotension	20	1.2
Hypertension	23	1.4
Cramps	44	2.7
Fatigue	76	4.7
Pain	136	8.5
Voluntary	1195	74.4
Other	73	4.5
Total	**1607**	**100**

Mean adherence levels to IDE across HD units

In each unit, mean adherence to exercise sessions ranged from 60.6% to 92.0% (Table 4.4.).

Implementation dose: mean weekly exercise dose and exercise dose per exercise session

Implementation dose is illustrated in Table 4.10. Weekly, patients performed 2.2±0.6 aerobic exercise sessions completing 86.3±29.0 min/week. Strength exercise had a lower implementation being performed by 80.4% (n=279) of the patients. Frequency per week was 1.5±0.7 achieving a total workload of 217.9±306.4 (sets*Kg).

As shown in Table 4.10., aerobic exercise duration per exercise session was 38.3±7.3 min showing that, in a perfect scenario of patients performing all exercise sessions, mean duration would be 115min/week. For strength exercise, in average, patients performed 1.1 sets of the proposed exercises with a mean weight used of 0.5 Kg.

Table 4. 10. *Exercise dose/week and exercise dose/exercise session*

		Aerobic (n=347)	Strength (n=279)
Exercise dose/week	**Mean sessions/week**	2.2±0.6	1.5±0.7
	Mean duration/week (min)	86.3±29.0	---
	Total workload/week (sets.kg)	---	217.9±306.4
Exercise dose/ex session	**Mean duration/Exercise session (min)**	38.3±7.5	---
	Weight/Exercise session (Kg)	---	0.5±0.3
	Sets/Exercise session	---	1.1±0.7
	Total workload/Exercise session (sets.kg)		85.0±112.4

Data are mean±SD

RE-AIM dimension: Effectiveness

Effectiveness measures were analyzed comparing patients that completed the 1-year follow up in the non-exercise (n=394) and in the exercise (n=347) groups (Table 4.11.). Non-exercise group was older, had a higher dialysis vintage, a lower prevalence of arteriovenous fistula, a higher comorbidity index, a higher prevalence and number of CV diseases, a lower lean tissue index, and a higher overhydration. Taken together, this data suggests that the exercise group had a better general health condition at baseline.

Table 4. 11. *Comparison between the non-exercise and the exercise groups*

	Non-exercise (n=394)	**Exercise (n=347)**	**p**
Age (y)	64.9±14.5	61.5±13.9	**0.001**[1]
Female, n (%)	147 (37.3)	114 (32.9)	0.205[2]
Dialysis vintage (months)	86.9 (91.0)	61.3 (76.0)	**<0.001**[1]
Interdialytic Weight Gain (L)	2.7±1.1	2.9±1.1	0.060[1]
Vascular access			
Arteriovenous fistula, n (%)	296 (75.1)	294 (84.7)	**0.001**[2]
Arteriovenous graft, n (%)	42 (10.7)	32 (9.2)	
Central Venous Catheter, n (%)	56 (14.2)	21 (6.1)	
Treatment modality			
Hemodiafiltration, n (%)	349 (88.6)	327 (94.2)	0.527[2]
Hemodialysis, n (%)	45 (11.4)	20 (5.8)	
Blood pressure			
Systolic BP (mmHg)	140.5±20.8	139.0±19.5	0.310[3]
Diastolic BP (mmHg)	67.8±14.1	68.2±13.0	0.668[3]
Patients taking AH drugs, n (%)	237 (60.2)	212 (61.1)	0.793[2]
Age-adjusted Charlson Comorbidity Index	6.0±2.5	5.4±2.4	**<0.001**[1]
Diabetes Mellitus, n (%)	97 (24.6)	100 (28.8)	0.197[2]
CV Disease			
CV disease, n (%)	335 (85.0)	266 (76.7)	**0.004**[2]
No. of CV diseases	2.1±1.8	1.6±1.4	**<0.001**[1]
Body Composition			
Body Mass Index (Kg/m^2)	26.3±4.9	26.5±4.5	0.292[1]
Lean Tissue Index (Kg/m^2)	12.8±3.1	13.7±3.1	**0.002**[3]
Fat Tissue Index (Kg/m^2)	12.3±5.6	12.2±5.4	0.664[1]
Overhydration (%)	9.0±9.5	6.8±7.1	**<0.001**[1]
Phosphate (mg/dL)	4.6±1.3	4.4±1.3	0.108[1]
Hemoglobin (g/dL)	11.2±1.3	11.3±1.1	0.063[1]

Data are mean±SD; [1]Mann-Whitney U test; [2]Chi-square test; [3]Independent Samples T-test; BP: blood pressure; AH: antihypertensive; CV: cardiovascular

Safety

Incidence of adverse events is presented in Table 4.12. There was a significant lower incidence of cramps in the exercise group even after adjustment for ultrafiltration volume (p<0.001,

ES=0.15). There were no significant differences between groups for incidence of any other adverse events and in the total incidence of adverse events.

Table 4. 12. *Incidence of adverse events per 1000 HD sessions*

	Non-exercise (n=394)	Exercise (n=347)	p*	p#
Cramps	2.0±4.8	1.3±4.5	**0.001**	**<0.001[2]**
Headache	0.1±1.1	0.2±1.9	0.816	0.806[2]
Needle displacement	0.2±1.2	0.2±1.4	0.464	0.403[3]
Needle dislodgement	0.1±1.0	0.2±1.1	0.065	0.069[3]
Dyspnea	0.4±2.6	0.2±1.2	0.173	0.406[2]
Dysrhythmia	0.1±1.0	0.0±0.0	0.103	0.381[2]
Abdominal pain	0.3±2.1	0.1±1.1	0.479	0.508[2]
Chest pain	0.2±1.0	0.1±0.8	0.575	0.624[2]
Fatigue	0.0±0.6	0.1±0.7	0.870	0.870[2]
Hypertension	0.4±2.0	0.4±1.9	0.325	0.323[2]
Hypotension	5.6±12.7	5.9±13.4	0.717	0.485[2]
Hypoglycemia (diabetics)[1]	0.1±0.9	0.4±2.8	0.678	---
Nausea/vomiting	0.2±1.2	0.3±1.7	0.991	0.867[2]
Syncope	0.1±0.7	0.1±0.9	0.832	0.979[2]
Total Adverse Events	9.9±16.3	9.2±15.5	0.398	0.908[4]

Data are mean±SD; [1]analysis restricted to diabetic patients (n=196); *Unadjusted analysis using Mann-Whitney U test; #Adjusted analysis using Quade test; [2]Adjustment for ultrafiltration volume; [3]Adjustment for vascular access type; [4]Adjustment for ultrafiltration volume and vascular access type

Across HD units, mean incidence of adverse events (per 1000 HD sessions) varied between 1.5 and 19.3 and there is a non-significant correlation with the prevalence of non-eligibility (Figure 4.4.).

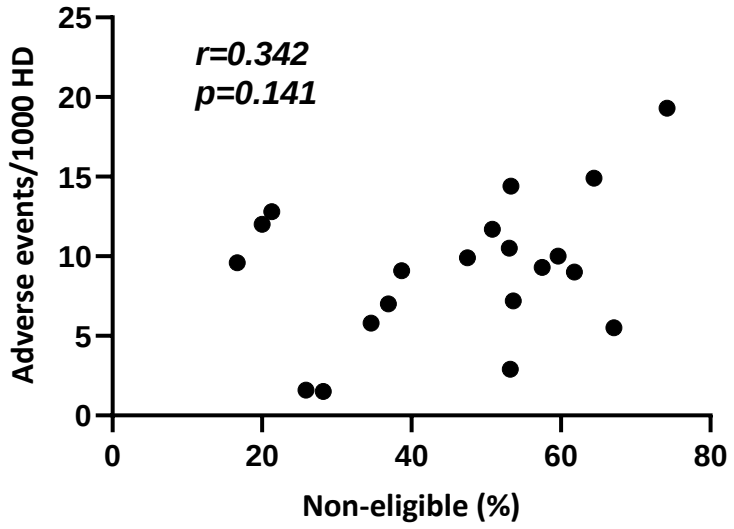


Figure 4. 4. *Correlation between the incidence of adverse events and the proportion of non-eligibility across the HD units*

Physical function

Compared to pre-intervention, a significant improvement in all physical function tests was observed after 1 year of regular exercise, except for handgrip strength that showed a reduction from 30.0±11.4 Kg to 29.1±11.5 Kg (p<0.001) (Table 4.13.).

Table 4. 13. *Physical function measures at baseline and 1-year*

	n	Baseline	1-year	p[1]
STS 30 (rep)	311	12.7±4.4	16.5±6.4	**<0.001**
8-foot UG (sec)	308	8.1±4.5	7.3±3.8	**<0.001**
Handgrip (kg)	260	30.0±11.4	29.1±11.5	**<0.001**
STS 5 (sec)	305	10.1±4.4	8.6±3.8	**<0.001**
SLS (sec)	309	17.6±17.4	22.0±18.6	**<0.001**

Data are mean±SD; STS: sit to stand; UG: Up and Go; SLS: single leg stance; [1]Wilcoxon Signed Rank Test

Comparison of variations in physical function in a lower exercise group (<124 exercise sessions) and in a higher exercise group (≥124 exercise sessions) are shown in Table 4.14. The higher exercise group had a significant higher improvement in STS 30, even after adjusting for baseline values (p=0.010, ES=0.226). Moreover, while the higher exercise group sustained handgrip strength (-0.4±5,6 Kg), a significant reduction was observed in the lower exercise group (-1.6±8.3 Kg) (p=0.049, ES=0.170).

Table 4. 14. *Variation of physical function in a lower and a higher exercise group*

	Lower exercise				Higher exercise				p[1]	p[2]
	n	Baseline	1-year	Δ	n	Baseline	1-year	Δ		
STS 30 (rep)	155	12.5±4.5	15.7±5.6	3.3±4.4	156	12.9±4.3	17.3±7.1	4.4±5.3	**0.012**	**0.010**
8-foot UG (sec)	151	8.7±5.4	7.7±4.1	-0.9±4.5	157	7.6±3.2	6.9±3.5	-0.7±2.8	0.616	0.382
Handgrip (kg)	126	28.6±12.1	27.0±11.4	-1.6±8.3	134	31.4±10.6	31.0±11.3	-0.4±5.6	0.126	**0.049**
STS 5 (sec)	150	10.4±4.5	8.9±3.8	-1.3±3.5	155	10.2±5.1	8.5±3.7	-1.6±3.4	0.705	0.419
SLS (sec)	153	16.7±17.5	20.9±18.8	4.2±10.6	156	18.5±17.3	23.1±18.5	4.6±12.9	0.786	0.992

Data are mean±SD; STS: sit to stand; UG: up and go; SLS: single leg stance; [1]unadjusted comparison of variation between groups (Mann-Whitney U test); [2]comparison of variation between groups adjusting for baseline values (Quade test)

Body Composition and fluid status

Variation in body composition is shown in Table 4.15. The non-exercise group reduced lean tissue mass (Kg) and lean tissue index (Kg/m^2), and the exercise group increased both outcomes, resulting that, after adjustment, significant differences between groups were observed for variations in lean tissue mass (p=0.045, ES=0.107) and lean tissue index (p=0.013, ES=0.120). Moreover, after adjustment for baseline values, the exercise group had a significantly higher increase in body cell mass (p<0.001, ES=0.143). No significant differences were found for variation in BMI, adipose tissue mass, fat mass, fat tissue index and overhydration.

Table 4. 15. *Variation in body composition measures*

	No exercise				Exercise				p*	p#
	n	Baseline	1-year	Δ	n	Baseline	1-year	Δ		
BMI (Kg/m²)	350	26.4±4.9	26.4±5.0	0.0±1.5	335	26.5±4.5	26.5±4.6	0.0±1.1	0.592[1]	0.680[3]
ATM (Kg)	339	33.9±13.8	34.2±14.6	0.3±6.6	333	33.4±14.1	32.9±14.1	-0.4±5.1	0.132[1]	0.129[3]
FM (Kg)	339	24.9±10.2	25.1±10.7	0.2±4.8	333	24.5±10.4	24.2±10.3	-0.3±3.7	0.133[1]	0.130[3]
FTI (Kg/m²)	340	12.6±5.4	12.8±5.7	0.1±2.4	333	12.3±5.4	12.1±5.4	-0.2±1.9	0.159[1]	0.143[3]
LTM (Kg)	340	35.3±9.6	35.1±10.2	-0.2±5.3	333	37.8±10.3	38.1±10.5	0.3±3.9	0.122[1]	**0.045[3]**
LTI (Kg/m²)	340	12.9±2.8	12.8±3.0	-0.1±1.9	333	13.6±3.1	13.8±3.1	0.1±1.4	0.064[1]	**0.013[3]**
BCM (Kg)	332	18.1±6.6	19.2±6.9	1.0±9.6	322	18.9±7.3	21.3±7.1	2.4±10.0	0.081[2]	**<0.001[4]**
OH (L)	350	1.6±1.4	1.6±1.5	0.1±1.6	335	1.2±1.2	1.2±1.4	0.0±1.1	0.767[1]	0.101[3]

Data are mean±SD; BMI: body mass index; ATM: adipose tissue mass; FM: fat mass; FTI: fat tissue index; LTM: lean tissue mass; LTI: lean tissue index; BCM: body cell mass; OH: overhydration; *unadjusted comparison of variation between groups; #comparison of variation between groups adjusted for baseline values; [1]Mann-Whitney U-Test; [2]Independent samples T-test; [3]Quade test; [4]ANCOVA

Blood pressure control

No differences between groups were observed for variation in systolic and diastolic BP (Table 4.17.). AH drugs prescription is illustrated in Tables 4.16. and 4.17. Variation in the number of AH drugs prescribed was significantly different (p=0.032, ES=0.168) with a slight increase (0.07±0.78) and a slight reduction (-0.06±0.77) in the exercise and in the non-exercise groups, respectively (Table 4.17.). This finding was mainly due to a higher prescription of betablockers in the exercise group (p=0.031, ES=0.188). However, variation in the total dose of drugs prescribed was not significantly different (p=0.101) (Table 4.17.). Moreover, the exercise group increased the dose of angiotensin receptor blockers (2.36±20.73 mg), while the non-exercise group had a reduction (-2.94±30.60 mg), resulting in a significant different variation (p=0.003, ES=0.20) (Table 4.17.). No significant differences were observed for variations in other AH drugs and in the proportion of patients taking AH drugs at baseline and at 1-year (Table 4.16.).

Table 4. 16. *Patients with antihypertensive drugs at baseline and at 1-year*

	Non-exercise group (n=394)		Exercise group (n=347)		p[1]	p[1]
	Baseline	1-year	Baseline	1-year	(baseline)	(1-year)
Betablockers, n (%)	145 (36.8)	141 (35.8)	124 (35.7)	141 (40.6)	0.763	0.175
ACE inhibitors, n (%)	86 (21.8)	82 (20.8)	78 (22.5)	78 (22.5)	0.831	0.582
ARB, n (%)	37 (9.4)	32 (8.1)	36 (10.4)	38 (11.0)	0.654	0.189
Clonidine, n (%)	21 (5.3)	21 (5.3)	13 (3.7)	21 (5.3)	0.304	0.654
Minoxidil, n (%)	8 (2.0)	11 (2.8)	4 (1.2)	5 (1.4)	0.345	0.207
Rilmenidine, n (%)	9 (2.3)	6 (1.5)	9 (2.6)	8 (2.3)	0.785	0.435
AH drug*, n (%)	237 (60.2)	232 (58.9)	212 (61.1)	219 (63.1)	0.793	0.239

[1]Qui-square test for differences at baseline and at 1-year; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; AH: antihypertensive drugs; *patients taking any AH drug

Table 4. 17. *Variation in blood pressure and antihypertensive drugs*

		No exercise (n=394)			Exercise (n=347)			p unadjusted	p adjusted*
		Baseline	1-year	Δ	Baseline	1-year	Δ		
BP	Sys BP (mmHg)	140.5±20.9	141.7±22.1	1.24±19.63	139.0±19.5	141.0±19.4	1.95±18.65	0.613[1]	0.926[3]
	Dia BP (mmHg)	67.9±14.0	68.3±15.5	0.40±11.81	68.2±13.0	68.7±12.9	0.45±11.32	0.900[2]	0.710[4]
Ca Chanel Blockers	Amlodipine (mg)	0.95±2.86	0.88±3.02	-0.06±1.96	1.10±2.91	1.40±3.17	0.30±3.05	0.126[2]	**0.016[4]**
	Diltiazem (mg)	0.84±12.90	0.91±11.08	0.08±11.82	1.04±19.33	0.52±9.66	-0.52±9.66	0.538[2]	0.235[4]
	Lercanidipine (mg)	0.04±0.56	0.14±1.42	0.10±1.44	0.15±1.33	0.07±0.81	-0.07±1.32	0.082[2]	0.091[4]
	Nifedipine (mg)	11.4±28.7	11.1±30.0	-0.35±22.60	7.8±22.0	7.6±24.6	-0.16±15.88	0.729[2]	0.214[4]
	Number of Ca Channel Blockers	0.33±0.48	0.31±0.47	-0.03±0.37	0.32±0.47	0.33±0.48	0.01±0.39	0.214[2]	0.242[4]
	Total Ca Channel Blockers dose (mg)	13.4±31.2	13.0±31.7	-0.37±25.57	10.3±28.8	9.6±26.1	-0.63±18.81	0.740[2]	0.390[4]
Betablockers	Atenolol (mg)	1.28±9.20	1.46±10.37	0.18±6.34	0.01±0.14	0.00±0.00	-0.01±0.14	0.636[2]	**0.010[4]**
	Bisoprolol (mg)	0.52±1.70	0.57±1.69	0.05±1.08	0.40±1.30	0.47±1.41	0.07±1.30	0.888[2]	0.907[4]
	Carvedilol (mg)	4.84±11.84	4.35±12.08	-0.49±8.24	4.42±10.47	4.34±9.74	-0.08±7.27	0.601[2]	0.448[4]
	Propranolol (mg)	0.56±5.97	0.33±2.94	-0.23±4.86	0.12±1.52	0.20±2.87	0.09±1.59	0.686[2]	0.934[4]
	Number of Betablockers	0.37±0.48	0.36±0.48	-0.01±0.30	0.36±0.49	0.41±0.49	0.05±0.34	**0.017[2]**	**0.031[4]**
	Total Betablockers dose (mg)	7.20±15.40	6.71±15.53	0.49±11.28	4.95±10.43	5.02±9.95	0.06±7.50	0.418[2]	0.550[4]
ACE inhibitors	Captopril (mg)	0.16±2.27	0.06±1.26	-0.10±1.41	0.19±2.60	0.08±1.43	-0.11±2.26	0.350[2]	0.135[4]
	Enalapril (mg)	0.56±3.36	0.50±3.57	-0.06±2.20	0.77±4.32	0.77±4.54	-0.00±3.18	0.509[2]	0.656[4]
	Lisinopril (mg)	1.76±6.36	1.66±5.77	-0.10±4.83	0.99±4.01	1.43±6.26	0.43±6.15	0.539[2]	0.811[4]
	Perindopril (mg)	0.08±0.81	0.05±0.63	-0.03±0.50	0.23±1.47	0.26±1.60	0.03±0.93	0.126[2]	**0.010[4]**
	Ramipril (mg)	0.31±1.58	0.29±1.37	-0.02±1.36	0.26±1.50	0.25±1.50	-0.01±1.11	0.635[2]	0.581[4]
	Number of ACE inhibitors	0.22±0.41	0.21±0.41	-0.01±0.38	0.23±0.43	0.22±0.42	-0.00±0.37	0.791[2]	0.625[4]
	Total ACE inhibitors dose (mg)	2.89±7.44	2.56±6.81	-0.30±5.58	2.44±6.80	2.78±7.85	0.34±7.58	0.497[2]	0.427[4]
ARB' s	Irbesartan (mg)	5.05±35.64	2.26±23.49	-2.79±27.04	2.52±24.29	3.03±28.92	0.50±13.73	**0.041[2]**	0.160[4]
	Losartan (mg)	5.80±22.99	5.65±22.70	0.15±14.36	5.33±19.33	7.19±24.55	1.86±15.58	**0.055[2]**	**0.012[4]**
	Number of ARB	0.09±0.29	0.08±0.27	-0.01±0.19	0.10±0.31	0.11±0.31	0.01±0.21	0.221[2]	0.111[4]
	Total ARB dose (mg)	10.85±41.72	7.91±32.28	-2.94±30.60	7.86±30.60	10.22±37.35	2.36±20.73	**0.011[2]**	**0.003[4]**
Other AH drugs	Clonidine (mg)	16.18±82.60	14.91±74.16	-1.27±70.04	9.33±51.53	13.02±66.54	3.69±49.25	0.371[2]	0.563[4]
	Minoxidil (mg)	0.10±0.92	0.16±1.10	0.06±0.70	0.09±0.85	0.09±0.75	-0.00±0.39	0.276[2]	0.106[4]
	Rilmenidine (mg)	0.03±0.25	0.02±0.19	-0.01±0.15	0.03±0.20	0.03±0.21	-0.00±0.22	0.459[2]	0.360[4]
All AH drugs	Number of AH drugs	1.1±1.1	1.1±1.1	-0.06±0.77	1.1±1.1	1.2±1.2	0.07±0.78	**0.029[2]**	**0.032[4]**
	Total dose of AH drugs	50.5±123.4	45.3±107.4	-5.19±82.26	34.8±81.3	40.8±100.6	5.99±69.48	0.081[2]	0.101[4]

Data are mean±SD; *BP: blood pressure; Ca: calcium; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; AH: antihypertensive; [1]Independent samples T-test; [2]Mann-Whitney U test; [3]ANCOVA; [4]Quade test; *unadjusted comparison of variation between groups; #comparison of variation between groups adjusted for baseline values*

Hemoglobin balance

Hb and EPO dose variations are described in Table 4.18. After adjusting for baseline values, no differences between groups were observed for Hb (g/dL) variation. However, variation in EPO dose was significantly different (p=0.008, ES=0.139), with the exercise group reducing and the non-exercise group increasing EPO dose prescription. Both groups slightly reduced the proportion of patients taking EPO from baseline to 1-year (Table 4.19.).

Table 4. 18. *Variation in hemoglobin and EPO dose*

	No exercise				Exercise				p[1]	p[2]
	N	Baseline	1-year	Δ	n	Baseline	1-year	Δ		
Hb (g/dL)	351	11.2±1.3	11.2±1.3	0.0±1.5	301	11.4±1.1	11.2±1.2	-0.1±1.2	**0.054**	0.255
EPO dose	394	4462±4456	4708±5169	246±4597	347	3534±4079	3201±3742	-333±3623	0.248	**0.008**

Data are mean±SD; Hb: hemoglobin; EPO: erythropoietin; [1]Unadjusted comparison of variation between groups (Mann-Whitney U test); [2]comparison of variation between groups adjusting for baseline values (Quade test)

Table 4. 19. *Patients with EPO at baseline and at 1-year*

	Non-exercise group (n=394)		Exercise group (n=347)		p[1]	p[1]
	Baseline	1-year	Baseline	1-year	(baseline)	(1-year)
EPO, n (%)	321 (81.5)	311 (78.7)	259 (74.6)	255 (73.5)	**0.024**	0.082

Phosphate control

No significant differences between groups were observed in variation of serum phosphate (mg/dL) and in phosphate binders' prescription (Table 4.21.). No important differences were observed in the proportion of patients taking phosphate binders at baseline and at 1-year (Table 4.20.).

Table 4. 20. *Patients with phosphate binders at baseline and at 1-year*

	Non-exercise group (n=394)		Exercise group (n=347)		p[1]	p[1]
	Baseline	1-year	Baseline	1-year	(baseline)	(1-year)
Ca acetate, n (%)	50 (12.7)	36 (9.1)	39 (11.2)	32 (9.2)	0.544	0.968
Ca acetate Mg Carbonate, n (%)	80 (20.3)	88 (22.3)	90 (25.9)	94 (27.1)	0.069	0.134
Lanthanum Carbonate, n (%)	1 (0.25)	0 (0.0)	1 (0.3)	0 (0.0)	0.928	---
Sevelamer, n (%)	30 (7.6)	34 (9.8)	59 (15.0)	55 (15.9)	0.291	0.742
Aluminum Hydroxyde, n (%)	1 (0.25)	1 (0.25)	1 (0.3)	1 (0.3)	0.928	0.928
Phosphate binder*, n (%)	154 (39.1)	172 (43.7)	153 (44.1)	168 (48.4)	0.167	0.194

[1]Chi-square test; *patients taking any phosphate binder; Ca: calcium; Mg: magnesium

Table 4. 21. *Variation in serum phosphate and in phosphate binder's prescription*

	No exercise (n=394)				Exercise (n=347)				P	p
	n	Baseline	1-year	Δ	n	Baseline	1-year	Δ	unadjusted[1]	adjusted[2]
Serum phosphate (mg/dL)	341	4.5±1.3	4.5±1.4	-0.05±1.43	296	4.4±1.2	4.4±1.2	0.03±1.16	0.447	0.886
Phosphate binders										
Ca acetate (mg)	394	220±703	186±681	-35±573	347	224±695	171±636	-53±608	0.858	0.575
Ca acetate Mg carbonate (mg)	394	456±1085	482±1085	26±928	347	562±1137	603±1165	41±1077	0.642	0.159
Lanthanum Carbonate (mg)	394	3.8±75.6	0.0±0.0	-3.8±75.6	347	4.3±80.5	0.0±0.0	-4.3±80.5	0.928	0.875
Sevelamer (mg)	394	250±991	425±1154	176±1066	347	263±927	479±1297	217±1136	0.652	0.342
Aluminum Hydroxyde (mg)	394	2.3±45.5	0.2±4.9	-2.0±40.6	347	2.9±53.7	2.6±48.9	-0.3±72.7	0.590	0.336
Number of phosphate binders	394	0.4±0.5	0.5±0.6	0.06±0.50	347	0.5±0.6	0.5±0.6	0.05±0.56	0.703	0.756
Total dose of phosphate binders	394	932±1519	1093±1608	161±1376	347	1056±1499	1256±1775	200±1671	0.457	0.127

Data are mean±SD; Ca: calcium; Mg: magnesium; [1]Unadjusted comparison of variation between groups (Mann-Whitney U test); [2]comparison of variation between groups adjusting for baseline values (Quade test).

4.5. Discussion

To the author´s knowledge, this is the first implementation study describing a large implementation of an IDE program at a nation-wide level. Taken together, these are encouraging results demonstrating that IDE implementation and scalability is possible as an integral part of standard care of HD patients. Moreover, this is a safe intervention, and its effectiveness seems to be preserved in real-world conditions to improve physical function, body composition and Hb control. Thus, compliance with the UKKA recommendation of implementing IDE in all HD units (3) is feasible, however some concerns emerged from this investigation: only about half of the HD units adopted the intervention; there was a high proportion of non-eligible patients; a high attrition rate mainly due to voluntary withdrawal; adherence levels were good but limited by voluntarily missed exercise sessions; and the exercise dose achieved was not enough to meet the UKKA PA recommendations for HD patients (3). Yet, there was a wide variation in the quality of implementation with some units performing better than others. This suggests that is realistic to aim for better implementation outcomes that could also increase the health impact of IDE provided as part of routine care of HD patients.

During its first year, IDE was adopted by 55.6% of the HD units. There is no data addressing the reasons why the nurse and medical directors declined to participate. As previously described, safety concerns, the perceived patient disinterest and staff workload may have discouraged adoption by these decisive actors (66). However, these commonly used reasons for non-IDE implementation are not consistent with our results. The safety of the intervention was confirmed by the non-increase in the incidence of adverse events and patient interest was demonstrated by half of the patients that completed the 1-year intervention with a good adherence (75.0±19.7%). The staff workload increase was minimized by the simplistic exercise protocol with low supervision requirements and by the defined inclusion criteria, only selecting patients that were able to cycle without help.

Reach was affected by the high proportion of patients excluded from the intervention (44.2%), mainly due to physical/cognitive incapacity (50.8%) and CV risk (34.6%). There was a broader disparity between HD units for eligibility (16.7% to 74.2%) meaning that some units adopted a more flexible while others a more conservative patient selection. There was a non-significant correlation between the prevalence of non-eligibility in each unit and the occurrence of adverse events. These results suggest that there is room to safely reduce non-eligibility using a more flexible screening of patients to IDE. This would be of utmost importance since those who were non-eligible were also those who would benefit most from exercise (older and sickest patients). Moreover, a more inclusive approach would increase the representativeness of IDE participants, improving the reach and so, the overall health impact of IDE. A substantial paradigm shift toward a more liberal screening for exercise has been adopted for the general population and diabetic patients (229) and our data advocates for its application in HD patients too. Non-eligibility due to physical/cognitive incapacity may also be explained by the low supervision nature of our exercise protocol delivered by the existing dialysis staff. Support from an exclusively dedicated exercise professional has been advocated (168, 230) and may increase eligibility to IDE. Among those eligible to IDE, a substantial proportion of patients refused the intervention (36.1%). The wider prevalence of refusals between HD units (0% to 60.7%) is indicative that the way IDE is presented to patients may be decisive for IDE acceptance. To increase PA engagement, a

combination of proven approaches that are grounded in relevant theories (e.g., focus on small quantities of exercise and increase self-regulation) can lead to better outcomes (224). The approach to potential participants to integrate IDE programs should also address important motivators as improvements in quality of life and physical function, and the will to have a healthier lifestyle (94). Likewise, family involvement and the support from dialysis staff are important promoters of exercise in HD patients (95). Patients refusing IDE were significantly older, had more comorbidities and had a lower lean tissue index than IDE participants. This is consistent with previous studies demonstrating that the perception of having too medical conditions and the perception of inability are important barriers to exercise (66). This must be demystified when approaching older and sicker patients for IDE participation.

Maintenance was affected by a considerable attrition rate (57.2% at 1-year) and voluntary withdrawal was, by far, its most common reason (52.4%). This is a disappointing finding since it is a loosed opportunity to improve health outcomes in such an at-risk population. Wide variation between units (0.0% to 63.0%) suggests that improvements can be made. Strategies to enhance long-term sustainability of exercise interventions are described for older adults (231) and could be valuable for HD patients too. The stage of change is a known predictor of adherence to exercise in chronic patients (232). This concept emerged from the transtheoretical model, which defines a series of behavior change stages: pre-contemplation, contemplation, preparation, action and maintenance (233). This study does not have an initial assessment of the patients' stage of change. Nevertheless, it is plausible that a mismatch between the patients' stage of change and an ambitious exercise prescription could have contributed for the considerable drop-out observed, especially for patients without any exercise routine. Moreover, self-efficacy is associated with dropouts from exercise interventions in HD patients (234). Thus, self-efficacy assessment and management could be a way to prevent voluntary withdrawal and would be particularly important during the first six months (period with the highest incidence of voluntary withdrawal). Due the simplistic nature of the exercise protocol, the program may have become an unchallenging activity for some patients. Thus, a progression including a variety of different exercises, preferably supported by an exclusively dedicated exercise professional, could lead to better maintenance outcomes.

Adherence to exercise sessions (75.0±19.7%) was superior to that observed in a previous multicentric and pragmatic study that had a median (IQR) adherence of 47 (28–77) % (134). Nevertheless, opportunity for improvement is demonstrated by the high heterogeneity between HD units (60.6% to 92.0%) and because the participants' own decision was, effectively, the main reason for missing an exercise session (61.5%). A smaller study considering only 900 HD sessions found similar results, adding that patients were more than twice as likely to exercise if an exercise professional was present (235).

Implementation dose was analyzed separately for aerobic and strength exercise. For aerobic exercise, mean duration was 86.3 min/week, thus achieving 57.5% of the UKKA recommendation that HD patients should aim for 150 min per week of moderate intensity PA (3). Mean duration per exercise session was 38.3 min, which means that in a hypothetical scenario of patients complying with all exercise sessions, 115min/week would be achieved (77% of the recommendation (3)). Strength exercise was accepted by 80% of the participants. Additionally, frequency/week of strength exercise was lower than aerobic exercise, 1.5±0.4 and

2.2±0.6, respectively. Moreover, strength exercise volume was minimal due to a low load of ankle weights (0.5±0.3 Kg) and sets performed (1.1±0.7). Taken together, our data suggests that a substantial aerobic exercise volume can be achieved through IDE. Nevertheless, this exercise strategy alone was far from reaching the recommended PA levels, mainly for strength exercise. Thus, a more comprehensive and individualized strategy has been advocated, that may include low-intensity activities (e.g., housework and gardening), IDE, and progression to higher-intensity activities and recreational sports. Ideally, an exercise specialist would work directly with patients to design a personalized exercise and PA promotion program (236). This approach would be even more valuable for strength exercise since it has been proposed that only 4% of HD patients (data from a population of 5763 patients) practice this type of exercise (209).

Despite not being implementation studies, two previous multicentric exercise trials in dialysis patients have reported some important implementation outcomes (134, 237). Even with the modest home-based exercise prescription of the EXCITE trial (237), there was also an important dropout (31% at six months) and about 50% of those completing the intervention had low adherence to the exercise protocol (<60%). Moreover, 36% of those eligible refused to participate. Accordingly, the PEDAL trial exercise prescription (twice per week) had a median adherence of 47% and a similar withdrawal at six months (33.7%) (134). Adding to the data of the present study, these findings suggest that the exercise implementation challenge should be subsidized by supportive programs based on self-monitoring, verbal reinforcement and motivation that may reduce voluntary withdrawals (238) and through quality improvement projects that may increase acceptability to IDE (239). Moreover, behavior change techniques at a patient and staff level may improve the overall implementation of IDE (97). In routine practice, the dialysis staff must accommodate IDE with the already existing HD-related tasks, which may generate dissatisfaction. Thus, behavior change techniques at staff level could improve the way patients are routinely approached to perform IDE, which may lead to an important progress in implementation outcomes.

IDE demonstrated to be safe with no increase in the incidence of intradialytic adverse events. This is an important result as a recently published Cochrane systematic review concluded that there is insufficient evidence to assess the safety of exercise in HD patients (138) which may discourage IDE adoption. Moreover, as previously discussed, there is no correlation between the proportion of non-eligibility and the incidence of adverse events, suggesting that a more flexible patient screening could be safely adopted. Indeed, IDE participants had a significant lower incidence of cramps. This is an extremely painful symptom that can compromise HD efficacy and may affect about 80% of HD patients (240). Since this is a highly prioritized symptom (241), our finding could motivate IDE participation in HD patients. Previous studies have reported concordant findings; however exercise protocols were performed immediately before (242) and after an HD session (243). To date, several mechanisms have been proposed to be responsible for dialysis-related cramps as hypoxia (caused by hypotension and vasoconstriction), osmotic shifts, hyponatremia, hypomagnesemia, carnitine deficiency and lack of angiotensin II activity (240). Future studies are needed to understand how IDE may influence these mechanisms. Since post-exercise hypotension is a possible adverse event following an exercise session (244), intradialytic hypotension was an anticipated concern. However, the incidence of hypotension was similar between groups, what agrees with previous studies demonstrating that IDE does not exacerbate hemodynamic instability during HD (245).

IDE patients significantly improved STS 30, 8-foot UG, STS 5 and SLS. However, there was a significant but slightly reduction in handgrip strength. These findings are concordant with a previous study (246) and may be explained by the simplistic exercise protocol that focused mainly on aerobic exercise using the lower limbs. However, an additional analysis comparing patients with a lower and a higher exercise frequency, demonstrated that only the lower exercise frequency group had a significant handgrip strength reduction. Also, this group had a significant lower improvement in STS 30. Our data suggests a dose-response of exercise and raises awareness for the critical importance of high adherence rates to further increase physical function. These results are of great importance as we know that most of these physical function measures are known predictors of mortality in this population (247). Yet, there is evidence that higher physical function improvements might be achieved combining IDE with an exercise prescription guided by an exercise professional (248).

BMI remained unchanged in the exercise and in the non-exercise group. Obesity paradox explains why BMI is not a good indicative of body composition in HD patients (249), thus a further analysis distinguishing lean body mass and fat mass is recommended. The non-exercise group increased adipose tissue mass, fat mass and fat tissue index, while the exercise group have decreased. Despite this favorable trend, difference in the variation from baseline to 1-year was not significant between groups. Non-exercise group decreased lean tissue mass and lean tissue index, whereas the exercise group have increased. Adjusted analysis revealed a significant difference of variations from baseline to 1-year for both outcomes. Additionally, exercise group had a higher increase in body cell mass leading to significant differences in variations of both groups in adjusted analysis. Body cell mass includes fat-free mass without the bone mineral mass and extracellular water. Thus, body cell mass is not affected by hydration status and consists of all metabolically active cells of the body, being sensitive to muscle depletion (250). Evidence of the effect of exercise on body composition of HD patients is inconclusive due the heterogeneity of the designed exercise programs and the estimation of lean tissue that is influenced by fluid management between HD sessions (251). Moreover, exercise programs usually consisted in specific training of the leg muscles, no matter if aerobic or resistance exercise, that may have precluded whole body lean mass improvements (252). Nevertheless, exercise (in particular strength exercise) is known to improve muscle mass in HD patients (252). Our promising findings demonstrate that, even with an exercise dose below the recommended level, the benefits of IDE in body composition may be kept under real-world conditions. The long follow up period could have made muscle wasting observable in the non-exercise group, while it was prevented in the exercise group. Previous investigations demonstrated that, in older adults, aerobic exercise mitigates long-term decrements in muscle mass due to a reduction in catabolic mRNA expression, induction of mitochondrial biogenesis and dynamics, and increased muscle protein synthesis favoring myofiber and whole muscle hypertrophy (253). Considering the deleterious evolution of body composition in this population (254), maintaining patient´s condition should, *per se*, be regarded as a positive result of exercise (236). Evidence of the benefits on muscle mass and body cell mass with IDE are noteworthy findings for HD patients because these are predictors of mortality in this population (53, 255). The weak ES are possibly explained by the low exercise dose, especially for strength exercise. IDE with high-load resistance training elicit greater improvements in skeletal muscle index (256) and could be a worthy addition to our routine clinical practice.

Hypertension may affect 90% of HD patients and the use of AH drugs is very common in this population (257). Proposed effects of exercise on key mechanisms of vascular disease in CKD include improvements in nitric oxide bioavailability secondary to chronic intermittent increases in shear stress, endothelial repair through mobilization of bone marrow-derived endothelial progenitor cells, reduction in oxidative stress due the expression of various antioxidant enzymes, and the known anti-inflammatory effects of exercise (50). All these mechanisms may be related with improvements in BP control. However, in this study, no significant differences between groups were found for variations in pre-HD systolic and diastolic BP. Moreover, prescription of AH drugs had a slight increase in the exercise group, due to an increase in the prescription of betablockers and angiotensin receptor blockers. This finding contrasts with a previous study where intradialytic cycling for six months decreased the use of AH medications (258). Older age and lower baseline BP of our sample may explain the dissimilar findings. Hence, a future sub-analysis restricted to hypertensive patients should be of interest, despite being beyond the scope of this implementation study. In HD patients, BP control is complicated by missed dialysis treatments, excessive interdialytic weight gain, medication non-adherence, medication clearance with dialysis, intradialytic BP changes, and which BP (i.e., pre-dialysis, post-dialysis, home) to use as the appropriate target of therapy (257). All these factors may challenge the exercise benefits on BP control of HD patients. Our findings are in agreement with a previous meta-analysis of RCT´s showing no effects of intradialytic cycling to reduce BP (259). However, broader meta-analysis including interdialytic exercise and strength training, demonstrates the benefit of exercise to improve BP, but these results were only significant for combined aerobic and resistance exercise programs (138, 260). Whilst speculative, it is plausible that the complex nature of hypertension in HD patients requires a more comprehensive exercise prescription to improve BP control in this population. Thus, the focus on aerobic training with a very low dose of strength exercise may explain these null results.

Compared to the general population, prevalence of anemia is twice in CKD, and increases with disease progression from 8.4% at stage 1 to 53.4% at stage 5 (261). The progressive reduction of EPO levels has traditionally been pointed to play a preeminent role. However, other factors may contribute to anemia, such as an absolute iron deficiency due to blood losses or an impaired iron absorption, an ineffective use of iron stores due to increased hepcidin levels, systemic inflammation, a reduced bone marrow response to EPO due to uremic toxins, a reduced red cell life span, or vitamin B12 or acid folic deficiencies (261). The possible underlying mechanisms by which exercise promote red blood cell production come mainly from bone marrow, including stimulated erythropoiesis with hyperplasia of the hematopoietic bone marrow, improvement of the hematopoietic microenvironment and hormone and cytokine accelerated erythropoiesis (262). Therefore, exercise has been proposed as an adjunctive therapy in cancer-related anemia (263), and our findings highlight the potential of exercise for anemia in HD patients too. Adjusting to baseline values, variations on Hb were not statistically different between groups. However, the non-exercise group increased EPO weekly dose while the exercise group decreased, and variations from baseline to 1-year were statistically different after adjusting for baseline levels. These reduction is meaningful because EPO hypo-responsiveness is associated with mortality (264) and anemia management is expensive and mainly driven by erythropoiesis-stimulating agents (265). Our findings are in agreement with the very limited existing evidence in HD patients (82, 85, 266-269) that is jeopardized by very small samples sizes (82, 85, 266),

uncontrolled methodology (267) and simplistic exercise protocols with only two studies including strength training (268, 269). Since the influence of exercise on erythrocyte production is osteoblast-dependent, and strength exercise has been shown to have a modulatory effect on bone metabolism (262), future well-designed RCT´s with combined aerobic and strength exercise are needed to confirm the role of exercise to improve anemia management in HD patients. Moreover, simulated altitude exercise has been used in other chronic conditions (270), however nothing is known of its application in CKD patients. This could be of importance as altitude may increase endogenous EPO production and EPO responsiveness in HD patients (271).

The rationale for IDE to improve dialysis adequacy is the increase in blood flow to the skeletal muscles, which holds a large proportion of the total body water and would be a low perfused tissue bed during HD (77). Simulation models predicted IDE to increase solute clearance and almost eliminate post dialysis urea rebound (272). It is estimated that 60 minutes of IDE may be equivalent to 20 minutes increase in HD duration (273). Regarding phosphate removal, it was speculated that during IDE, phosphate is produced from skeletal muscle metabolism (274), inhibiting phosphate generation from the erythrocytes and bone. After exercise, phosphate released from the skeletal muscle is then used for energy replenishment leading to reduced serum phosphate levels (275). However, in this study, no significant results were found for serum phosphate levels and for phosphate binders' prescription. These findings are somehow conflicting with a previous systematic review demonstrating the benefits of IDE to improve phosphate removal (77). The high serum phosphate levels at baseline of the included studies differ from the normophosphatemic sample of the present study. Thus, a sub-analysis restricted to hyperphosphatemic patients is recommended, but beyond the scope of this implementation study. Other possible explanation is that most of the studies included in the systematic review collected blood samples before and after a single HD session to measure phosphate clearance during dialysis. In the present study, phosphate samples were taken 1 year apart. Thus, serum phosphate could have been influenced by several factors as phosphorus ingestion and variations in body composition (e.g., increased muscle mass in the exercise group). Therefore, our findings call into question if the described acute benefits of IDE to improve serum phosphate levels are prolonged beyond the dialysis period and result in a better chronic phosphate control. If so, this could lead to a reduction of phosphate binder's prescription that highly contribute to the pill burden of HD patients (6-12 pills a day) and is associated with non-adherence and poor phosphate control (276).

The major limitation of the present study is the absence of qualitative data involving the different stakeholders for a better understanding of reasons for HD units´ non-adoption, patients´ refusal, voluntary withdrawal and missed exercise sessions. This would be very informative for future quality improvement projects. Additionally, the cost of the intervention should be addressed in future analysis as part of the implementation dimension of the RE-AIM framework (132). Effectiveness may have been influenced by the observational design of the study. The use of pre-HD BP is not the best measurement as it is poorly correlated with BP obtained in the interdialytic period and the latter has more robust prognostic value (257). Moreover, AH drugs and phosphate binders' analysis was based on prescription instead of pill count and, thus may have been influenced by non-adherence.

4.6. Conclusion

Overall, IDE has demonstrated to be a realistic and safe strategy in routine practice. High variability across HD units suggests room to improve implementation outcomes. Adoption could be improved raising awareness of medical and executive boards for the importance to implement IDE. Reach could also be enhanced by assuming a more flexible patient selection and by finding strategies to reduce the prevalence of IDE rejection. Maintenance in IDE is severely affected by voluntary withdrawal (especially during the first six months) and its prevention is of major importance. Implementation fidelity (adherence) was mostly affected by voluntarily missed exercise sessions. Thus, improving the way the dialysis staff approach IDE participants, may further increase patient's adherence. Despite a substantial implementation dose, IDE was not enough to achieve the recommended PA levels, mainly for strength training. Thus, complementary exercise interventions should be added to IDE. Effectiveness was sustained in real-world conditions for physical function, body composition and Hb balance; however weak ES suggest that higher exercise doses could elicit further health benefits. Hence, more personalized approaches including increasing PA levels as a component of a comprehensive behavior change, would complement IDE, helping HD patients to meet the current PA recommendations with higher health impacts.

Chapter 5: Association of intradialytic exercise with mortality and hospitalization: a cohort study

5.1. Abstract

Background: HD patients are at an increased mortality and hospitalization risk. As discussed in Chapter 3, PA may improve these hard endpoints. However, whether IDE improves mortality and hospitalization outcomes in this at-risk population remains poorly investigated.

Objective: to analyze the association of IDE with mortality and hospitalization in HD patients.

Design, setting and participants: this multicentric prospective cohort study was based on an IDE program implemented at a nation-wide level in Portugal. IDE exposure quantification was measured during the first year and then, patients were followed for more three years.

Exposure: IDE participation was measured based on aerobic exercise dose in minutes/week. Accordingly, patients were divided in three groups: a non-exercise (patients who refused IDE), a low exercise (<87min/week) and a high exercise group (≥87min/week). Also, a subanalysis restricted to IDE participants and considering exposure as a continuous variable was performed.

Outcomes and measurements: time to all-cause mortality and hospitalization, and number of and days of hospitalization/year. Vascular access-related hospitalizations were excluded from the analysis. Outcomes were investigated using time-dependent proportional hazards models and Quade´s test.

Results: a total of 741 patients were included with a mean (SD) age of 63.3 (14.3) years. During the median follow-up of 33.2 months, 129 (17.4%) deaths occurred. A total of 318 (42.9%) patients were hospitalized summing 644 hospitalizations (0.9±1.4 hospitalization/patient) and 7859 hospitalization days (10.6±24.1 days of hospitalization/patient). For adjusted all-cause mortality, no differences were found between the low and the non-exercise group (HR=1.12; 95% CI, 0.74-1.68; p=0.602). However, the high exercise group had a significantly reduced mortality risk compared to the non-exercise group (HR=0.38; 95% CI, 0.20-0.72; p=0.003). In the subanalysis restricted to IDE participants, a significant mortality risk reduction was found per each 50 minutes increase in aerobic exercise dose (HR=0.46; 95% CI, 0.27-0.79; p=0.005). Adjusted hospitalization risk was not significantly different in the non-exercise compared with the low exercise groups (HR=0.90; 95% CI, 0.60-1.19; p=0.459). Yet, compared to the non-exercise group, the high exercise group had a significantly lower hospitalization risk (HR=0.73; 95% CI, 0.54-0.98; p=0.037). Adjusted number of hospitalizations/year was gradually decreased with increased exercise doses (non-exercise: 0.7±1.5; low exercise: 0.5±1.4; high exercise: 0.4±1.7). Yet, no significant differences were found between the non-exercise and the low exercise groups (p=0.447). Likewise, there was a gradual reduction of days of hospitalization/year with greater exercise doses (non-exercise: 7.4±20.1; low exercise: 6.5±23.2; high exercise: 5.2±20.1). Again, no differences were observed between the non-exercise and the low exercise groups (p=0.309). Nevertheless, compared to the non-exercise group, the high exercise group had a significant lower number of and days of hospitalization/year (p=0.023 and p=0.029, respectively).

Conclusions: above a considerable exercise volume, IDE is associated with better mortality and hospitalization outcomes in HD patients. However, many patients may not achieve an effectively protective exercise dose. These findings suggest that more support is needed to increase

exercise dose in HD patients which may include moving from an IDE stand-alone strategy to a more comprehensive and personalized PA intervention.

Keywords: CKD; HD, exercise, physical activity, hard endpoints.

5.2. Background

As already debated in Chapter 1, Section 1.2., CKD patients have an increased mortality and hospitalization risk. The increased risk of death rises with disease progression and is evident both for lower GFR and higher albuminuria (104). For those on dialysis, mortality is about 16 times higher than in the general population with CV and non-CV mortality contributing equally to this increased mortality risk (105). Risk of sudden cardiac death is 59 times higher in HD patients than the general population, being the main cause of CV mortality in this population (25% of all deaths) (106). The higher non-CV mortality risk is mostly explained by infectious diseases (82-fold higher) and malignancies (2.9-fold higher) (277). Taken together, CV and infectious diseases account for up to 70% of all deaths in CKD (110), while cancer deaths account for 6.1% (109). Likewise, hospitalization risk increases with CKD progression (111) and is 15 times higher than in the general population (113). Main causes of hospitalization in HD patients are CV (21%) and infections (17%). CV admissions are mainly due to hypertension (4%) and myocardial infarction (3%), while infection admissions are mostly related to pneumonia (5%) and sepsis (5%) (116). Even when compared to several types of cancer (colorectal, prostate and breast), mortality and hospitalization are higher in dialysis patients (278). Thus, mortality and hospitalizations are critically important outcomes for many HD stakeholders (140), which highlights the need of interventions to improve these endpoints in this at-risk population (113, 278).

Higher PA is associated with a lower mortality risk in the general population (191) and in HD patients (Chapter 3) (63), but 94% of HD patients are still insufficiently active (2). Making use of otherwise sedentary time, IDE is a convenient way to increase PA in this population (71) and its implementation is recommended for all HD units (3). Nevertheless, despite its proven cost-effectiveness (98), IDE remains underused in clinical settings (78). Evidence of its benefit on relevant endpoints as mortality and hospitalization is lacking and may have precluded its dissemination (138). These are research priorities for exercise in CKD (141) and evidence on the benefit of IDE on such important outcomes could trigger a wider translation into clinical practice. Therefore, the aim of this study is to analyze the association of IDE with mortality and hospitalization in HD patients.

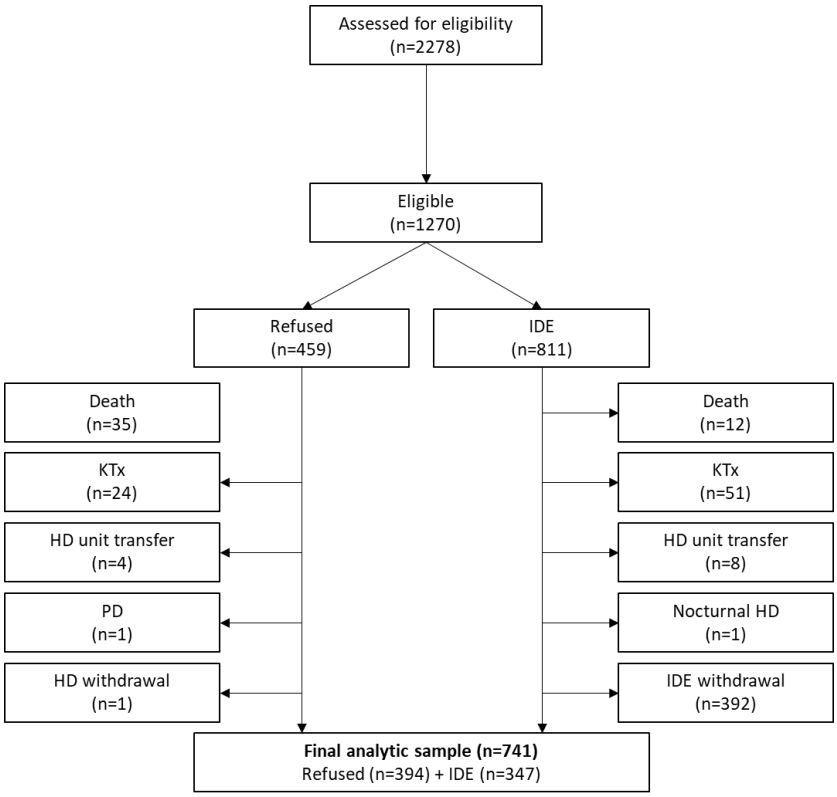
5.3. Methods

This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies (279) and received ethical approval from the Fresenius Medical Care Portugal Health Ethics Committee (04/2021).

Study design, setting and participants

This is a cohort study including 741 patients from 20 HD units in Portugal who were approached to join an IDE program that was previously described earlier in this thesis (Chapter 2, Section 2.1.). This study was developed between September 2016 and January 2021. During the first year, exposure to IDE was quantified according to the mean aerobic exercise dose (minutes/week) and then patients were followed for death and hospitalization throughout the following three years. This investigation is based on an ongoing clinical exercise program. Thus, after one year of IDE, the intervention continued, and patients could have exercised during part, or the entire three-year follow up period.

Eligibility criteria for IDE were already described in General Methods (Chapter 2, Section 2.1.). Among 2270 patients assessed for eligibility, 1270 were deemed eligible. Of those, 459 refused IDE and 811 accepted. After the first year of IDE, the final study sample was composed of 347 patients that remained in the exercise group and 394 patients that remained in the refusals group (Figure 5.1.). The main reasons for non-inclusion in the final sample were death (n=35) and KTx (n=24) in the group of patients who refused IDE; and IDE withdrawal (n=392) and KTx (n=51) in the group of IDE participants.



IDE: intradialytic exercise; KTx: transplant; PD: peritoneal dialysis; HD: hemodialysis

Figure 5. 1. *Flowchart of sample selection*

Intradialytic exercise protocol

The IDE protocol was described in detail in General Methods (Chapter 2, Section 2.1.).

Exposure measure: aerobic exercise dose

The lower acceptance of strength exercise precluded its use as an exposure variable. Thus, the aerobic exercise dose was used computing the mean aerobic exercise duration per week throughout the first year of IDE participation. Patients were divided in non-exercisers and those who completed exercise, with the latter being divided according to the median of aerobic exercise performed (i.e., 87 minutes/week). Therefore, three categories were created: 1) a non-exercise group of patients who were eligible but refused to exercise (n=394); 2) a low exercise group of patients who exercised <87min/week (n=174), and 3) a high exercise group of patients who exercised ≥87min/week (n=173). The reference category was the non-exercise group.

Outcomes: mortality and hospitalization

Mortality and hospitalization data was obtained from the medical records, being extracted from EuCliD (227). Causes of death and hospitalization were determined using the International Statistical Classification of Diseases, 10th Revision and classified as CV or non-CV.

Results specifically addressing CV and non-CV causes were explored only using descriptive data. A hospitalization was considered for at least an overnight stay. Hospitalizations related with the vascular access were excluded from the analysis. Besides time to first hospitalization (hospitalization risk), number and days of hospitalizations/year were also investigated.

Covariates

Potential confounders were assessed just before the IDE implementation and included age (years), sex, HD vintage (months), vascular access (arteriovenous fistula, arteriovenous graft or central venous catheter), treatment modality (HDF or HD), BP assessed before HD (average of three consecutive treatments), comorbidities (Charlson Comorbidity Index, diabetes, CV disease), body composition including BMI and bioimpedance spectroscopy (lean tissue index, fat tissue index and overhydration), phosphate (mg/dL), Hb (mg/dL), and potassium (mEq/L). If there was a statistically significant difference between the three groups, the covariate was included as a confounder in the adjusted analysis.

Statistical analysis

Data were presented as mean values and ± SD. Normality was checked and, if non-normally distributed, statistical analysis was performed on the logarithmically transformed data. Differences between groups were analyzed using Chi-square test (categorical variables), Kruskal-Walli's test (non-normally distributed continuous variables) and One-way ANOVA (normally distributed continuous variables).

Survival analysis was performed using Cox proportional hazards regression models to calculate the HR and 95% CI for the association of aerobic exercise dose group with mortality and hospitalization (time to first hospitalization). Thus, the low and the high exercise dose groups were compared with the non-exercise group (reference group). Besides unadjusted analysis (model 1), adjusted analysis was performed controlling for age (model 2), and additionally for dialysis vintage and vascular access (model 3), adding age-adjusted Charlson comorbidity index and number of CV diseases (model 4), and a full-adjusted model also controlling for lean tissue index and overhydration. A further analysis restricted to the IDE participants (both low and high exercise groups) was performed considering aerobic exercise dose as a continuous variable (minutes/week).

Quade´s test was used to analyze differences between groups for number of hospitalizations/year and days of hospitalization/year. Adjustment analysis was made as described in the previous paragraph for time-to-event analysis.

Missing data of the variables in the final model were very low (Table 5.1.) and were replaced by the mean value for the corresponding exercise dose group.

Table 5. 1. *Incidence of missing data (%) for the variables in the final model*

	Overall	Non-exercise	Low exercise	High exercise
Age (y)	0.0%	0.0%	0.0%	0.0%
Dialysis vintage (months)	1.6%	1.3%	2.3%	1.7%
Vascular access	0.0%	0.0%	0.0%	0.0%
Age-CCI	0.4%	0.8%	0.0%	0.0%
No. of CVD	0.0%	0.0%	0.0%	0.0%
Leant Tissue Index	5.7%	8.1%	1.7%	4.0%
Overhydration	5.4%	7.6%	1.7%	4.0%

CCI: Charlson comorbidity index; CVD: cardiovascular disease

5.4. Results

The analytic sample included 741 patients divided in three categories: non-exercise group (n=394), <87min/week (n=174) and ≥87min/week (n=173). The non-exercise group was older, with a higher dialysis vintage, a higher prevalence of central venous catheters, a higher comorbidity index with a higher prevalence of CV disease, a lower lean tissue index and a higher overhydration (Table 5.2.). Comparing the low exercise (<87min/week) and the high exercise (≥87min/week) groups, significant differences were only observed in BMI and fat tissue index (Table 5.3.). Measures of IDE participation are presented in Table 5.4.

Table 5. 2. *Descriptive characteristics for the total sample and by exercise dose groups*

	Overall (n=741)	**Aerobic exercise dose group, min/week**			
		No exercise (n=394)	**<87min (n=174)**	**≥87min (n=173)**	**p**
Age (y)	63.3±14.3	64.9±14.5	60.6±15.1	62.4±12.6	**0.002**[1]
Female, n (%)	261 (35.2)	147 (37.3)	65 (37.4)	49 (28.3)	0.095[2]
Dialysis vintage (months)	75.0±85.9	86.9±91.6	55.3±71.0	67.4±82.0	**<0.001**[1]
Vascular access, n (%)					
Arteriovenous fistula	590 (79.6)	296 (75.1)	143 (82.2)	151 (87.3)	**0.002**[2]
Arteriovenous graft	74 (10.0)	42 (10.7)	16 (9.2)	16 (9.2)	
Central Venous Catheter	77 (10.4)	56 (14.2)	15 (8.6)	6 (3.5)	
Treatment modality, n (%)					
Hemodiafiltration	695 (93.8)	368 (93.4)	163 (93.7)	164 (94.8)	0.751[2]
Hemodialysis	46 (6.2)	26 (6.6)	11 (6.3)	9 (5.2)	
Blood pressure					
Systolic BP (mmHg)	140±20	141±21	140±20	139±19	0.459[1]
Diastolic BP (mmHg)	70±14	68±14	69±13	67±13	0.369[1]
Patients taking AH drugs, n (%)	449 (60.6)	237 (60.2)	106 (60.9)	106 (61.3)	0.964[2]
Comorbidities					
Age-adjusted CCI	5.7±2.4	6.0±2.5	5.3±2.4	5.5±2.4	**0.001**[1]
Diabetes Mellitus, n (%)	197 (26.6)	97 (24.6)	49 (28.2)	51 (29.5)	0.418[2]
CV disease, n (%)	601 (81.1)	335 (85.0)	128 (73.6)	138 (79.8)	**0.005**[2]
No. of CV diseases	1.8±1.7	2.1±1.8	1.5±1.3	1.6±1.5	**0.001**[1]
Body Composition					
Body Mass Index (Kg/m^2)	26.4±4.7	26.3±4.9	27.0±4.7	26.0±4.1	0.172[1]
Lean Tissue Index (Kg/m^2)	13.3±3.0	12.9±2.8	13.4±3.3	13.9±2.8	**0.002**[3]
Fat Tissue Index (Kg/m^2)	12.3±5.4	12.5±5.4	12.9±5.7	11.5±5.0	0.065[1]
Overhydration (%)	7.9±8.5	9.0±9.5	6.7±7.4	6.8±6.7	**<0.001**[1]
Phosphate (mg/dL)	4.5±1.3	4.6±1.3	4.5±1.4	4.3±1.2	0.128[1]
Hemoglobin (g/dL)	11.3±1.2	11.2±1.3	11.3±1.1	11.3±1.1	0.173[1]
Potassium (mEq/L)	5.3±0.7	5.3±0.7	5.4±0.7	5.3±0.7	0.262[1]

Data are mean±SD; [1]Kruskal-Wallis test; [2]Chi-square test; [3]One-Way ANOVA; BP: blood pressure; AH: antihypertensive; CCI: Charlson comorbidity index; CV cardiovascular

Table 5. 3. *Comparison of low and high exercise groups*

	Low exercise (n=174)	High exercise (n=173)	p
Age (y)	60.6±15.1	62.4±12.6	0.302[1]
Female, n (%)	65 (37.4)	49 (28.3)	0.073[2]
Dialysis vintage (months)	55.3±71.0	67.4±82.0	0.376[1]
Vascular access, n (%)			
Arteriovenous fistula	143 (82.2)	151 (87.3)	0.131[2]
Arteriovenous graft	16 (9.2)	16 (9.2)	
Central Venous Catheter	15 (8.6)	6 (3.5)	
Treatment modality, n (%)			
Hemodiafiltration	163 (93.7)	164 (94.8)	0.664[2]
Hemodialysis	11 (6.3)	9 (5.2)	
Blood pressure			
Systolic BP (mmHg)	140±20	139±19	0.627[3]
Diastolic BP (mmHg)	69±13	67±13	0.204[3]
Patients taking AH drugs	106 (60.9)	106 (61.3)	0.946[2]
Comorbidities			
Age-adjusted CCI	5.3±2.4	5.5±2.4	0.385[1]
Diabetes Mellitus, n (%)	49 (28.2)	51 (29.5)	0.786[2]
CV disease, n (%)	128 (73.6)	138 (79.8)	0.172[2]
No. of CV diseases	1.5±1.3	1.6±1.5	0.604[1]
Body Composition			
Body Mass Index (Kg/m^2)	27.0±4.7	26.0±4.1	**0.049[3]**
Lean Tissue Index (Kg/m^2)	13.4±3.3	13.9±2.8	0.077[3]
Fat Tissue Index (Kg/m^2)	12.9±5.7	11.5±5.0	**0.012[3]**
Overhydration (%)	6.7±7.4	6.8±6.7	0.880[3]
Phosphate (mg/dL)	4.5±1.4	4.3±1.2	0.203[1]
Hemoglobin (g/dL)	11.3±1.1	11.3±1.1	0.781[1]
Potassium (mEq/L)	5.4±0.7	5.3±0.7	0.331[3]

Data are mean±SD; [1]Mann-Whitney U test; [2]Chi-square test; [3]Independent Samples T-test; BP: blood pressure; AH: antihypertensive; CCI: Charlson comorbidity index; CV: cardiovascular

Table 5. 4. *Intradialytic exercise participation in low and high exercise dose groups*

	Low exercise (n=174)	High exercise (n=173)	p[1]
Adherence (%)	62.5±19.7	87.4±8.8	**<0.001**
Exercise sessions/week	1.9±0.6	2.6±0.3	**<0.001**
Aerobic exercise (min/week)	63.2±18.7	109.6±16.0	**<0.001**
Strength training workload (kg*rep)	72.2±123.8	278.9±360.4	**<0.001**

Data are mean±SD; [1]Mann-Whitney test.

Median follow-up was 33.2 months, during which 132 patients (17.8%) were lost to follow-up: discontinuation of HD (n=6), HD unit transfer (n=24) and KTx (n=102) (loss to follow-up by exercise dose group is presented in Table 5.5.). During the follow-up, 129 patients died and 318 were hospitalized (644 hospitalizations summing 7859 hospitalization days). CV and non-CV mortality had a similar incidence (37.2% and 35.7%, respectively). Cause of mortality was unknown for 27.1% of the events. Non-CV hospitalizations were predominant (48.8%), followed by CV hospitalizations (26.1%). In 25.1% of the hospitalizations the cause is unknown. Causes of mortality and hospitalization are illustrated in Tables 5.6. and 5.7., respectively.

Table 5. 5. *Loss to follow-up by exercise dose group*

Reason for loss to follow up	Overall (n=741)	Non-exercise (n=394)	Low exercise (n=174)	High exercise (n=173)
Discontinuation of HD, n (%)	6 (0.8%)	4 (1.0%)	1 (0.6%)	1 (0.6%)
HD unit transfer, n (%)	24 (3.2%)	14 (3.6%)	5 (2.9%)	5 (2.9%)
KTx, n (%)	102 (13.8%)	36 (9.1%)	35 (20.1%)	31 (17.9%)
Total, n (%)	**132 (17.8%)**	**54 (13.7%)**	**41 (23.6%)**	**37 (21.4%)**

HD: hemodialysis; KTx: kidney transplant.

Table 5. 6. *Causes of death according to the ICD*

		No exercise (n=394)	Low exercise (n=174)	High exercise (n=173)	Total (n=741)
ICD	**Cardiovascular deaths**				
I61.9	Nontraumatic intracerebral hemorrhage, unspecified	1	1	0	**2**
I63.9	Cerebral infarction, unspecified	2	2	0	**4**
I46.9	Cardiac arrest cause unspecified	5	2	0	**7**
I21.9	Acute myocardial infarction, unspecified	4	2	3	**9**
I50.9	Heart failure, unspecified	4	1	0	**5**
K55.0	Vascular disorders of intestine	6	1	0	**7**
K55.2	Angiodysplasia of colon	3	0	0	**3**
J81.-	Acute pulmonary edema	1	0	0	**1**
I64.-	Stroke, not specified as haemorrhage or infarction	1	0	0	**1**
I35.0	Nonrheumatic aortic (valve) stenosis	1	0	0	**1**
I45.8	Other specified conduction disorders	3	1	1	**5**
I73.8	Other specified peripheral vascular diseases	0	1	0	**1**
R57.0	Cardiogenic shock	2	0	0	**2**
	n	**33**	**11**	**4**	**48**
	% Incidence	**8.4**	**6.3**	**2.3**	**6.5**
ICD	**Non-cardiovascular deaths (trauma)**				
T93.8	Sequelae of other specified injuries of lower limb	1	0	0	1
S09.9	Unspecified injury of face and head	1	0	0	1
S36.5	Injury of colon	1	0	0	1
	n	3	0	0	3
	% Incidence	0.8	0	0	0.4
ICD	**Non-cardiovascular deaths (infection)**				
J15.9	Unspecified bacterial pneumonia	6	3	2	11
A41.9	Sepsis, unspecified organism	7	1	2	10
B34.2	Coronavirus infection, unspecified	2	0	0	2
B37.7	Candidal sepsis	1	0	0	1
A41.0	Sepsis due to Staphylococcus aureus	0	0	1	1
	n	16	4	5	25
	% Incidence	4.1	2.3	2.9	3.4
ICD	**Non-cardiovascular deaths (malignancy)**				
C64.-	Malignant neoplasm of kidney, except renal pelvis	1	0	0	1
C50.8	Malignant neoplasm of overlapping sites of breast	1	0	0	1
C95.9	Leukemia, unspecified	1	0	0	1
C61.-	Malignant neoplasm of prostate	0	1	0	1
	n	3	1	0	4
	% Incidence	0.8	0.6	0.0	0.5
ICD	**Non-cardiovascular deaths (other)**				
Y60.2	During kidney dialysis or other perfusion	0	1	0	1
D69.8	Other specified hemorrhagic conditions	1	0	0	1
E87.5	Hyperkalemia	0	1	0	1
W79.0	Inhalation and ingestion of food causing obstruction of respiratory tract	0	1	0	1
J96.1	Chronic respiratory failure	1	0	0	1
Q44.6	Cystic disease of liver	0	1	0	1
N18.9	Chronic kidney disease, unspecified	1	0	0	1
F01.8	Other vascular dementia	0	1	0	1
J44.8	Other specified chronic obstructive pulmonary disease	0	1	0	1
K63.1	Perforation of intestine (nontraumatic)	0	1	0	1
E64.0	Sequelae of protein-calorie malnutrition	3	1	0	4
	n	6	8	0	14
	% Incidence	1.5	4.6	0.0	1.9

Non-cardiovascular deaths (total)					
	n	**28**	**13**	**5**	**46**
	% Incidence	**7.1**	**7.5**	**2.9**	**6.2**
Unknown causes of death					
	n	24	9	2	35
	% Incidence	6.1	5.2	2.2	4.7

ICD: international statistical classification of diseases

Table 5. 7. *Causes of hospitalization according to the ICD*

		No exercise (n=394)	**Low exercise (n=174)**	**High exercise (n=173)**	**Total (n=741)**
ICD	**Cardiovascular hospitalizations**				
D64.9	Anemia, unspecified	1	0	0	**1**
E10.6	Type 1 diabetes mellitus with other specified complications	0	1	1	**2**
F01.8	Other vascular dementia	0	1	0	**1**
I11.9	Hypertensive heart disease without (congestive) heart failure	0	2	0	**2**
I13.2	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	0	1	0	**1**
I20.9	Angina pectoris, unspecified	0	0	1	**1**
I21.9	Acute myocardial infarction, unspecified	9	0	7	**16**
I24.8	Other forms of acute ischemic heart disease	2	1	0	**3**
I26.0	Pulmonary embolism with mention of acute cor pulmonale	0	1	0	**1**
I30.9	Acute pericarditis, unspecified	0	1	0	**1**
I34.9	Nonrheumatic mitral valve disorder, unspecified	1	0	0	**1**
I35.0	Aortic (valve) stenosis	1	0	0	**1**
I45.5	Other specified heart block	1	1	0	**2**
I46.9	Cardiac arrest, unspecified	2	1	1	**4**
I48.-	Atrial fibrillation and flutter	3	1	7	**11**
I50.9	Heart failure, unspecified	10	2	2	**14**
I61.9	Intracerebral hemorrhage, unspecified	2	3	1	**6**
I63.9	Cerebral infarction, unspecified	6	3	5	**14**
I64.-	Stroke, not specified as hemorrhage or infarction	0	2	0	**2**
I71.4	Abdominal aortic aneurysm, without mention of rupture	0	0	1	**1**
I72.8	Aneurysm and dissection of other specified arteries	1	0	0	**1**
I73.8	Other specified peripheral vascular diseases	36	12	10	**58**
I73.9	Peripheral vascular disease, unspecified	3	0	0	**3**
I74.9	Embolism and thrombosis of unspecified artery	1	1	0	**2**
I77.0	Arteriovenous fistula, acquired	9	1	0	**10**
I80.0	Phlebitis and thrombophlebitis of superficial vessels of lower extremities	1	0	0	**1**
K55.0	Acute vascular disorders of intestine	4	0	2	**6**
K55.2	Angiodysplasia of colon	1	0	1	**2**
	n	**94**	**35**	**39**	**168**
	Hospitalization/patient	**0.2**	**0.2**	**0.2**	**0.2**
ICD	**Non-cardiovascular hospitalizations (trauma)**				
S06.5	Traumatic subdural hemorrhage	1	0	0	1
S06.7	Intracranial injury with prolonged coma	0	1	0	1
S42.3	Fracture of shaft of humerus	1	0	0	1
S72.0	Fracture of neck of femur	6	3	1	10
S72.1	Pertrochanteric fracture	0	1	0	1
S72.2	Subtrochanteric fracture	3	1	0	4
S72.8	Fractures of other parts of femur	1	0	0	1
S72.9	Fracture of femur, part unspecified	3	1	1	5
	n	15	7	2	24
	Hospitalization/patient	0.04	0.04	0.01	0.03
ICD	**Non-cardiovascular hospitalizations (infection)**				
A41.8	Other specified sepsis	3	0	0	3
A41.9	Sepsis, unspecified	11	2	3	16
A46.-	Erysipelas	2	0	0	2
B18.2	Chronic viral hepatitis C	3	0	0	3
B34.2	Coronavirus infection, unspecified site	2	0	0	2
H66.3	Other chronic suppurative otitis media	1	0	0	1
J11.1	Influenza with other respiratory manifestations, virus not identified	2	0	0	2
J15.9	Bacterial pneumonia, unspecified	19	12	10	41
J22.-	Unspecified acute lower respiratory infection	28	12	9	49
J32.9	Chronic sinusitis, unspecified	1	0	0	1

N39.0	Urinary tract infection, site not specified	2	0	0	2
R50.9	Fever, unspecified	3	2	0	5
U07.1	COVID-19, virus identified	2	0	0	2
	n	79	28	22	129
	Hospitalization/patient	0.2	0.2	0.1	0.2
ICD	**Non-cardiovascular hospitalizations (malignancy)**				
C15.9	Malignant neoplasm: Esophagus, unspecified	3	0	0	3
C18.9	Malignant neoplasm: Colon, unspecified	2	0	1	3
C20.-	Malignant neoplasm of rectum	2	0	1	3
C26.0	Malignant neoplasm: Intestinal tract, part unspecified	4	0	0	4
C34.9	Malignant neoplasm: Bronchus or lung, unspecified	2	1	0	3
C55.-	Malignant neoplasm of uterus, part unspecified	2	0	0	2
C63.9	Malignant neoplasm: Male genital organ, unspecified	1	0	0	1
C64.-	Malignant neoplasm of kidney, except renal pelvis	1	0	1	2
C67.9	Malignant neoplasm: Bladder, unspecified	1	0	0	1
C88.9	Malignant immunoproliferative disease, unspecified	0	1	0	1
C90.0	Multiple myeloma	1	0	1	2
	n	19	2	4	25
	Hospitalization/patient	0.05	0.01	0.02	0.03
Non-cardiovascular hospitalizations (other)					
D69.8	Other specified hemorrhagic conditions	2	0	0	2
D82.8	Immunodeficiency associated with other specified major defects	2	0	0	2
E21.1	Secondary hyperparathyroidism, not elsewhere classified	2	2	1	5
E64.0	Sequelae of protein-energy malnutrition	4	0	0	4
E87.5	Hyperkaliemia	4	2	0	6
G40.9	Epilepsy, unspecified	1	0	0	1
H18.8	Other specified disorders of cornea	0	1	0	1
H40.2	Primary angle-closure glaucoma	0	1	0	1
H43.8	Other disorders of vitreous body	0	0	1	1
J44.9	Chronic obstructive pulmonary disease, unspecified	1	0	0	1
J96.9	Respiratory failure, unspecified	23	2	2	27
J98.4	Other disorders of lung	0	0	1	1
J98.9	Respiratory disorder, unspecified	2	0	0	2
K27.0	Peptic ulcer, site unspecified: acute with hemorrhage	6	0	1	7
K35.9	Acute appendicitis, unspecified	1	0	1	2
K36.-	Other appendicitis	0	1	0	1
K52.2	Allergic and dietetic gastroenteritis and colitis	2	5	0	7
K52.9	Noninfective gastroenteritis and colitis, unspecified	2	0	0	2
K56.6	Other and unspecified intestinal obstruction	1	0	0	1
K57.5	Diverticular disease of both small and large intestine without perforation or abscess	1	0	0	1
K57.9	Diverticular disease of intestine, part unspecified, without perforation or abscess	1	0	0	1
K62.3	Rectal prolapse	1	0	0	1
K63.1	Perforation of intestine (nontraumatic)	1	0	0	1
K63.8	Other specified diseases of intestine	1	0	0	1
K65.0	Acute peritonitis	2	0	0	2
K80.2	Calculus of gallbladder without cholecystitis	3	0	2	5
K80.3	Calculus of bile duct with cholangitis	2	0	0	2
K80.5	Calculus of bile duct without cholangitis or cholecystitis	1	0	0	1
K80.8	Other cholelithiasis	1	0	2	3
K81.1	Chronic cholecystitis	1	0	0	1
K82.9	Disease of gallbladder, unspecified	1	0	0	1
K83.0	Cholangitis	1	0	0	1
K83.9	Disease of biliary tract, unspecified	1	0	0	1
K85.-	Idiopathic acute pancreatitis	3	0	1	4
L89.-	Decubitus ulcer and pressure area	1	0	0	1
M16.1	Other primary coxarthrosis	1	0	0	1
N02.9	Recurrent and persistent hematuria: unspecified	3	0	0	3
N12.-	Tubulo-interstitial nephritis, not specified as acute or chronic	0	1	0	1
N28.1	Cyst of kidney, acquired	0	1	0	1
N40.-	Hyperplasia of prostate	2	0	0	2
T42.4	Poisoning: Benzodiazepines	0	1	0	1
T82.3	Mechanical complication of other vascular grafts	10	3	3	16
Y83.8	Other surgical procedures	0	3	3	6
Z04.8	Examination and observation for other specified reasons	3	1	0	4
	n	94	24	18	136
	Hospitalization/patient	0.2	0.1	0.1	0.2
Non-cardiovascular hospitalizations (total)					
	n	**207**	**61**	**46**	**314**
	Hospitalization/patient	**0.5**	**0.4**	**0.3**	**0.4**

Unknown causes of hospitalizations					
	n	98	35	29	162
	Hospitalization/patient	0.2	0.2	0.2	0.2

ICD: international statistical classification of diseases

Overall, mortality incidence was 17.4%. Comparing to the non-exercise group that had a 21.6% mortality incidence, there was a slight reduction in the low exercise group (19.0%), but a noticeable decrease in the high exercise group (6.4%). This trend of incident mortality reduction is observed for CV and for the unknown causes of death (Table 5.8.). For non-CV mortality, the reduction was observed only for the high exercise group. Kaplan-Meier analysis shows a significant different all-cause mortality risk between groups (log rank p<0.001) (Figure 5.2.). As described in Table 5.9., comparing to the non-exercise group, unadjusted analysis shows a non-significant difference in mortality risk for the low exercise group (HR=0.89, 95% CI 0.60-1.34, p=0.581), but a significant risk reduction for the high exercise group (HR=0.29, 95% CI 0.16-0.55, p<0.001). These results remained virtually unchanged in all the adjusted analysis with the full-adjusted model showing a similar mortality risk between the non-exercise and the low exercise groups (HR=1.12, 95% CI 0.74-1.68, p=0.602), but a significant risk reduction for the high exercise group (HR=0.38, 95% CI 0.20-0.72, p=0.003).

Table 5. 8. *Mortality incidence by causes and exercise dose group*

	Overall (n=741)	**No exercise (n=394)**	**<87min/week (n=174)**	**≥87min/week (n=173)**
Cardiovascular mortality, n (%)	48 (6.5)	33 (8.4)	11 (6.3)	4 (2.3)
Non-cardiovascular mortality, n (%)	46 (6.2)	28 (7.1)	13 (7.5)	5 (2.9)
Unknown cause mortality, n (%)	35 (4.7)	24 (6.1)	9 (5.2)	2 (1.2)
All-cause Mortality, n (%)	129 (17.4)	85 (21.6)	33 (19.0)	11 (6.4)

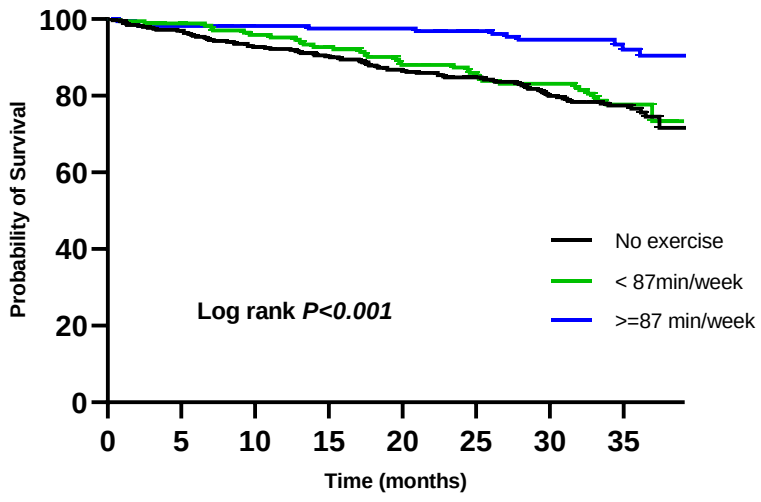


Figure 5. 2. *Kaplan-Meier analysis for differences in mortality risk between groups*

Table 5. 9. *Association of exercise dose categories with all-cause mortality*

	Aerobic exercise dose group, min/week		
	No exercise	**<87min/week**	**≥87min/week**
Model 1			
HR (95% CI)	Reference group	0.89 (0.60-1.34)	**0.29 (0.16-0.55)**
p value	---	0.581	**<0.001**
Model 2			
HR (95% CI)	Reference group	1.02 (0.68-1.53)	**0.32 (0.17-0.59)**
p value	---	0.920	**<0.001**
Model 3			
HR (95% CI)	Reference group	1.06 (0.70-1.61)	**0.34 (0.18-0.64)**
p value	---	0.770	**0.001**
Model 4			
HR (95% CI)	Reference group	1.11 (0.73-1.67)	**0.35 (0.19-0.66)**
p value	---	0.626	**0.001**
Model 5			
HR (95% CI)	Reference group	1.12 (0.74-1.68)	**0.38 (0.20-0.72)**
p value	---	0.602	**0.003**

HR: hazard ratio; CI: confidence interval. **Adjustment for confounders:** Model 1 – unadjusted analysis; Model 2 – age (years); Model 3 – model 2 + vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter), dialysis vintage (months); Model 4 – model 3 + age-adjusted Charlson Comorbidity Index, number of CV diseases; Model 5 – model 4 + lean tissue index (Kg/m^2) and overhydration relative to extracellular water (%). HR: hazard ratio; CI: confidence interval

Restricting the analysis to IDE participants and considering exercise dose as a continuous exposure variable (minutes/week), for each 50minutes/week increase, the mortality risk reduction was significant in the unadjusted model and in all the adjusted models (Table 5.10.).

Table 5. 10. *Association of exercise dose (min/week) with all-cause mortality*

	Per 50min/week increase
Model 1	
HR (95% CI)	**0.42 (0.25-0.69)**
p value	**0.001**
Model 2	
HR (95% CI)	**0.42 (0.25-0.69)**
p value	**0.001**
Model 3	
HR (95% CI)	**0.43 (0.26-0.72)**
p value	**0.001**
Model 4	
HR (95% CI)	**0.39 (0.23-0.66)**
p value	**0.001**
Model 5	
HR (95% CI)	**0.46 (0.27-0.79)**
p value	**0.005**

HR: hazard ratio; CI: confidence interval. **Adjustment for confounders:** Model 1 – unadjusted analysis; Model 2 – age (years); Model 3 – model 2 + vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter), dialysis vintage (months); Model 4 – model 3 + age-adjusted Charlson Comorbidity Index, number of CV diseases; Model 5 – model 4 + lean tissue index (Kg/m^2) and overhydration relative to extracellular water (%). HR: hazard ratio; CI: confidence interval

Overall, 42.9% of patients were hospitalized, summing 644 hospitalizations and 7859 hospitalization days. Hospitalization risk was investigated during a median follow-up of 25

months. Incidence of hospitalization was gradually decreased with increasing exercise doses, from 47.7% in the non-exercise group to 40.8% and 34.1% in the low and high exercise groups, respectively. Kaplan-Meier analysis have shown a significant different hospitalization risk between groups (log rank p=0.016) (Figure 5.3.). Unadjusted analysis demonstrates a non-significant hospitalization risk reduction for the low exercise group (HR=0.82, 95% CI 0.62-1.08, p=0.149), but a significant reduction for the high exercise group (HR=0.66, 95% CI 0.49-0.89, p=0.006). These results were sustained in all the adjusted models as shown in Table 5.11.

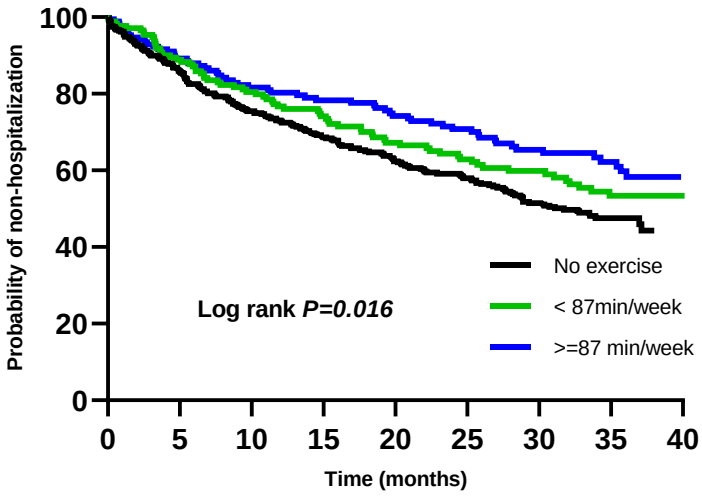


Figure 5. 3. *Kaplan-Meier analysis for differences in hospitalization risk between groups*

Table 5. 11. *Association of exercise dose categories with hospitalization*

	Aerobic exercise dose group, min/week		
	No exercise	**<87min/week**	**≥87min/week**
Model 1			
HR (95% CI)	Reference group	0.82 (0.62-1.08)	**0.66 (0.49-0.89)**
p value	---	0.149	**0.006**
Model 2			
HR (95% CI)	Reference group	0.86 (0.66-1.14)	**0.67 (0.50-0.90)**
p value	---	0.291	**0.008**
Model 3			
HR (95% CI)	Reference group	0.85 (0.64-1.12)	**0.68 (0.50-0.91)**
p value	---	0.244	**0.010**
Model 4			
HR (95% CI)	Reference group	0.90 (0.68-1.19)	**0.71 (0.53-0.96)**
p value	---	0.464	**0.024**
Model 5			
HR (95% CI)	Reference group	0.90 (0.68-1.19)	**0.73 (0.54-0.98)**
p value	---	0.459	**0.037**

HR: hazard ratio; CI: confidence interval. **Adjustment for confounders:** Model 1 – unadjusted analysis; Model 2 – age (years); Model 3 – model 2 + vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter), dialysis vintage (months); Model 4 – model 3 + age-adjusted Charlson Comorbidity Index, number of CV diseases; Model 5 – model 4 + lean tissue index (Kg/m^2) and overhydration relative to extracellular water (%).

Excluding the non-exercise group and looking for exercise dose as a continuous variable (minutes/week), increasing exercise dose in 50minutes/week had no significant changes in hospitalization risk, independently of the adjustment model (Table 5.12.).

Table 5. 12. *Association of exercise dose (min/week) with hospitalization*

	Per 50min/week increase
Model 1	
HR (95% CI)	0.86 (0.64-1.15)
p value	0.306
Model 2	
HR (95% CI)	0.84 (0.62-1.13)
p value	0.240
Model 3	
HR (95% CI)	0.86 (0.63-1.16)
p value	0.315
Model 4	
HR (95% CI)	0.85 (0.63-1.15)
p value	0.297
Model 5	
HR (95% CI)	0.89 (0.65-1.21)
p value	0.454

HR: hazard ratio; CI: confidence interval. **Adjustment for confounders:** Model 1 – unadjusted analysis; Model 2 – age (years); Model 3 – model 2 + vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter), dialysis vintage (months); Model 4 – model 3 + age-adjusted Charlson Comorbidity Index, number of CV diseases; Model 5 – model 4 + lean tissue index (Kg/m^2) and overhydration relative to extracellular water (%)

Number and days of hospitalization by group and causes are described in Table 5.13. Overall, during the entire follow-up period, number and days of hospitalizations/year was 0.6±1.5 and 6.7±20.9, respectively. Both gradually decreased with increasing exercise doses, but in the full-adjusted model, the difference was significant only between the non-exercise and the high exercise groups (Table 5.14 and Figure 5.4.).

Table 5. 13. *Number and days of hospitalization by causes and exercise dose group*

		Overall (n=741)	**No exercise (n=394)**	**Low exercise (n=174)**	**High exercise (n=173)**
Follow-up months, median (IQR)		33 (11)	33 (11)	33 (17)	33 (10)
No. of hosp.	**All-cause hospitalizations**	**644**	**399**	**131**	**114**
	Cardiovascular hospitalizations	168	94	35	39
	Non-cardiovascular hospitalizations	314	207	61	46
	Unknown cause hospitalizations	162	98	35	29
Mean hosp./patient	**All-cause hospitalizations**	**0.9**	**1.0**	**0.8**	**0.7**
	Cardiovascular hospitalizations	0.2	0.2	0.2	0.2
	Non-cardiovascular hospitalizations	0.4	0.5	0.4	0.3
	Unknown cause hospitalizations	0.2	0.2	0.2	0.2
Days of hosp.	**All-cause hospitalizations**	**7859**	**4720**	**1703**	**1436**
	Cardiovascular hospitalizations	2586	1373	553	660
	Non-cardiovascular hospitalizations	3247	2131	764	352
	Unknown cause hospitalizations	2026	1216	386	424
Mean days of hosp./patient	**All-cause hospitalizations**	**10.6**	**12.0**	**9.8**	**8.3**
	Cardiovascular hospitalizations	3.5	3.5	3.2	3.8
	Non-cardiovascular hospitalizations	4.4	5.4	4.4	2.0
	Unknown cause hospitalizations	2.7	3.1	2.2	2.5

IQR: interquartile range; No.: number; Hosp.: hospitalization

Table 5. 14. *Number and days of hospitalizations/year by exercise group*

		p (Covariance analysis)	Aerobic exercise dose group, min/week (Pairwise comparisons)		
			No exercise	<87min/week	≥87min/week
No. of Hospitalizations/year	**Mean±SD**	---	0.7±1.5	0.5±1.4	0.4±1.7
	Model 1	**0.002**	Reference	0.099	**0.001**
	Model 2	**0.010**	Reference	0.282	**0.002**
	Model 3	**0.015**	Reference	0.277	**0.004**
	Model 4	**0.022**	Reference	0.409	**0.006**
	Model 5	0.075	Reference	0.447	**0.023**
Days of Hospitalization/year	**Mean±SD**	---	7.4±20.1	6.5±23.2	5.2±20.1
	Model 1	**0.003**	Reference	0.071	**0.001**
	Model 2	**0.013**	Reference	0.220	**0.004**
	Model 3	**0.021**	Reference	0.200	**0.006**
	Model 4	**0.030**	Reference	0.293	**0.008**
	Model 5	0.088	Reference	0.309	**0.029**

SD: standard deviation. **Adjustment for confounders:** Model 1 – unadjusted analysis; Model 2 – age (years); Model 3 – model 2 + vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter), dialysis vintage (months); Model 4 – model 3 + age-adjusted Charlson Comorbidity Index, number of CV diseases; Model 5 – model 4 + lean tissue index (Kg/m^2) and overhydration relative to extracellular water (%)

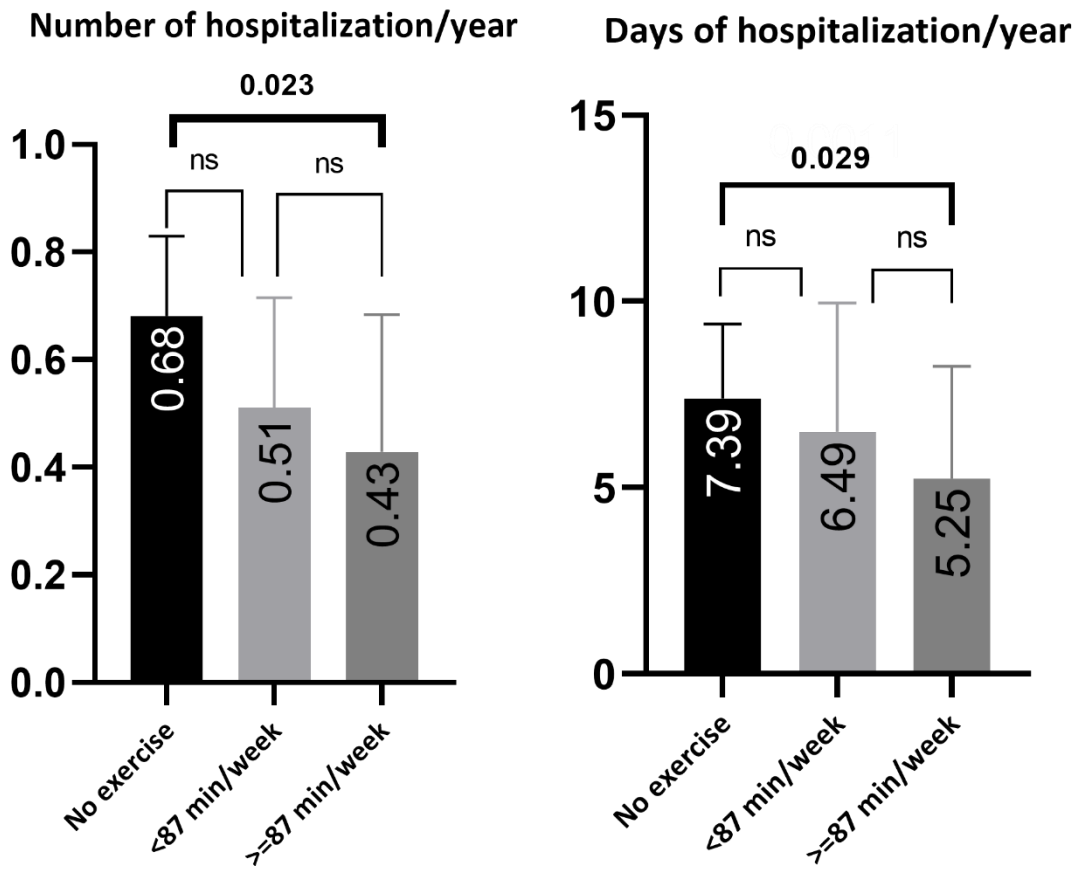


Figure 5. 4. *Full-adjusted comparison of number and days of hospitalization/year between groups*

Adjustment for confounders: Model 1 – unadjusted analysis; Model 2 – age (years); Model 3 – model 2 + vascular access (arteriovenous fistula, arteriovenous graft, central venous catheter), dialysis vintage (months); Model 4 – model 3 + age-adjusted Charlson Comorbidity Index, number of CV diseases; Model 5 – model 4 + lean tissue index (Kg/m^2) and overhydration relative to extracellular water (%)

5.5. Discussion

Results from this cohort study show that, above a considerable exercise dose, IDE is associated with better mortality and hospitalization outcomes in HD patients. This was demonstrated by a reduced mortality and hospitalization risk, and by a lower number of hospitalization events (hospitalizations/year), and duration of each hospitalization (days of hospitalization/year). However, these benefits were only significant for the group of patients exercising ≥87min/week. Compared to the non-exercise group, this group had a 62% and a 27% reduced mortality and hospitalization risk, respectively.

Compelling evidence demonstrates the health benefits of exercise in CKD patients, including improvements in chronic inflammation, cardiorespiratory function and muscle and bone strength (47). These benefits may explain the role of IDE to improve mortality and hospitalization in HD patients.

Immune dysfunction and chronic inflammation are key contributors for CV disease and infections, two major causes of mortality and hospitalization in CKD (280). Exercise-mediated alterations in circulating pro-inflammatory (e.g., IL-6 and tumor necrosis factor (TNF) and anti-inflammatory (e.g., IL-10) cytokines are well described in CKD patients (43). Several mechanisms could underlie the anti-inflammatory effect of exercise. An increase of the activity of the nuclear factor erythroid-2 related factor 2 (NRF2) pathway in peripheral blood mononuclear cells (PBMCs) that impedes nuclear-factor Kappa B signaling and subsequent pro-inflammatory cytokine synthesis (44); a reduced activation of monocytes (determined by HLA-DR expression) and T cells (determined by CD69 expression) (45); a reduction in the proportion of the pro-inflammatory intermediate monocyte subset and an increase in the number of regulatory T (T_{reg}) cells (46); and a reduced expression of chemokine receptor CCR5 by monocytes and T cells, that may reduce immune cell infiltration into adipose, cardiac, muscle and vasculature tissue sites (47). These mechanisms could explain the better outcomes observed in the high exercise group for CV and infectious-related mortality and hospitalization. Nevertheless, conclusions should be drawn carefully as there is no clear evidence that aerobic IDE improves inflammatory mediators and larger ES are attributed to vigorous intensity resistance IDE (unlike our exercise protocol) (43). Even so, a recent systematic review concluded that the low-quality evidence available suggests that aerobic and resistance IDE improves systemic inflammation biomarkers in HD patients (43).

More than 50% of dialysis patients have CV disease and CV mortality is much higher in HD patients than in the general population (48). LVH, a hallmark of uremic cardiomyopathy, is highly prevalent and is an independent risk of mortality in HD patients (129). Causes of LVH are multifactorial, including afterload (arterial stiffness), preload (volume overload), and non-hemodynamic factors (anemia). Evidence suggests that regular aerobic exercise may reduce arterial stiffness (49) in consequence of improved endothelial function and vasodilation, due to an increase in nitric oxide bioavailability (50). Resistance training may improve anemia by improving iron status and reducing ferritin and hepcidin (51). Although exercise does not reduce volume overload in HD patients, fluid status control is of such importance for the benefits of exercise to occur (47). In the CYCLE-HD trial, six months of IDE resulted in a clinically relevant reduction of left ventricular mass, tested by cardiac magnetic resonance imaging, that was

associated with a beneficial ventricular remodeling (52). As in our program, the CYCLE-HD intervention included three times a week progressive intradialytic cycling of moderate intensity. Due the similitude between this intervention and the exercise protocol of the present study, it is likely that the LVH benefits also have taken place in this study, contributing for the reduced CV mortality with increasing exercise doses. Another mechanism that may explain the improved survival with IDE is the potential to mitigate myocardial stunning during HD (281). Indeed, the stresses of HD and ultrafiltration acutely affect cardiac function, hemodynamics, and physiology, largely driven by the immediate effects on left ventricular loading (pre-load). Throughout an HD session, total circulation of blood volume and reciprocal filling of the left ventricle are reduced. This reduction in cardiac loading leads to a reduction in stroke volume. To maintain cardiac output, a physiological increase of heart rate occurs causing the shortening of diastole (period when coronary filling occurs), exposing myocardium to ischemia and consequent functional disturbance (89). Even in the absence of symptomatic episodes of intradialytic hypotension, myocardial stunning during HD, manifested as regional wall motion abnormalities (RWMA), is documented and associated with adverse outcomes (130). Despite the underlying mechanisms are not completely understood, two previous exploratory studies demonstrated that IDE may be acutely cardioprotective, reducing RWMA (127, 128). Both studies compared RWMA occurrence in a HD session with and another HD session without intradialytic cycling. In both studies, IDE was performed in the first half of the HD treatment. The duration was 30 minutes in McGuire et al. study (127) and 30-60 minutes in Penny et al. study (128). Given the similarity between these interventions with our exercise protocol, there may have been a RWMA reduction that reduced CV mortality with higher IDE doses.

HD patients have an increased cancer-related mortality risk (282). Epidemiologic research has identified the role of PA to prevent and improve survival for several cancers (283). Regular exercise increases the elimination of immunogenic cancer cells, leading to the containment of cancers in a "precancerous" equilibrium state, thus reducing the incidence of clinically diagnosed cancers (131). This could in part explain why, unlike the non- and the low exercise groups, there is no cancer-related deaths in the high exercise group.

Hospitalizations/patient due to trauma and fractures were similar among the non and the low exercise groups, while there were markedly less events in the high exercise group. Disturbances in mineral and bone metabolism are highly prevalent in CKD and are an important cause of morbidity, decreased quality of life, and extra skeletal calcification that are also associated with CV mortality (37). Previous evidence shows that exercise may improve bone health in CKD (219) by reducing sclerostin and FGF-23 and by increasing klotho release from bone (47). Nevertheless, this explanation has low plausibility since the exercise protocol used in the present study may not provide the optimal osteogenic stimulus (e.g., impact loading exercises as jumps and progressive resistance exercise training) (47). Moreover, despite the existing evidence that IDE may improve phosphate removal during HD (77), this is not an explanation for our findings since this benefit was not confirmed in our data as analyzed in Chapter 4, Section 4.4. On the other hand, a reduction of falls may explain the lower fracture-related hospitalization and this explanation is reinforced by the improvement in static and dynamic balance observed during the first year as described in Chapter 4, Section 4.4.

Sarcopenia and its traits (low muscle strength, low muscle mass and low physical performance) are highly prevalent and are associated with poor health outcomes in HD patients (53). Etiologic mechanisms leading to muscle loss in CKD are diverse and are related to kidney disease itself, the dialysis procedure and chronic low-grade inflammation. These factors act together increasing protein degradation and decreasing protein synthesis, leading to a negative protein balance (54). Previous evidence demonstrated the benefits of exercise on sarcopenia traits in CKD patients (55). This was also observed in the present study as demonstrated by the improvements in muscle strength, muscle mass and physical performance after 1 year (Chapter 4, Section 4.4.) and could have contributed for the observed benefits on mortality and hospitalization.

Overall, it was observed that the benefits of IDE on mortality and hospitalization were dose dependent. In the general population, numerous high-quality observational studies have shown that increasing PA is associated with a mortality risk reduction in a dose-response fashion (284). The WHO recommendation of 150 minutes of moderate-intensity weekly exercise (285) appeared to be based on the minimal amount required to reduce the all-cause mortality rate. However, exercise dose and mortality relationship does not demonstrate a meaningful inflection point at this specific exercise dose. In fact, the largest risk reduction (20%) occurs with 90min/week (284). In our study, this evidence is also confirmed for the HD population, with the high exercise group achieving about 110±16 min/week (below the WHO PA recommendation) but having a significant mortality risk reduction. However, a non-significant association was found for the low exercise group who performed about 63±19 min/week. Previous findings suggest that this amount may be insufficient to reduce mortality in the general population (284) and our findings suggest the same for HD patients.

Observational studies demonstrate the association of PA with better survival in ESKD patients (63) (Chapter 3). Nevertheless, studies showing the benefit of exercise interventions on such important outcomes as mortality and hospitalization are lacking. The EXCITE trial has shown a reduction in hospitalization during a six-month intervention period (237) and a long-term reduction in a composite endpoint combining mortality and hospitalization (286). The latter also demonstrated a dose-response relationship with significant results observed only in a higher exercise dose group, as was observed in the present study. However, the EXCITE trial is a very different exercise protocol consisting of a home-based, low intensity walking exercise with a lower exercise dose (20min, three days/week), limiting comparisons with this study. To the author´s knowledge, five previous studies analyzed the impact of IDE on mortality or hospitalizations (98, 134-137). Like the present study, the PEDAL trial (134) was designed to test a pragmatic, clinically implementable IDE intervention that consisted of aerobic exercise (cycling), three times per week, during the first two hours of HD. Twice per week, participants also performed lower extremity resistance exercises. However, the number of hospitalizations and CV mortality was not noticeable different between the intervention and the control group. Possible explanations are the short observation period (six months), the low compliance to the exercise sessions (only 47%) and the sample size not powered to detect differences for the secondary outcomes of mortality and hospitalization (n=243). A RCT found that 60 minutes thrice weekly IDE (aerobic exercises in the form of repetitive specified movements and strength exercises performed with body weight, cuffs, dumbbells and elastic bands), with an high adherence (81%±6%), improves survival of HD patients (135). However, these findings are

limited by a low sample size (n=74) and a short observation period (1 year) with a low occurrence of events (n=11) that led to an imprecise effect estimation. The DIATT trial (136), an IDE large multicentric RCT (n=917), found no improvement in mortality risk, but a significant reduction in the number of hospitalizations/patient (p=0.024) and in hospitalization days/patient (p=0.036). However, the follow-up lasted only 12 months during which exercise was interrupted between 11 to 32 weeks due the COVID outbreak. Furthermore, the low mortality rate (8%), probably caused by the short follow-up, may have limited survival analysis. Parker et al. (137) assessed the effect of a six-month intradialytic cycling program on hospital admissions and length of stay. This was a retrospective cohort study including 102 participants that compared the six months prior to and the six months during the IDE intervention. There was a non-significant reduction in hospitalization rate, but a significant reduction in hospital length of stay. However, the exercise dose was low (4.5 sessions/month), and the large proportion of incident patients (26%) puts into question if the reduction in hospitalization seen during the six months of IDE may have been due to HD stability rather than a true benefit of exercise. Moreover, the absence of a control group limits the interpretation of these findings. Hospitalization data was also analyzed in a cost-effectiveness analysis of the CYCLE-HD trial (98). During the six-months of the intervention and in the six-months post-intervention, the IDE group had a more pronounced reduction in hospital admissions and hospital duration of stay. However, the scope of the study was not to compare hospitalization between groups and results were presented only from an economic point of view.

Accordingly, this is the first pragmatic and multicentric study, with a large sample size, and long intervention and observation periods demonstrating the association of IDE on both mortality and hospitalization. Yet, this analysis shows that, for these benefits to occur, many patients may need additional support as a considerable exercise dose is needed.

Strengths and limitations

This is a study with high external validity as it is based on a large nation-wide IDE program implemented as part of routine practice with the existing dialysis staff. Moreover, the long intervention period (one year) allows for a long-term, real-world understanding of IDE participation. Nevertheless, 1008 patients were non-eligible (44.2%) making our sample a subset of healthier HD patients. This puts into question if our results are totally generalizable to a more fragile and at-risk HD population.

Residual confounding is an issue in examining the association between lifestyle factors and health outcomes. Reverse causality could have occurred as patients who are more likely to participate in IDE, may also adopt a healthier lifestyle (e.g., compliance with medication and nutritional recommendations), that may also reduce mortality and hospitalization. However, the results were consistent after multivariable adjustment for a broad range of relevant confounders. Given the strength of the associations observed (specially for mortality), it is unlikely that residual confounding would negate our results. Furthermore, the mortality results were sustained even when the non-exercise group was excluded from the analysis and the exercise dose was considered as a continuous variable. Moreover, while the unhealthier status

of the non-exercise group could predict worst health outcomes, the similitude between the low and the high exercise groups, would predict similar outcomes. Nonetheless, the high exercise group had better survival and hospitalization outcomes, which suggests a dose-dependent association of exercise with hard endpoints in HD patients.

Because the exposure measure was restricted to the exercise performed during dialysis, we have no data of the overall PA performed during the intervention period. Nevertheless, due the inactivity of this population, it is not expected that PA or any type of exercise at all performed outside HD could have biased our findings. Moreover, resistance exercise was not considered as an exposure variable. Considering its importance in HD patients, this is a limitation of the present study.

A dose-response relationship is important in public health. However, our sample size precluded the formation of more exercise dose groups, which limited a more detailed dose-response analysis.

The number of events without a defined cause for mortality (27%) and hospitalization (25%) precluded a reliable specific analysis for CV and non-CV causes. Moreover, this separate analysis would limit the adjustment models to follow the recommendation of 10 events per confounder (287). For this reason, the analysis of specific CV and non-CV causes was made only looking for descriptive data.

Implications for practice and research

Taken together, our data demonstrates that IDE may improve hard clinical endpoints in HD patients, however a substantial exercise volume is required, and many patients may not achieve it only with IDE. Typically, exercise prescriptions for HD patients have been restricted to IDE, failing to incorporate all the basic exercise principles (i.e., frequency, intensity, time, type, volume, and progression) (288) and to meet the PA volume recommended by the UKKA (3). These limitations may explain why exercise is still not part of the standard care in HD units (236). Moreover, a rigorous acknowledgement of the dose should be addressed in exercise prescriptions for HD patients. Thus, developing strategies for increasing the volume and intensity of exercise must be an important priority if we hope to significantly improve the efficacy of exercise interventions (236). In complement to IDE, alternative and more personalized interventions have been proposed, including PA as a component of a comprehensive behavior change intervention (236). Future research should test this type of approach and compare it with this stand-alone IDE intervention. A more detailed dose-response analysis would also allow the investigation of the minimal exercise amount needed to improve hard endpoints in this at-risk population.

5.6. Conclusion

This study shows that IDE, when performed above a certain exercise dose, is associated with better mortality and hospitalization outcomes in HD patients. Nevertheless, this may not be achieved by a substantial proportion of patients due to their deconditioning and low motivation levels. Therefore, IDE requires strategies to increase patients´ acceptance and adherence and should be complemented by other alternative exercise interventions that may include online exercise classes. This intervention may combine the advantages of a home-based intervention (highly convenient and desired by HD patients) (65) and the advantages of a interdialytic intervention (supervised higher intensity exercise with superior cardiovascular adaptations) (71). However, so far, there is no evidence on the implementation and effectiveness of this interventions in HD patients. During the COVID-19 pandemic, this IDE program was suspended, and an alternative online intervention was rapidly adopted. Despite all the constraints of the pandemic, this was a unique opportunity to test this approach. Depending on the results, its relevance beyond the pandemic could be considered to fulfill the need to increase the exercise dose of the current stand-alone IDE intervention. Therefore, an implementation study was performed also for the online exercise intervention that is presented in the next chapter.

Chapter 6: Video conferencing telehealth exercise intervention: a controlled nation-wide effectiveness-implementation study

6.1. Abstract

Background: COVID-19 pandemic was particularly distressing for HD patients further aggravating their inactivity (Chapter 1, Section 1.2.). Moreover, most HD units suspended their IDE programs. Thus, urgent and innovative methods to increase PA, while allowing for social distancing were needed. Videoconferencing telehealth exercise (VCTE) may combine advantages of inter-dialytic exercise (supervision and higher exercise intensity) and IDE (higher convenience). However, VCTE interventions may face additional challenges in HD patients: risk of adverse events (e.g., falls), and low proficiency, and motivation to use mobile health technology. Therefore, implementation studies are needed to analyze how realistic this novel intervention could be for this population. Thus, the aim of this study is to evaluate a nation-wide implementation of a VCTE intervention hereinafter referred to as PEF_OnLine, settled during the pandemic to substitute IDE. This present chapter simultaneously examines the implementation outcomes and its effectiveness on safety, physical function, body composition, sleep quality, depressive symptoms, and fatigue.

Design, setting, participants and measurements: This is a hybrid type II implementation study examining the implementation and effectiveness of a 12-week VCTE intervention. A retrospective analysis using the RE-AIM framework (Reach, Effectiveness, Adoption, Implementation and Maintenance) was performed (previously described in Chapter 2, Section 2.1.). Effectiveness outcomes were analyzed comparing a group of PEF_OnLine participants with a group of patients who refused the intervention. Safety was analyzed based on the report of adverse events during the exercise sessions. Physical function measures included STS 30, handgrip strength, 8-foot UG, STS 5 and SLS. Body composition was determined by multifrequency bioimpedance using the BCM (Fresenius Medical Care, Bad Homburg, Germany). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI) (Appendix 3). The Center of Epidemiologic Studies Depression Scale (CES-D) was used to investigate depressive symptoms and the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-F) was used to assess fatigue (Appendix 4 and 5, respectively).

Results: *Adoption:* Of all the HD units invited, 66.7% adopted PEF_OnLine (n=16). *Reach:* 2063 patients were assessed for eligibility and 313 (15.2%) were eligible. Of those, 229 (73.2%) refused and 84 (26.8%) accepted the intervention. Thus, the intervention reached 4.1% of the population. *Maintenance:* all HD units continued the intervention, but 40.5% of the patients dropped out, mainly due to voluntary withdrawal (65%). *Implementation*: adherence (%) was 73.1±18.8. Mean number of exercise sessions/patient was 26.3±6.8 and of exercise sessions/week was 2.2±0.6. *Effectiveness:* rare minor adverse events occurred, without severe consequences for patients. Comparing baseline to 12 weeks, the PEF_Online group (n=50) significantly improved STS 30 ($p<0.001$), handgrip strength ($p=0.003$), STS 5 ($p=0.008$), and SLS ($p=0.044$), but not the 8-foot UG test ($p=0.640$), while the non-exercise group (n=131) had no significant differences in any of the physical function tests. Variations in STS 30 ($p<0.001$) and in STS 5 ($p<0.001$) were significantly different between groups, favoring PEF_OnLine. Patients with depressive symptoms increased in the non-exercise group (22.1% to 26.7%), while an important reduction was observed in the PEF_OnLine group (36.0% to 16.0%). There was a non-significant variation of depressive symptoms in the non-exercise group ($p=0.522$), but a marginally significant reduction in the PEF_OnLine group ($p=0.071$). Nevertheless, after adjusting for the

baseline values, the comparison between the variations was not statistically significant (p=0.138). Both groups significantly improved fatigue (p<0.001), but a higher improvement was observed in the PEF_OnLine group (5.2±6.0 vs. 3.3±7.6), resulting in a marginally significant difference between groups (p=0.070). Moreover, there was an important reduction of patients with fatigue in the PEF_Online group (from 44% to 26%), and at a lesser extent in the non-exercise group (from 31.3% to 26%). No significant differences were found for body composition and for sleep quality.

Conclusion: A VCTE intervention was feasible even during the COVID-19 pandemic context. The intervention was safe and improved physical function, depressive symptoms, and fatigue, and its application should be considered beyond the pandemic as a complement to IDE. Nevertheless, implementation outcomes were somehow limited and should be improved in future VCTE interventions, specifically increasing patients' eligibility (by promoting proficiency and motivation to use mobile health technology) and reducing refusals and voluntary withdrawals.

Keywords: CKD; COVID; PA; telehealth.

6.2. Background

COVID-19 pandemic was particularly distressing for HD patients (Chapter 1, Section 1.2.). As a lifesaving treatment, HD treatments could not be suspended, making physical distancing measures impossible, not only during the treatment, but also during shared transportation to and from HD units. Thus, HD patients had a high infection rate (152), and CKD was a strong predictor for severe COVID disease and death (153-155). Moreover, COVID-19 further exacerbated CV disease (156), hospitalization risk (157), with a high prevalence of long-COVID symptoms (158). Not surprisingly, anxiety and depression were further aggravated during the pandemic (160-162) with negative impacts on health-related quality of life as well (289).

The pandemic caused a reduction in global PA (163), that was also observed in HD patients and had a further impact on their physical function (166, 289). Moreover, most HD units suspended their IDE programs (typical form of exercise for HD patients (288)) to accommodate an unprecedent pressure on HD units that had to rapidly adopt extraordinary infection control procedures to safeguard patients and staff while still supporting continuation of dialysis services (167). Thus, considering the association of poor physical function with the mortality of dialysis patients (53), urgent and innovative methods to increase PA while allowing for social distancing, were needed for HD patients during the COVID-19 pandemic.

Internet has long been used to deliver public health interventions across a wide range of conditions and population segments (290). Digital based PA promotion was recommended to safely counteract the lockdown-induced inactivity in healthy subjects and in patients with chronic diseases (291). Telehealth exercise interventions (counseling or exercise programs) may be delivered via phone, video conferencing, web-based or smartphone applications (292). Advantages of this type of interventions include reducing financial costs (e.g., savings in commuting expenses and equipment), and increasing accessibility for a wider range of populations (e.g., remote places, unfavorable climate conditions, people with social restrictions or certain medical conditions) (293). Availability and popularity of video conferencing platforms (e.g., Zoom® and MS Teams®) rapidly increased during the COVID pandemic. This approach has the additional benefit of specialized remote, real-time supervision by an exercise professional, as well as gathering patients in small-sized groups. VCTE interventions seem to be a promising strategy to be implemented for HD patients as 1) home is their preferred location to exercise (65); 2) have no infection risk; and 3) is time flexible in a population where time constraints is a barrier to exercise (66). Thus, VCTE could combine advantages of inter-dialytic exercise (higher exercise intensity and potential to undertake a greater range of exercises) and IDE (higher convenience) (71). Moreover, being a supervised exercise intervention, it may have a more pronounced effectiveness than the traditional home-based exercise programs (176). Therefore, its applicability may subsist beyond the pandemic and be used to complement IDE, insufficient to fulfill the current PA recommendations for HD patients (3) (Chapter 4, Section 4.4.), and to increase accessibility to out-of-dialysis supervised exercise interventions. However, despite its potential, VCTE programs may face special challenges in HD patients. From a safety perspective, the absence of an in-person exercise professional could limit the prevention of adverse events such as falls, that may have dramatic consequences in this population (294). Moreover, readiness, proficiency, and motivation to use mobile health technology could be an implementation barrier, especially for older HD patients (177). Therefore, implementation

studies are needed to analyze how realistic this novel intervention could be for HD patients. The aim of the study presented in this chapter is to evaluate a nation-wide implementation of a VCTE intervention (i.e., PEF_OnLine) implemented during the pandemic as an alternative to IDE. We examined implementation outcomes and its effectiveness on safety, physical function, body composition, sleep quality, depressive symptoms and fatigue.

6.2. Methods

This study follows the recommendation of the Standards for Reporting Implementation Studies statements (226). Checklists are available in Appendix 6. This study was approved by the NephroCare Portugal Ethics Committee (Chapter 2, Section 2.1.).

Study design

This is a hybrid type II implementation study testing both the effects on health outcomes and on PEF_OnLine use (225). This study design is used when there is an "implementation momentum" within a clinical setting, but the intervention effectiveness is somewhat unknown. Thus, both the impact of the implementation strategy on intervention usage and the impact on health status are the dual focus of a hybrid type II design (225).

As it was performed for IDE (Chapter 4), the PEF_OnLine implementation was examined using the RE-AIM framework. The intervention lasted 12 weeks (March to June 2021) during which all the RE-AIM dimensions were analyzed. Safety data was taken in every exercise session. Assessments for the other effectiveness outcomes (physical function, body composition, sleep quality, depressive symptoms, and fatigue) were taken at baseline and immediately after the intervention period. PEF_OnLine participants (exercise group) was compared with a non-exercise group of patients who were eligible but refused the intervention.

Context

Immediately after the first COVID pandemic outbreak in Portugal (March 2020), the IDE program previously described in Chapter 4, was suspended. Thus, during the critical lockdown periods with consequently exacerbated inactivity, vulnerable HD patients were not able to continue performing their most typical form of exercise. As such, there was a need to rapidly adapt the implemented exercise intervention to the new pandemic context. Using the unique resources of six MSc level exercise physiology students, the previously mentioned PEF_Online was developed as a VCTE intervention which was run using the Zoom platform (Zoom Video Communications). This team was in close collaboration with the existing IDE staff (national and local coordinators) that were still working in-person at their HD units.

During the intervention period, Portugal moved from a state of emergency with a strict lockdown at the intervention beginning (March 22), to less stringent measures (reopening of schools and restaurants) on April 30th (295).

Targeted sites and participants

All HD units included in the IDE program were invited to join the PEF_Online. Inclusion and exclusion criteria were the same for IDE (Chapter 4, Section 4.3.), but the following inclusion criteria were also added: 1) internet access at home; 2) device with a functioning camera

(smartphone, tablet, personal computer); and 3) patient or supportive relative with basic digital skills (including access to e-mail).

Those who refused the intervention were invited to join the non-exercise group only performing the assessment measures at baseline and at 12 weeks.

Description of the implementation strategy

Just after the first COVID-19 lockdown, starting on the 13th of March 2020 in Portugal, the IDE program (presented in Chapter 4) was suspended in all HD units. At that time, four MSc level Exercise and Health students (University of Maia, Portugal) were performing their internships in three different HD units. To continue their academic activities and to deliver an alternative to the suspended IDE program, these students implemented a first VCTE intervention in 11 patients. The following academic year, a new group of six students initiated a new internship, who then worked on the effective implementation of the PEF_Online VCTE program at a nationwide level.

Using the network previously established for the IDE (national and local coordinators – see Chapter 2, Section 2.1.), all NephroCare Portugal units with IDE received a formal invitation with a brief description of this new intervention. Decision to integrate PEF_OnLine was made by consensus of the medical and nurse directors of each dialysis unit.

In those clinics where the PEF_Online was adopted, an extensive description of this intervention was then provided by the national IDE coordinator, before subsequently starting the recruitment strategy, considering the defined eligibility criteria.

Patients were first approached during HD by the local coordinators to explain the importance of PEF_OnLine as an alternative to IDE. Then, the national IDE coordinator in collaboration with the MSc students who took part in this project, phone-called all the eligible patients to describe the intervention further thoroughly. At this point, the patients' preferred exercise schedule was taken into consideration before any final allocation to the exercise groups. The invitation to join the program was also extended to interested family members. Those who refused the intervention were still requested to complete the physical function assessments at baseline and 12 weeks later, but withdrawal was permitted.

Having the list of participants with their preferences, nine different time schedules were made with a maximum of eight patients in each. The final time schedule was confirmed with every participant before starting the program.

During the HD treatments, local IDE coordinators instructed every participant on how to get access to all Zoom® sessions, and on how to make their camera and the microphone available.

A first exercise session was completed with each participant as a familiarization to avoid any technological issues and to set with the participant the best location and camera position during the exercise session. Participants were instructed to use the same device and location throughout the intervention.

The day before each exercise session, the participants received a reminding email with the equipment needed for the following session.

With the actual start of the intervention, a weekly update regarding adherence, adverse events and dropouts was sent to the respective local coordinators, and medical and nursing directors.

Methods and techniques used in this implementation strategy are described in Table 6.1. and were based on the Proctor et al. framework (179).

Table 6. 1. *Methods and techniques used in the PEF_OnLine implementation strategy*

	Pilot experience	**1st phone call**	**Zoom training**	**Weekly feedback to dialysis staff**
Actors	Research team	Research team	Dialysis staff	Research team and dialysis staff
Actions	Pre-implementation in a small group of patients	Phone call to describe the intervention and to ask what the patient´s preferred schedule	Previous Zoom training sessions with every patient	Weekly report of patient's participation
Targets	Address implementation challenges and safety	Assess patient´s interest and preferred schedules	Teach patients how to use Zoom	Involve dialysis staff to motivate patients
Temporality dose	Pre-implementation	Pre-implementation	Pre-implementation During dialysis Repeated as needed	During implementation
Implementation outcomes affected	Reach, Effectiveness, Adoption, Implementation, Maintenance	Reach	Reach	Maintenance
Justification	Adaptation of our IDE to the 1st COVID lockdown	Motivate patients to join PEF_OnLine Try to have all the preferred schedules	Increase readiness, proficiency, and motivation to use Zoom	Work in close collaboration with the dialysis staff to increase patient´s motivation

IDE: intradialytic exercise;

Description of the intervention

PEF_OnLine was an online and live exercise program via Zoom (Zoom Video Communications). This application was chosen due to its suitability to the intended audience: user-friendly interface, no need for participants to pre-install it on their devices, no need for preregistration.

Every exercise session included two exercise physiologists (MSc students). One was leading the session and was synchronously performing the exercises with patients. The second was the assistant, assuming technological issues and supporting the patients to execute the exercises correctly. All exercise sessions were also remotely supervised by a dialysis nurse.

The intervention was 12 weeks long and was performed three times per week on non-HD days. Each session lasted about 45 min. Three different sessions were designed using the same training principles, but with some variations in the exercises performed (Table 6.3.). Ankle weights were provided to patients from the HD units' inventory. Other equipment such as chairs,

cushions, water bottles, milk cartons, food packages, backpacks, books, pillows were proposed and used as easily available home essentials.

Exercise intensity was monitored by rate of perceived exertion using the OMNI Resistance Exercise Scale (OMNI-RES) (0-10) (296). Target intensity was 6 (somewhat hard) to 8 (hard). The first week was used as a familiarization, and exercises were performed without any external load. OMNI-RES was applied at week two and every four weeks since then. If the OMNI-RES score <6, the patient would be advised to increase the load, and the opposite would be done when the OMNI-RES score >8. Additionally, adaptations to certain exercises were proposed when needed to respond to any individual requirements/incapacities (e.g., adapted squat: chair STS) and progressions (e.g., squat without chair support and using a backpack for extra weight).

A brief screening protocol was applied before each exercise session to check for exercise contraindications (Table 6.2).

Table 6. 2. *Pre-screening protocol applied in all sessions*

Question 1	Do you have fever, cough, or shortness of breath?
Question 2	Do you have nausea, palpitations, or cramps?
Question 3	Do you feel pain in your chest, neck, or left arm?
Question 4 *(for diabetics)*	What is your blood glucose now? *If <100 or >300, the patient was advised not to perform the exercise session* Do you feel weakness or uncommon sweeting?

Table 6. 3. *PEF_OnLine Exercise protocol*

Session A	Warm-up	**Joint mobility exercises:** spine twist, shoulder rotation, head rotation, inverted pointer, cat and cow, scapular protraction, and retraction **Aerobic exercises (2 sets, 20´´ on/30´´off):** low skipping, jumping jacks, jabs, adapted mountain climbers
	Main part	**1st circuit (2 sets, 12 reps, 1´off):** squat (with or without chair support), wall push up, heel raises **2nd circuit (2 sets, 12 reps, 1´off):** seated row, biceps curl, leg abduction (with chair support)
	Cool-down	**Stretching exercises:** lumbar stretch, latissimus dorsi dynamic stretch, posterior chain stretch, piriformis stretch, glute stretch, quadriceps stretch, deep breaths
Session B	Warm-up	**Joint mobility exercises:** spine twist, shoulder rotation, head rotation, inverted pointer, cat and cow, scapular protraction, and retraction **Aerobic exercises (2 sets, 20´´ on/30´´off):** low skipping, jumping jacks, jabs, adapted mountain climbers
	Main part	**1st circuit (2 sets, 12 reps, 1´off):** shoulder press, static lounges, chest press **2nd circuit (2 sets, 12 reps, 1´off):** hip elevation, back arm elevation (flies), triceps extension (French triceps)
	Cool-down	**Stretching exercises:** lumbar stretch, latissimus dorsi dynamic stretch, posterior chain stretch, piriformis stretch, glute stretch, quadriceps stretch, deep breaths
Session C	Warm-up	**Joint mobility exercises:** spine twist, shoulder rotation, head rotation, inverted pointer, cat and cow, scapular protraction, and retraction **Aerobic exercises (2 sets, 20´´ on/30´´off):** low skipping, jumping jacks, jabs, adapted mountain climbers
	Main part	**1st circuit (2 sets, 12 reps, 1´off):** sit to stand, unilateral row, sumo squat (with or without chair support), **2nd circuit (2 sets, 12 reps, 1´off):** arms front raise, knee extension, arms lateral raise
	Cool-down	**Stretching exercises:** lumbar stretch, latissimus dorsi dynamic stretch, posterior chain stretch, piriformis stretch, glute stretch, quadriceps stretch, deep breaths

Implementation and Effectiveness Outcomes

Similar to what was done for IDE (Chapter 4, Section 4.3.), the RE-AIM framework was adapted to PEF_OnLine, following this sequence: adoption, reach, maintenance, implementation and effectiveness (Table 6.4.).

Table 6. 4. *PEF_OnLine implementation and effectiveness outcomes (RE-AIM dimensions)*

Dimension	Measures
Adoption	Proportion of HD units who accepted PEF_OnLine
Reach	Number and proportion of eligible patients, participants and patients who refused the intervention Comparison of refusals with PEF_OnLIne participants
Maintenance (setting level)	Proportion of HD units who continued the intervention
Maintenance (patient level)	Attrition rate with reasons Timing of voluntary withdrawal Comparison of voluntary withdrawals with completers
Implementation (fidelity)[1]	Adherence (%): performed exercise sessions among the total number of available exercise sessions, number and proportion of fully, partially and non-performed exercise sessions Implementation fidelity outcomes in patients also performing IDE
Implementation (dose)[1]	Mean number of exercise sessions/patient and exercise sessions/week Implementation dose outcomes in patients also performing IDE
Effectiveness[1]	Safety, physical function, body composition, sleep quality, depressive symptoms, fatigue

HD: hemodialysis; IDE: intradialytic exercise

Safety was studied based on the incidence of adverse events that may be associated with the exercise sessions. All other effectiveness measures (physical function, body composition, sleep quality, depressive symptoms, and fatigue) were taken at baseline and at 12 weeks.

Physical function measures included the isometric handgrip strength measured by handheld dynamometry and STS 30, STS 5, 8-foot UG, and SLS (previously explained in Chapter 2, Section 2.1.). Body composition was determined by multifrequency bioimpedance using the BCM (Fresenius Medical Care, Bad Homburg, Germany). This method was also already described in Chapter 2, Section 2.1.

Sleep quality was measured using the PSQI, the most commonly used in CKD patients (297). This instrument takes 5-10 min to be answered and includes 19 questions yielding seven components: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medications and daytime dysfunction. Each component is scored from 0 to 3, making a global score from 0 to 21. Higher scores are indicative of poor sleep quality and scores ≥6 is indicative of clinically significant poor sleep quality. The portuguese version demonstrated to be a valid and reliable instrument (298).

The CES-D is one of the most used questionnaires to measure depressive symptoms in CKD and ESKD patients (299). CES-D has good psychometric properties comparing with the gold standard "structured clinical interview for depression" (300). It was validated to the portuguese population (301) and includes a 20-item Likert scale, in which each item is given a scale of four

points corresponding to the frequency of depressive symptoms during the last week. The total score ranges from 0 to 60 with higher scores indicating worst depressive symptoms (302). The cut-off used was 18 as already proposed for HD patients. (300).

Fatigue was measured using the FACIT-F scale that measures fatigue and its impact on daily activities and function. It was initially developed for cancer patients, but it is also a reliable and valid measure in other clinical populations including CKD (303, 304). It includes 13 questions with a 5-point Likert scale (0 = "not at all" to 4 = "very much") based on a 7-day recall period. The total score ranges from 0 to 52, with higher scores meaning lower fatigue levels. Fatigue was considered if the FACIT-F score is <36, a cut-off previously proposed for breast cancer patients (305). This instrument has good face validity to access anemia-related fatigue, a common condition in HD patients (306). The Portuguese version was used (available at www.facit.org).

Data collection and analysis

The exercise physiologists who lead the exercise sessions were instructed on how to use a logbook to record the data of interest from all the exercise sessions, including attendance, adverse events, withdrawals and technological issues. Patient descriptive and clinical data was extracted from the EuCliD (227).

Descriptive data is presented as mean values and SD (mean±SD). All data was checked for normality using Kolmogorov-Smirnov test. If non-normally distributed, a logarithmic transformation to base 10 was performed, and normality was rechecked. Comparison between groups at baseline (refusals vs. PEF_OnLine participants, voluntary withdrawals vs. PEF_OnLine completers, non-exercise vs. PEF_OnLine) was performed using Mann-Whitney U test (non-normally distributed variables) and independent samples t-test (normally distributed variables). Chi-squared test was used for categorical variables.

Differences from baseline to 12 weeks in each group were analyzed using the Wilcoxon Signed Rank test (non-normally distributed variables) or with paired samples t-test (normally distributed variables). Variations from baseline to 12 weeks were computed. Normally distributed variations were compared using independent samples t-test (unadjusted analysis) and ANCOVA (adjusted for baseline values). Non-normally distributed variations were compared using Mann-Whitney U test (unadjusted analysis) and Quade´s ANCOVA (adjusted for baseline values). ES were calculated by hand, dividing the difference between the means of the groups by the pooled SD (228). Statistical significance was accepted at $p<0.05$.

6.3. Results

RE-AIM dimension: Adoption

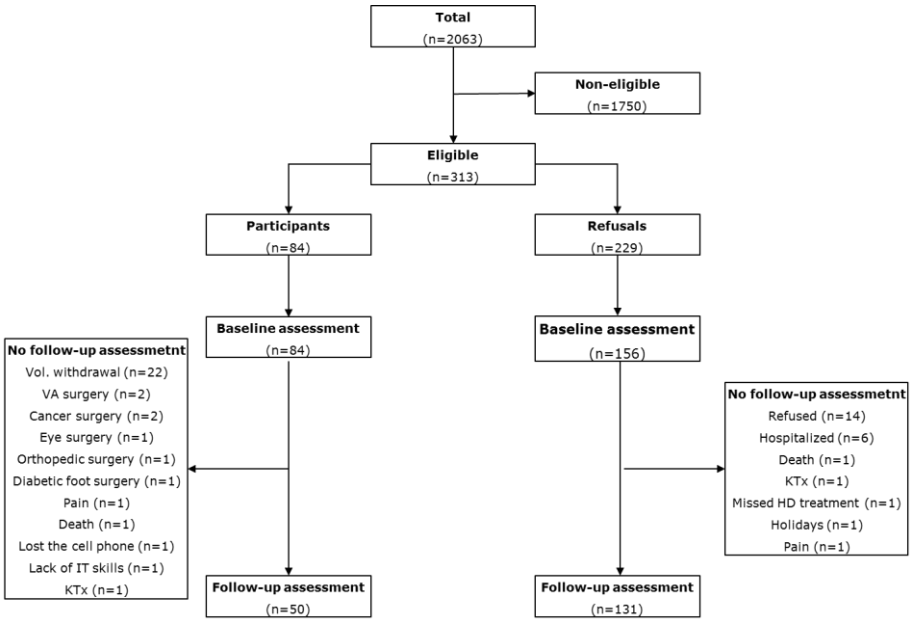
Proportion of HD units who accepted PEF_OnLine

All the HD units participating in the IDE program were invited (n=24) and 16 adopted the intervention (66.7%).

RE-AIM dimension: Reach

Number and proportion of eligible patients, participants and patients who refused the intervention

Among the 2063 patients assessed for eligibility, 313 (15.2%) were eligible. Of those, 229 (73.2%) refused and 84 (26.8%) accepted the intervention (Figure 6.1.). Thus, the intervention reached 4.1% of the intended population.



VA: vascular access; IT: information technology; KTx: kidney transplant; HD: hemodialysis

Figure 6. 1. *Enrollment flowchart for PEF_OnLine*

Comparison of refusals with PEF_OnLine participants

As shown in Table 6.5., PEF_OnLine participants have a higher proportion of females (50.0% vs. 32.7%), a higher level of education (e.g., only 48.1% had a secondary education against 69.0% in

the group of PEF_OnLine participants), and a lower lean tissue index (12.2±2.6 Kg/m^2 vs. 13.7±2.7 Kg/m^2) when compared with the patients who refused the intervention. Moreover, PEF_OnLine participants also show more indicatives of a poorer health status: lower handgrip strength (24.3±11.2 Kg vs. 30.4±12.0 Kg), higher sedentarism (587±97 vs. 519±108 min/day) and a lower PA level, confirmed by lower steps/day (3631±2513 vs. 5846±3504 steps/day), lower light PA (131±56 vs. 177±68 min/day) and lower moderate-to-vigorous PA (15±17 vs. 33±30 min/day). No significant differences were found for age, marital status, vascular access, treatment modality, dialysis vintage, comorbidities, sleep quality, depressive symptoms and fatigue.

Table 6. 5. *Comparison of refusals with PEF_OnLine participants*

	Overall (n=240)	Refusals (n=156)	PEF_OnLine participants (n=84)	p
Age (y)	59.2±13.0	58.8±12.8	59.9±13.4	0.552[1]
Female, n (%)	93 (38.8)	51 (32.7)	42 (50.0)	**0.009**[2]
Education (ISCED), n (%%)				
Early childhood education	4 (1.7)	3 (1.9)	1 (1.2)	
Primary education	103 (42.9)	78 (50.0)	25 (29.8)	
Lower secondary education	50 (20.8)	35 (22.4)	15 (17.9)	
Upper secondary education	45 (18.8)	26 (16.7)	19 (22.6)	**<0.001**[2]
Post-secondary education	2 (0.8)	2 (1.3)	0 (0.0)	
Short-cycle tertiary education	10 (4.2)	1 (0.6)	9 (10.7)	
Bachelor´s or equivalent	23 (9.6)	11 (7.1)	12 (14.2)	
Master´s or equivalent	2 (0.8)	0 (0.0)	2 (2.4)	
Doctoral or equivalent	1 (0.4)	0 (0.0)	1 (1.2)	
Marital status, n (%)				
Divorced	28 (11.6)	20 (12.8)	8 (9.5)	
Married	154 (64.2)	100 (64.1)	54 (64.3)	0.719[2]
Non-married partner	6 (2.5)	4 (2.6)	2 (2.4)	
Unmarried	37 (15.4)	21 (13.5)	16 (19.0)	
Widower	15 (6.3)	11 (7.0)	4 (4.8)	
Vascular access, n (%)				
Arteriovenous fistula	202 (84.2)	134 (85.9)	68 (81.0)	0.541[2]
Arteriovenous graft	15 (6.3)	8 (5.1)	7 (8.3)	
Central venous catheter	23 (9.5)	14 (9.0)	9 (10.7)	
Treatment modality, n (%)				
Hemodiafiltration	206 (85.8)	137 (87.8)	69 (82.1)	0.229[2]
Hemodialysis	34 (14.2)	19 (12.2)	15 (17.9)	
Dialysis vintage (months)	91.0±103.9	85.8±105.3	100.6±101.3	0.146[1]
Comorbidities				
Age-adjusted Charlson comorbidity index	5.1±2.4	5.0±2.3	5.4±2.6	0.324[3]
Diabetes Mellitus, n (%)	50 (20.8)	33 (21.2)	17 (20.2)	0.868[2]
Body Composition				
Body Mass Index (Kg/m^2)	26.1±4.6	26.4±4.7	25.4±4.3	0.091[1]
Lean Tissue Index (Kg/m^2)	13.2±2.8	13.7±2.7	12.2±2.6	**<0.001**[1]
Fat Tissue Index (Kg/m^2)	12.3±5.4	12.1±5.5	12.5±5.3	0.307[3]
Physical function				
Sit-to-stand 30 (rep)	15.5±5.6	15.6±5.6	15.2±5.6	0.378[3]
Handgrip (Kg)	29.6±10.6	30.4±12.0	24.3±11.2	**0.001**[3]
8-foot Up&Go (sec)	6.5±2.7	6.5±2.9	5.8±3.0	0.270[3]
Sit-to-stand 5 (sec)	8.8±3.2	8.6±2.9	9.2±3.6	0.149[3]
Single leg stance (sec)	27.1±17.9	27.3±17.7	26.8±18.5	0.833[3]
Sleep quality	6.8±4.0	6.7±4.0	7.1±4.1	0.419[3]
Depressive symptoms	12.9±10.0	12.4±10.1	13.9±9.7	0.164[3]
Fatigue	36.6±6.0	36.5±6.4	36.8±5.3	0.727[3]
Physical activity*				
Steps/day	4994±3321	5846±3504	3631±2513	**0.009**[3]
Sedentary time/day (min)	545±109	519±108	587±97	**0.013**[1]
Light PA time/day (min)	159±67	177±68	131±56	**0.006**[1]
MVPA time/day (min)	26±27	33±30	15±17	**0.005**[1]

[1]Independent samples t-test; [2]Chi-square test; [3]Mann-Whitney test; *analysis restricted to 65 patients (40 in the refusals and 25 in the PEF_OnLine group); PA: physical activity; MVPA: moderate-to-vigorous physical activity

RE-AIM dimension: maintenance

Proportion of HD units who continued the intervention

All HD units who assigned PEF_OnLine (n=16) completed the intervention period.

Attrition rate with reasons

Attrition rate was 40.5% (n= 34), mostly due to voluntary withdrawal (Table 6.6.).

Table 6. 6. *Reasons for attrition from PEF_OnLine*

Reason	n	%
Kidney transplant	1	2.9
Lack of digital skills	1	2.9
Lost the mobile phone	1	2.9
Death	1	2.9
Pain	1	2.9
Surgery	7	20.5%
Voluntary withdrawal	22	65.0
Total	**34**	**100**

Timing of voluntary withdrawal

Most of the voluntary withdrawals happened during the first month (59.1%). A deceleration occurred with the other 40.1% of the voluntary withdrawals happening in the next two months (Figure 6.2.).

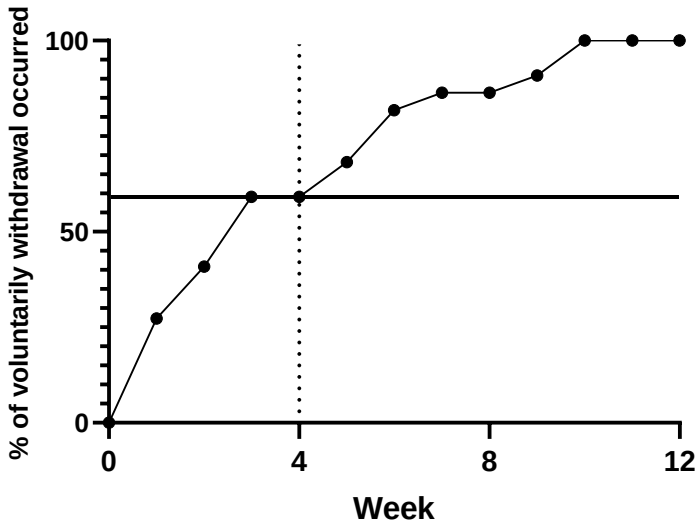


Figure 6. 2. *Occurrence of voluntary withdrawal over time*

Comparison of voluntary withdrawals with completers

Comparing to patients who voluntarily withdrew the intervention, the PEF_OnLine completers group was older (61.7±12.8 years vs. 54.6±14.6 years), with a higher prevalence of married patients (68.8% vs. 38.1%) and had a better STS 5 performance (8.3±2.0 seconds vs. 10.8±5.9 seconds). Moreover, an analysis restricted to 25 patients (five in the voluntary withdrawals and 20 in the PEF_OnLine group) demonstrated that those who completed the intervention were already more active at baseline: more steps/day (4110±2554 vs. 1713±1072), more light PA time (143±55 min/day vs. 84±33 min/day) and low sedentarism (583±101 min/day vs. 601±89 min/day) (Table 6.7.).

Table 6. 7. *Comparison of voluntary withdrawals with PEF_OnLine completers*

	Overall (n=72)	**Voluntary withdrawals (n=22)**	**PEF_OnLine completers (n=50)**	**p**
Age (y)	59.5±13.7	54.6±14.6	61.7±12.8	**0.043**[1]
Female, n (%)	37 (51.4)	12 (54.5)	25 (50.0)	0.722[2]
Education (ISCED), n (%%)				
Early childhood education	1 (1.4)	0 (0.0)	1 (2.0)	
Primary education	22 (30.5)	5 (22.7)	17 (34.0)	
Lower secondary education	9 (12.5)	3 (13.6)	6 (12.2)	
Upper secondary education	17 (23.6)	8 (36.4)	9 (18.4)	0.388[2]
Post-secondary education	0 (0.0)	0 (0.0)	0 (0.0)	
Short-cycle tertiary education	9 (12.5)	1 (4.5)	8 (16.3)	
Bachelor's or equivalent	12 (16.7)	4 (18.2)	8 (16.3)	
Master's or equivalent	1 (1.4)	1 (4.5)	0 (0.0)	
Doctoral or equivalent	1 (1.4)	0 (0.0)	1 (2.0)	
Marital status, n (%)				
Divorced	8 (11.1)	3 (13.6)	5 (10.0)	
Married	44 (61.1)	9 (40.9)	35 (70.0)	**0.048**[2]
Non-married partner	2 (2.8)	2 (9.1)	0 (0.0)	
Unmarried	15 (20.8)	6 (27.3)	9 (18.0)	
Widower	3 (4.2)	2 (9.1)	1 (2.0)	
Vascular access, n (%)				
Arteriovenous fistula	59 (81.9)	18 (81.8)	41 (82.0)	0.593[2]
Arteriovenous graft	6 (8.3)	1 (4.6)	5 (10.0)	
Central venous catheter	7 (9.7)	3 (13.6)	4 (8.0)	
Treatment modality, n (%)				
Hemodiafiltration	58 (80.6)	16 (72.7)	42 (84.0)	0.266[2]
Hemodialysis	14 (19.4)	6 (27.3)	8 (16.0)	
Dialysis vintage (months)	103.6±104.8	118.8±111.2	96.9±102.3	0.427[3]
Comorbidities				
Age-adjusted Charlson comorbidity index	5.1±2.3	4.9±2.4	5.2±2.3	0.579[1]
Diabetes Mellitus, n (%)	14 (19.4)	4 (18.2)	10 (20.0%)	0.857[2]
Body Composition				
Body Mass Index (Kg/m^2)	25.2±4.5	24.5±3.6	25.5±4.8	0.438[1]
Lean Tissue Index (Kg/m^2)	12.3±2.6	11.6±3.3	12.7±2.2	0.089[1]
Fat Tissue Index (Kg/m^2)	12.2±5.4	12.3±5.6	12.2±5.4	0.945[1]
Physical function				
Sit-to-stand 30 (rep)	15.6±5.9	14.9±6.8	15.9±5.5	0.522[1]
Handgrip (Kg)	26.6±8.2	26.7±10.2	26.6±7.4	0.355[1]
8-foot Up&Go (sec)	6.5±2.5	7.1±4.3	6.2±1.3	0.204[1]
Sit-to-stand 5 (sec)	9.1±3.8	10.8±5.9	8.3±2.0	**0.008**[1]
Single leg stance (sec)	26.4±18.6	22.8±20.3	27.9±17.9	0.287[1]
Sleep quality	6.9±3.9	6.8±4.9	6.9±3.5	0.967[1]
Depressive symptoms	13.7±9.7	14.4±11.7	13.4±8.9	0.695[1]
Fatigue	37.0±4.5	37.3±3.2	36.9±5.0	0.763[1]
Physical activity*				
Steps/day	3660±2562	1713±1072	4110±2554	**0.005**[1]
Sedentary time/day (min)	589±98	601±89	583±101	**0.713**[1]
Light PA time/day (min)	131±58	84±33	143±55	**0.010**[1]
MVPA time/day (min)	16±17	8±6	17±19	0.065[1]

[1]Independent samples T-test; [2]Qui square test; [3]Mann-Whitney U Test; *analysis restricted to 25 patients (5 in the voluntary withdrawals and 20 in the PEF_OnLine group); PA: physical activity; MVPA: moderate-to-vigorous physical activity

RE-AIM dimension: Implementation

Implementation fidelity: adherence (%) (performed exercise sessions among the total number of exercise sessions), number and proportion of fully, partially and non-performed exercise sessions

Adherence (%) to PEF_OnLine was 73.1±18.8. Among the total possible exercise sessions (n=1800), 1246 (69.2%) were fully performed, 71 (4.0%) were partially performed and 483 (26.8%) were not performed (Figure 6.3.).

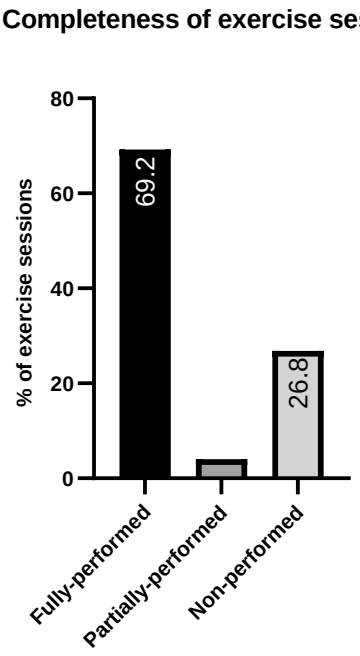


Figure 6. 3. *Completeness of exercise sessions in PEF_OnLine*

Implementation fidelity outcomes in patients also performing IDE

Very similar implementation fidelity outcomes were found for patients only performing PEF_OnLine and for patients performing both PEF_OnLine and IDE (Table 6.8.).

Table 6. 8. *Comparison of PEF_OnLine implementation fidelity outcomes between patients only performing PEF_OnLine and patients also performing IDE*

	PEF_OnLine only (n=31)	PEF_OnLine and IDE (n=19)
Adherence (%)	74.5±15.7	70.9±23.2
Total number of available exercise sessions	1116	684
Completely performed sessions, n (%)	781 (70.0)	465 (68.0)
Partially Performed sessions, n (%)	51 (4.6)	20 (2.9)
Non-performed sessions, n (%)	284 (25.4)	199 (29.1)

Implementation dose: mean number of exercise sessions/patient and exercise sessions/week

Mean number of exercise sessions/patient was 26.3±6.8 and mean number of exercise sessions/week was 2.2±0.6.

Implementation dose outcomes in patients also performing IDE

Very similar PEF_OnLine implementation dose outcomes were found for patients only performing PEF_OnLine and for patients also performing IDE (Table 6.9.).

Table 6. 9. *Comparison of PEF_OnLine implementation dose outcomes between patients only performing PEF_OnLine and patients also performing IDE*

	Overall (n=50)	PEF_OnLine only (n=31)	PEF_OnLine and IDE (n=19)
Exercise sessions/patient	26.3±6.8	26.8±5.6	25.5±8.4
Exercise sessions/week	2.2±0.6	2.2±0.5	2.1±0.7

RE-AIM dimension: effectiveness

The effectiveness analysis sample comprised 181 patients (131 in the non-exercise and 50 in the PEF_OnLine group). The PEF_OnLine group had a higher proportion of females (50.0% vs. 34.4%) and a higher level of education (42% had secondary education against 22.9% in the non-exercise group). However, the intervention group had a lower lean tissue index, a higher sedentary behavior, and lower levels of moderate-to-vigorous PA (Table 6.10.).

Table 6. 10. *Description of the effectiveness analysis sample*

	Overall (n=181)	Non-exercise (n=131)	PEF_OnLine (n=50)	p
Age (y)	59.9±12.8	59.2±12.8	61.7±12.8	0.249[1]
Female, n (%)	70 (38.7)	45 (34.4)	25 (50.0)	**0.053[2]**
Education (ISCED), n (%%)				
Early childhood education	4 (2.2)	3 (2.3)	1 (2.0)	
Primary education	84 (46.4)	67 (51.1)	17 (34.0)	
Lower secondary education	37 (20.4)	31 (23.7)	6 (12.0)	
Upper secondary education	28 (15.5)	19 (14.5)	9 (18.0)	**<0.001[2]**
Post-secondary education	2 (1.1)	2 (1.5)	0 (0.0)	
Short-cycle tertiary education	9 (5.0)	1 (0.8)	8 (16.0)	
Bachelor's or equivalent	16 (8.8)	8 (6.1)	8 (16.0)	
Master's or equivalent	0 (0.0)	0 (0.0)	0 (0.0)	
Doctoral or equivalent	1 (0.6)	0 (0.0)	1 (2.0)	
Marital status, n (%)				
Divorced	22 (12.2)	17 (13.0)	5 (10.0)	
Married	119 (65.7)	84 (64.1)	35 (70.0)	0.399[2]
Non-married partner	3 (1.7)	3 (2.3)	0 (0.0)	
Unmarried	26 (14.4)	17 (13.0)	9 (18.0)	
Widower	11 (6.0)	10 (7.6)	1 (2.0)	
Vascular access, n (%)				
Arteriovenous fistula	153 (84.5)	112 (85.5)	41 (82.0)	0.378[2]
Arteriovenous graft	11 (6.1)	6 (4.6)	5 (10.0)	
Central venous catheter	17 (9.4)	13 (10.0)	4 (8.0)	
Treatment modality, n (%)				
Hemodiafiltration	156 (86.2)	114 (87.0)	42 (84.0)	0.598[2]
Hemodialysis	25 (13.8)	17 (13.0)	8 (16.0)	
Dialysis vintage (months)	86.7±101.6	82.9±101.5	96.9±102.3	0.262[1]
Comorbidities				
Age-adjusted Charlson comorbidity index	5.0±2.3	5.0±2.3	5.2±2.3	0.366[3]
Diabetes Mellitus, n (%)	37 (20.4)	27 (20.6)	10 (20.0)	0.927[2]
Body Composition				
Body Mass Index (Kg/m^2)	26.4±4.8	26.7±4.8	25.5±4.8	0.095[1]
Lean Tissue Index (Kg/m^2)	13.4±2.7	13.7±2.8	12.7±2.2	**0.031[1]**
Fat Tissue Index (Kg/m^2)	12.4±5.6	12.5±5.7	12.2±5.4	0.874[3]
Physical function				
Sit-to-stand 30 (rep)	15.8±5.6	15.8±5.7	15.9±5.5	0.951[3]
Handgrip (Kg)	29.6±10.5	30.7±11.3	26.6±7.4	0.065[3]
8-foot Up&Go (sec)	6.5±2.7	6.7±3.0	6.2±1.3	0.573[3]
Sit-to-stand 5 (sec)	8.5±2.7	8.6±2.9	8.3±2.0	0.745[1]
Single leg stance (sec)	27.1±17.7	26.7±17.8	27.9±17.9	0.662[3]
Sleep quality	6.8±4.0	6.8±4.2	6.9±3.5	0.523[3]
Depressive symptoms	12.7±10.1	12.4±10.5	13.4±8.9	0.237[3]
Fatigue	36.5±6.1	36.4±6.5	36.9±5.0	0.973[3]
Physical activity*				
Steps/day	5159±3347	5816±3643	4110±2554	0.073[1]
Sedentary time/day (min)	546±102	522±98	583±100	**0.035[1]**
Light PA time/day (min)	164±68	177±73	143±55	0.077[1]
MVPA time/day (min)	27±27	31±27	17±18	**0.049[3]**

[1]Independent samples T-test; [2]Qui square test; [3]Mann-Whitney U Test; *Analysis restricted to 52 patients (non-exercise=32; PEF_OnLine=20); PA: physical activity; MVPA: moderate-to-vigorous physical activity

Safety

As seen in Table 6.11., adverse events were extraordinarily rare with a total of 5 adverse events (pain: n=1; vomit: n=1; dizziness: n=1; hypoglycemia: n=2) among the total 1317 exercise sessions. None of the events lead to hospitalization and all were controlled by the patient with the nurse support.

Table 6. 11. *Adverse events occurred during PEF_OnLine exercise sessions*

Adverse event	n events	n patients	% of exercise sessions
Musculoskeletal pain	1	1	0.08
Vomit	1	1	0.08
Dizziness	1	1	0.08
Hypoglycemia	2	2	0.15
Total	5	5	0.4

*Analysis restricted to diabetic patients

Physical function

Comparing baseline with 12 weeks, the PEF_Online group significantly improved the STS 30, handgrip strength, STS 5, and SLS. The only test with no significant improvements in the PEF_OnLine group was the 8-foot UG test, while the non-exercise group had no significant improvements in any of the tests. Comparing the variations occurred from baseline to 12 weeks in the two groups, significant differences were observed for STS 30 ($p<0.001$, ES=0.64) and for STS 5 ($p<0.001$, ES=0.40) favorable to the PEF_OnLine group, both in the unadjusted and in the adjusted analysis (Table 6.12. and Figure 6.4.).

Table 6. 12. *Physical function pre and post intervention in the non-exercise and in the PEF_OnLine group*

	Non-exercise (n=131)				PEF_OnLine (n=50)				p^2	p^3
	Baseline	**12 weeks**	**p^1**	**Δ**	**Baseline**	**12 weeks**	**p^1**	**Δ**		
STS 30 (rep)	15.7±5.7	15.6±5.2	0.896[4]	-0.1±2.7	15.9±5.5	17.6±5.0	**<0.001[5]**	1.7±3.1	**<0.001**	**<0.001**
Handgrip (kg)	30.6±11.3	31.0±11.1	0.057[4]	0.4±5.1	26.5±7.4	27.9±7.6	**0.003[5]**	1.4±3.0	0.351	0.539
8-foot UG (sec)	6.4±1.6	6.3±1.7	0.196[4]	-0.1±1.0	6.2±1.3	6.0±1.3	0.188[5]	-0.2±1.0	0.640	0.549
STS 5 (sec)	8.7±2.9	8.7±2.7	0.517[5]	0.03±1.65	8.3±2.1	7.6±2.2	**0.008[5]**	-0.65±1.85	**0.002**	**<0.001**
SLS (sec)	26.9±17.7	27.9±17.5	0.079[4]	0.9±9.4	27.8±18.0	31.3±16.6	**0.044[4]**	3.4±11.5	0.212	0.137

STS: sit to stand; UG: up and go; SLS: single leg stance; [1]p for differences between the baseline and 12 weeks; [2]unadjusted analysis (Mann-Whitney test); [3]Adjusted analysis (Quade test); [4]Wilkoxon signed rank test; [5]paired samples t-test; STS: sit-to-stand; UG: up and go; SLS: single leg stance

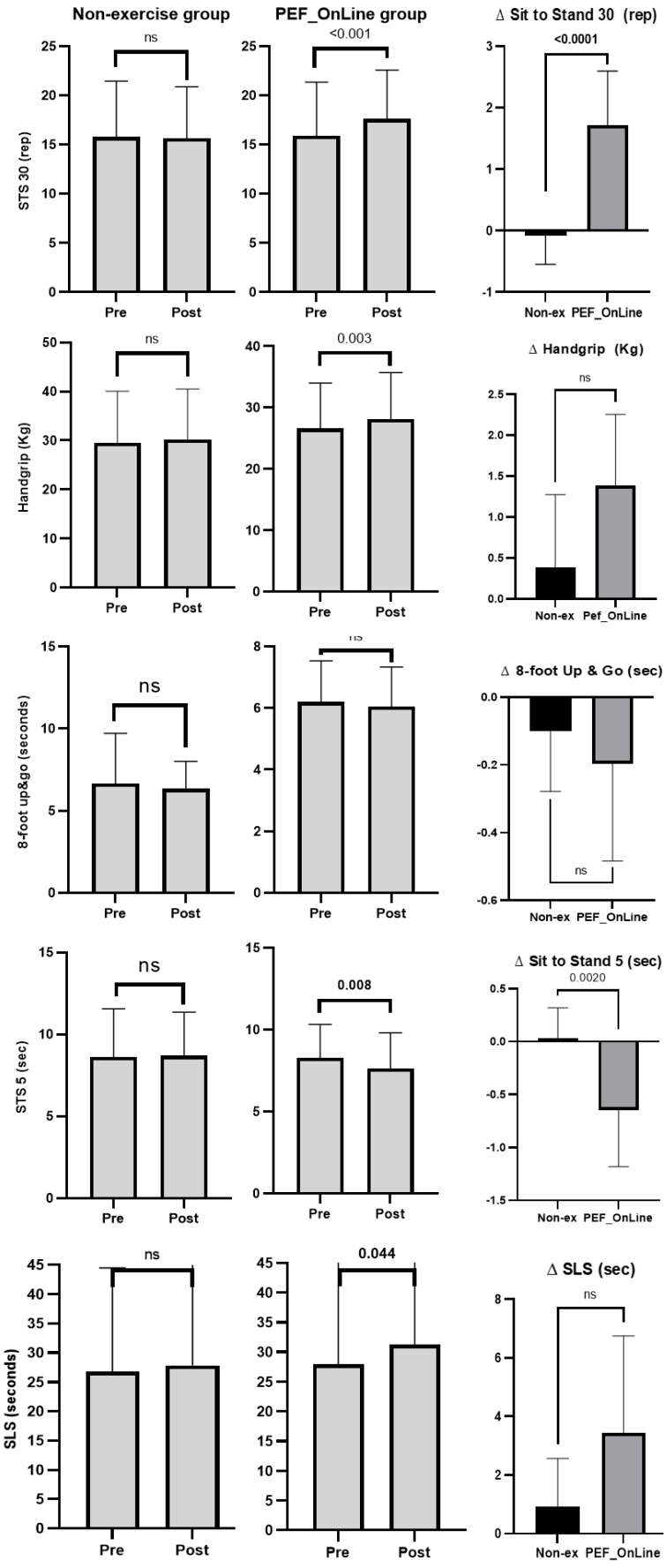


Figure 6. 4. *Physical function pre and post intervention in the non-exercise and in the PEF_OnLine group*

Body composition

Both the non-exercise and the PEF_OnLine groups had positive results in body composition and no significant differences were observed between the variations in any body composition parameter (Table 6.13.).

Table 6. 13. *Body composition pre and post intervention in the non-exercise and in the PEF_OnLine group*

	Non-exercise (n=131)				PEF_OnLine (n=50)				p^2	p^3
	Baseline	12 weeks	p^1	Δ	Baseline	12 weeks	p^1	Δ		
BMI (Kg/m²)	26.7±4.8	26.7±4.9	0.453[5]	-0.02±0.61	25.5±4.8	25.8±4.8	0.280[5]	0.23±1.49	0.309	0.256
ATM (Kg)	34.0±14.2	32.2±14.4	**<0.001[5]**	-1.8±3.2	32.6±13.6	30.6±13.7	**<0.001[5]**	-2.0±2.9	0.547	0.523
FM (Kg)	25.0±10.4	23.7±10.6	**<0.001[5]**	-1.3±2.3	24.0±10.0	22.5±10.1	**<0.001[5]**	1.5±2.1	0.547	0.537
FTI (Kg/m²)	12.5±5.7	11.9±5.8	**<0.001[4]**	-0.6±1.1	12.2±5.4	11.5±5.4	**<0.001[5]**	-0.8±1.1	0.460	0.452
LTM (Kg)	38.1±9.8	39.6±10.7	**<0.001[5]**	1.5±3.1	34.6±7.6	36.5±7.7	**<0.001[5]**	1.9±3.0	0.253	0.248
LTI (Kg/m²)	13.7±2.8	14.2±3.1	**<0.001[5]**	0.5±1.1	12.7±2.2	13.4±2.3	**<0.001[5]**	0.7±1.1	0.270	0.308
BCM (Kg)	21.1±6.5	22.2±7.2	**<0.001[5]**	1.1±2.2	18.8±5.0	20.2±5.1	**<0.001[5]**	1.4±2.1	0.270	0.272

[1]p for differences between the baseline and 12 weeks; [2]unadjusted analysis (Mann-Whitney test); [3]Adjusted analysis (Quade test); [4]Wilkoxon signed rank test; [5]paired samples t-test; BMI: body mass index; ATM: adipose tissue mass; FM: fat mass; FTI: fat tissue index; LTM: lean tissue mass; LTI: lean tissue index; BCM: body cell mass

Sleep quality

The PSQI demonstrated a high proportion of patients with a poor sleep quality (≥6) at baseline, 53.4% in the non-exercise group and 64% in the PEF_OnLine group (Figure 6.5.).

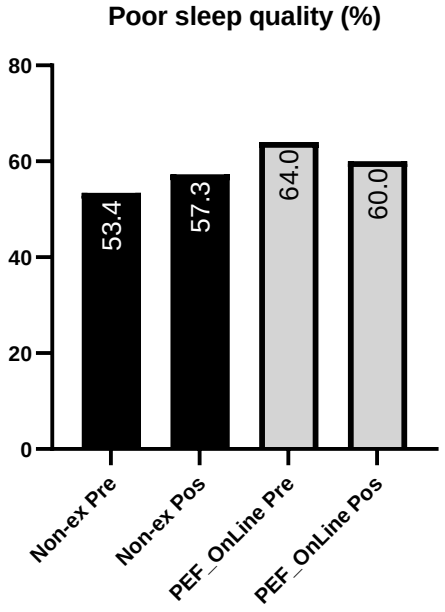


Figure 6. 5. *Proportion of patients with a poor sleep quality in the non-exercise and in the PEF_OnLine group*

No significant results were observed for global sleep quality score comparing the baseline to 12 weeks in both groups. Also, comparing the variations observed in the two groups, no significant differences were observed in unadjusted and adjusted analysis (Table 6.14.).

Table 6. 14. *Sleep quality pre and post intervention in the non-exercise and in the PEF_OnLine group*

	Non-exercise (n=131)				PEF_OnLine (n=50)				p^2	p^3
	Baseline	12 weeks	p^1	Δ	Baseline	12 weeks	p^1	Δ		
Subjective sleep quality	1.1±0.7	1.1±0.7	0.273[4]	-0.06±0.65	1.1±0.7	1.2±0.5	0.296[4]	0.08±0.72	0.164	0.159
Sleep latency	1.4±1.1	1.3±1.1	0.495[4]	-0.06±1.01	1.4±1.0	1.3±1.0	0.555[4]	-0.08±0.88	0.602	0.660
Sleep duration	0.9±1.0	1.2±1.1	**0.001**[4]	0.32±1.07	0.7±0.8	1.0±0.9	**0.028**[4]	0.24±0.74	0.544	0.440
Habitual Sleep Efficiency	0.7±1.1	0.3±0.6	**<0.001**[4]	-0.46±1.20	0.6±1.0	0.3±0.6	**0.040**[4]	-0.30±1.02	0.418	0.783
Sleep disturbances	1.1±0.6	1.1±0.6	0.423[4]	-0.05±0.65	1.2±0.5	1.2±0.6	0.808[4]	0.02±0.59	0.513	0.188
Use of sleep medicine	1.0±1.4	1.0±1.3	0.999[4]	0.00±0.89	1.2±1.4	1.2±1.4	0.916[4]	0.00±0.70	0.613	0.440
Daytime dysfunction	0.5±0.7	0.6±0.7	0.824[4]	0.02±0.76	0.7±0.7	0.5±0.7	0.160[4]	-0.16±0.79	0.149	0.460
Global sleep quality	6.8±4.2	6.5±3.5	0.376[4]	-0.29±3.17	6.9±3.5	6.7±3.5	0.618[5]	-0.20±2.81	0.976	0.698

[1]p for differences between the baseline and 12 weeks; [2]unadjusted analysis (Mann-Whitney test); [3]Adjusted analysis (Quade test); [4]Wilkoxon signed rank test; [5]paired samples t-test;

Depressive symptoms

Patients with depressive symptoms (CES-D ≥18) increased in the non-exercise group (22.1% to 26.7%), while an important reduction was observed in the PEF_OnLine group (36.0% to 16.0%) (Figure 6.6.).

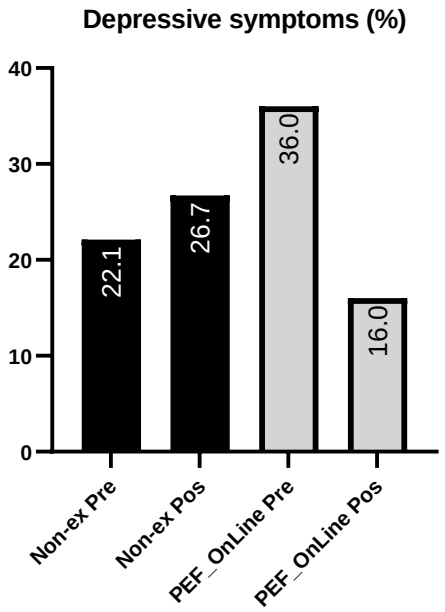


Figure 6. 6. *Proportion of patients with depressive symptoms in the non-exercise and in the PEF_OnLine group*

As shown in Table 6.15. and in Figure 6.7., there was a non-significant variation in the non-exercise group, but a marginally significant reduction of depressive symptoms in the PEF_OnLine group (p=0.071, ES=0.31). Nevertheless, after adjusting for the baseline values, the comparison of the variations between groups was not statistically significant (p=0.138).

Table 6. 15. *CES-D score pre and post intervention in the non-exercise and in the PEF_OnLine group*

	Non-exercise (n=131)				PEF_OnLine (n=50)				p^2	p^3
	Baseline	12 weeks	p^1	Δ	Baseline	12 weeks	p^1	Δ		
CES-D score	12.4±10.5	12.9±10.2	0.522[4]	0.4±7.7	13.4±8.9	11.5±6.5	0.071[4]	-1.9±6.9	0.062	0.138

[1]p for differences between the baseline and 12 weeks; [2]unadjusted analysis (Mann-Whitney test); [3]Adjusted analysis (Quade test); [4]Wilkoxon signed rank test; CESD-D: Center of Epidemiologic Studies Depression Scale

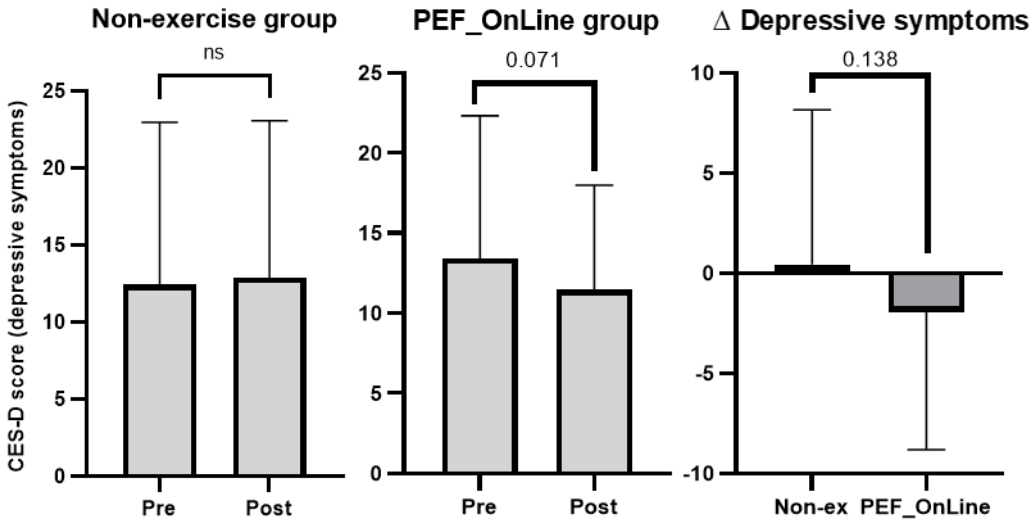


Figure 6. 7. *CES-D score pre and post intervention in the non-exercise and in the PEF_OnLine group*

Fatigue

As shown in Table 6.16., both groups improved the FACIT-F score, meaning lower fatigue levels. However, a higher improvement was observed in the PEF_OnLine group (5.2±6.0 vs. 3.3±7.6), resulting in a marginally significant difference between the variations of the two groups (p=0.070; ES=0.26). Moreover, as shown in Figure 6.8., when fatigue is analyzed as a dichotomous variable (cut-off 36), the PEF_OnLine group had a greater reduction in the proportion of patients with fatigue (18% vs. 5.3%). However, this result must be interpreted carefully since the baseline prevalence of fatigue was higher in the PEF_OnLine group (44.0% vs. 31.3%).

Table 6. 16. *FACIT-F score pre and post intervention in the non-exercise and in the PEF_OnLine group*

	Non-exercise (n=131)				PEF_OnLine (n=50)				p[2]	p[3]
	Baseline	12 weeks	p[1]	Δ	Baseline	12 weeks	p[1]	Δ		
FACIT-F score	36.4±6.5	39.7±9.3	**<0.001[4]**	3.3±7.6	36.9±5.0	42.1±7.7	**<0.001[4]**	5.2±6.0	0.070	0.070

[1]p for differences between the baseline and 12 weeks; [2]unadjusted analysis (Mann-Whitney test); [3]Adjusted analysis (Quade test); [4]Wilkoxon signed rank test; FACIT-F: Functional Assessment of Chronic Illness Therapy – Fatigue Scale

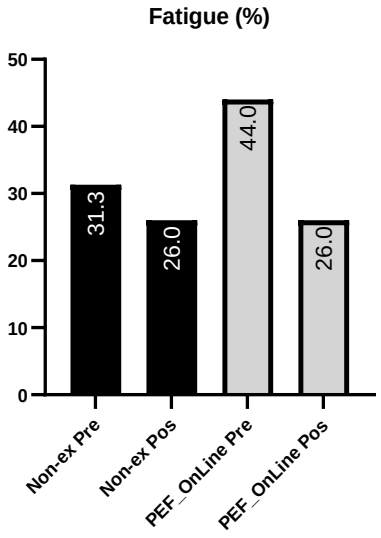


Figure 6. 8. *Proportion of patients with fatigue in the non-exercise and in the PEF_OnLine group*

6.4. Discussion

In this implementation study, developed at a nation-wide level, it was demonstrated that a VCTE program for HD patients is realistic and helpful for this vulnerable population during the unprecedent times of the COVID-19 pandemic. This was a safe intervention with clear benefits on physical function, and milder benefits on depressive symptoms and fatigue. As shown in Chapter 4, IDE on its own may not be sufficient to meet the UKKA PA recommendations for HD patients (3). As a considerable exercise dose was achieved (2.2±0.6 exercise sessions/week in non-HD days), this intervention could be a potential complement to IDE, even beyond the pandemic.

VCTE exercise programs hold great potential. In this first experience, about 67% of the units adopted the intervention, and 60% of the PEF_OnLine participants completed the intervention period. Adherence was good (73%±19%) and patients completed 2.2±0.6 exercise sessions/week. The intervention had clear benefits on their physical function. However, VCTE exercise applicability may be limited in HD patients due the lack of mobile health proficiency and some possible risks (e.g., falls) that may outweigh their benefits. Thus, despite the potential of this intervention, some caveats should be addressed.

Of all the invited units, 66.7% adopted the intervention. Reasons for not joining the program are unknown, but the extraordinary pressure on HD units during the COVID-19 pandemic (167) may explain why 33.3% of the units did not join PEF_OnLine.

Overall, PEF_OnLine only reached 4.1% of the patients. Indeed, only 15.2% were deemed eligible to partake which is less than what was found for IDE (55.8%, see Chapter 4, Section 4.4.). Clinical eligibility criteria were the same for both interventions, but some logistic inclusion criteria have been included for PEF_OnLine (internet access at home, device with a functioning camera, and patient or supportive relative with basic digital skills). The eligibility divergence between these two interventions may be related with the lack of mobile health readiness and proficiency. Mobile health readiness is a crucial prerequisite to the successful implementation of an online exercise program. Despite a previous study with a younger sample (just 27% over 70 years) that included also home dialysis patients (33%), found that HD patients were ready for and proficient in mobile health (167), we believe that patients not eligible to PEF_OnLine were older and with low levels of education, factors known to be related with a lower mobile health proficiency (177). Moreover, it should be considered that patients were recruited by the dialysis staff while they were facing the pandemic challenges in their HD units. This context could have limited our intervention to reach more participants. We should also stress that 73.2% of the eligible patients refused our intervention which is twice the refusals of IDE (36.1%, see Chapter 4, Section 4.4.). Thus, for future online exercise interventions beyond a pandemic situation, the accessibility to HD units by the exercise professionals could make the intervention reach more participants.

Compared to refusals, the PEF_OnLine group had a higher proportion of females and patients with higher levels of education. Previous studies in the general population and in cancer patients found similar findings (175, 307). Nevertheless, in contrast to what was observed for IDE (Chapter 4, Section 4.4.), the refusals group had a better health status (higher lean tissue index, handgrip strength and a higher PA level, also with a reduced sedentary time). A possible

explanation for this result is that those patients who felt more deconditioned by the pandemic imposed inactivity (and consequent suspension of IDE), would be more receptive to join PEF_OnLine.

Regarding the maintenance RE-AIM dimension, a considerable attrition rate (40.5%) should be pointed out. Like what was seen for IDE, the main reason for withdrawal was voluntary (65%) occurring mostly in the initial intervention period. Furthermore, comparing to voluntary withdrawals, patients who completed the intervention were older, but had a better baseline physical condition (better STS 5 performance, higher PA and lower sedentarism). These results highlight the importance of an initial exploration of participant's characteristics (308), to identify patients that, due to their poor physical function and low PA, would be at-risk of voluntary withdrawal. Thus, future online interventions should recognize these patients, providing a closer monitoring and additional motivational strategies to prevent voluntary withdrawals. Moreover, the completers group had a higher proportion of married patients. This was indicative of the importance of family support (308), fact that was potentiated encouraging family and other relatives to join the exercise sessions. Additionally, despite the video conferencing platforms facilitate social support from exercise professionals, periodic in-person exercise sessions (not recommended during the pandemic) could also have reduced voluntary withdrawals and should be considered in future online exercise interventions.

Implementation outcomes were very similar to those observed for IDE (Chapter 4, Section 4.4.). A high adherence was achieved (73.1%±18.8%), with participants completing 2.2±0.6 exercise sessions/week. This adherence is comparable to other online exercise interventions implemented for other populations (e.g., cancer survivors) (175). The analysis comparing the implementation outcomes of patients performing only PEF_OnLine and patients performing both PEF_OnLine and IDE, shows that the exercise dose of one intervention is not affected by the other, indicating that a summative exercise dose would be achieved by IDE and PEF_OnLine. This points out the potential of an online exercise intervention to complement the modest exercise dose achieved with IDE (Chapter 4, Section 4.4.).

The effectiveness of our intervention was investigated considering its safety and its effects on physical function, body composition, depressive symptoms, and fatigue.

This was a safe intervention with very rare adverse events. Nevertheless, two episodes of hypoglycemia occurred in two different type 1 diabetic patients. This should be a special concern in type 1 diabetic patients and, to a lesser extent, in people with type 2 diabetes using insulin or insulin secretagogues (309). Besides the routine pre-exercise blood testing performed by every diabetic, these two hypoglycemic episodes occurred. Those were not serious events, and were managed by the nurse attending the session, and the hypoglycemia was reverted with a carbohydrate intake and the immediate suspension of exercise. The event was reported to the dialysis staff that adjusted insulin dose and patients were recommended to eat an extra carbohydrate intake before exercise. Both patients continued the intervention without more hypoglycemic episodes. Especially because it was an online exercise intervention, the occurrence of falls was a concern. In fact, exercise is an effective strategy to prevent falls, however the risk of falls may rise during an exercise session (310). Special concerns were taken that may have prevented the occurrence of falls: the exercise protocol avoided moving from a

lying to a standing position and patients with balance impairment were recommended to perform the exercise sessions accompanied by a relative and holding on a chair while performing balance challenging exercises.

Regarding physical function, the non-exercise group did not significantly improve the performance of any physical function test. The PEF_OnLine group improved the performance in every test, except for 8-foot UG. The benefit on physical function observed in our study is in accordance with other online exercise interventions implemented in breast cancer survivors (311) and it is an important finding since impaired physical function is associated with an increased mortality risk in this population (53).

Curiously, both groups improved body composition and no significant results were found comparing the variations between the two groups for any of the body composition variables. Despite somehow speculative, several reasons may help to explain this intriguing result: 1) the relatively short follow-up period (12 weeks) may not be enough to observe differences between the two groups for body composition; also, 2) during the intervention period there was a move from a strict lockdown to a milder state that could have increased PA level in both groups; moreover, 3) several HD units restarted the IDE program at some point during the intervention period (48 patients in the non-exercise group were in fact practicing IDE when they performed the final assessment).

More than 60% of HD patients have poor sleep quality (312) that may be related with chronic fatigue, reduced quality of life and with a higher mortality risk (313). In our study, the prevalence of poor sleep quality slightly increased in the non-exercise group (from 53.4% to 57.3%) and slightly reduced in the PEF_Online group (from 64% to 60%). Nevertheless, no significant results were observed for global sleep quality in both groups. Despite the documented beneficial effects of exercise to improve the sleep quality of HD patients (314), no significant results were found. This could have been due the tremendous distress caused by COVID-19 pandemic, further aggravating the sleep quality in this population (315).

The prevalence of depression is three to four times higher in CKD and in HD patients compared with the general population, and two to three times higher compared to other chronic diseases (299). This scenario was further aggravated by COVID-19 pandemic (316), which is confirmed also by the high prevalence of depressive symptoms in our sample (26%). The antidepressant effect of exercise is well established for the general population (317), with the limited existing evidence also suggesting this benefit for HD patients (318). Our results agree with this previous evidence since there was an important reduction in the prevalence of depressive symptoms in the PEF_OnLine group (from 36.0% to 16.0%), while the non-exercise group slightly increased (from 22.1% to 26.7%). Moreover, there was a marginally significant reduction of the CES-D score in the PEF_OnLine group ($p=0.071$), while the non-exercise group remained virtually unchanged. Social isolation highly contributes for depressive symptoms (319) and, for many patients, the online exercise classes could have been one of the few social connections they had during the lockdown. This social support promotion could have contributed for the positive results of PEF_OnLine. Besides its psychosocial effects (self-esteem, social support, self-efficacy), exercise may influence biological processes implicated in the pathophysiology of depression as neuroplasticity (e.g., improving hippocampus volume), inflammation (e.g., reducing IL-6, IL-18,

CRP, leptin, fibrinogen, and angiotensin II), oxidative stress, neuroendocrine system (e.g., dampening hypothalamic-pituitary-adrenal axis and cortisol sensitivity) (320). The findings from this chapter are noteworthy since depressive symptoms are associated with poor clinical outcomes in this population (299). As such, online exercise interventions could be a promising exercise strategy not only for routine exercise, but particularly during vulnerable times (e.g., immediately after KTx, periods of isolation) when the risk of depression could be even greater.

The pathogenesis of fatigue in HD patients is possibly related with chronic inflammation, dysregulation of the hypothalamic-pituitary-adrenal axis and with rapid shifts in osmolality and fluids during HD (321). Thus, a high prevalence of fatigue subsists (20 to 86% depending on methods of ascertainment and patient characteristics) and is associated with poor health outcomes (322). IDE has been suggested to reduce fatigue levels in HD patients (321). The results presented in this chapter also suggest a positive influence of exercise since a greater improvement was observed in the PEF_OnLine group. Moreover, in the PEF_OnLine group, was observed a more obvious reduction in the proportion of patients with fatigue symptoms. Nevertheless, these results must be interpreted with caution since, although not so markedly, the non-exercise group also improved the global FACIT-F score and reduced the proportion of patients with fatigue. These results can be related with the softening of the lockdown measures during the intervention period and with the fact that, at some point, 48 patients in the non-exercise group restarted the IDE program. Moreover, the FACIT-F scale was not developed for HD patients and do not consider some specifications of fatigue in this population (e.g., symptom fluctuations as intradialytic fatigue and post dialysis fatigue (321)).

Some limitations should be mentioned. This is an implementation study that was not designed to study the efficacy of PEF_OnLine. Thus, the non-randomization design limits conclusions about its efficacy. Compared to our IDE study (Chapter 4, Section 4.4.), the follow up period was much shorter what may have limited the effectiveness analysis (e.g., declines in body composition were not observable in the non-exercise group as they were in the IDE study). Moreover, implementation outcomes must be interpreted in the context of a pandemic during which the dialysis staff was facing an unprecedent challenge. This fact may have limited PEF_OnLine implementation. During the intervention, two factors could have influenced our effectiveness results: the lockdown was softened, and the IDE was restarted in some HD units (48 patients in the non-exercise group and 19 patients in the PEF_OnLine group started IDE at some point during the intervention period). Finally, some questionnaires used to examine the effectiveness of our intervention may have some limitations. The FACIT-F score was developed for cancer patients and do not comprehend the unique features of fatigue in HD patients, and the sleep quality obtained with PSQI may not be associated with actigraphy in HD patients (323).

To the author of this thesis knowledge, this is the first report of a large-scale VCTE program implemented at a nation-wide level for HD patients. Taken together, this data suggest that this is a realistic and safe intervention that may be used to improve physical function in HD patients. This could be a noteworthy finding since home is the preferred location to exercise for HD patients (65). However, supervision is not possible in the typical home-based exercise programs, and VCTE interventions may overcome this barrier and become more popular in the near future. Nevertheless, some caveats should be addressed. This intervention was not adopted by 33.3% of the HD units and reached only 4.1% of the patients. As observed for IDE (Chapter 4, Section

4.4.), voluntary dropout was high (65% of the overall withdrawal). The pandemic context may explain in part this limited implementation. However, the need for innovative strategies to increase PA in HD patients should make the COVID-19 pandemic an incentive for progress in exercise interventions available to HD patients. Thus, future studies would be worthy to understand the role of online exercise interventions beyond the pandemic, namely in complement to IDE (typical form of exercise that is not enough to meet the recommended PA as described in Chapter 4, Section 4.4.).

6.5. Conclusion

This study suggests that a VCTE intervention was realistic even during the COVID-19 pandemic. The intervention appears to be safe (minor adverse events were reported) and had favorable results, specially to improve physical function. Thus, this intervention may be suitable to be applied beyond the pandemic, namely as a complementary exercise intervention to IDE that has known limitations and has been shown to not be sufficient to meet the current PA recommendations for HD patients (3). Nevertheless, implementation outcomes were somehow limited and should be improved increasing patients' eligibility (by promoting proficiency and motivation to use mobile health technology) and reducing refusals and voluntary withdrawals. This would be decisive to increase the health impact of future VCTE interventions in HD patients.

Chapter 7: General discussion

Evidence reported on this thesis suggests that PA may improve hard endpoints (mortality and hospitalization) in ESKD patients. Moreover, in the specific case of HD patients, IDE was a feasible and safe intervention, and its effectiveness is preserved in real-world conditions to improve physical function, body composition and Hb balance. Additionally, IDE was associated with a reduced mortality and hospitalization, but a considerable proportion of patients did not achieve an effectively protective exercise dose. During the COVID lockdown, an analysis was performed to a VCTE intervention that also demonstrated to be safe and effective to improve physical function, depressive symptoms, and fatigue. Thus, this intervention may be applied beyond the pandemic to complement IDE, so patients can achieve a higher and more effectively protective exercise dose.

In Chapter 3, a systematic review analyzed the evidence on the association of PA with mortality and hospitalization of ESKD patients. A protective association was found between PA and mortality while studies were lacking for hospitalization outcomes. Most of the included studies were in HD patients, however there were no studies regarding IDE. Thus, based on a database of a national implementation of an IDE program, this thesis examined its effectiveness and implementation outcomes and also its association with mortality and hospitalization (Chapters 4 and 5, respectively).

Chapter 4 concluded that IDE is a realistic and safe intervention in clinical settings. However, there is a high heterogeneity on implementation outcomes between HD units, indicating room for improvement. First, a substantial proportion of units did not adopt IDE (44%), which suggests that some key deciders may still be unaware of the importance of including this type of intervention as part of the clinical routine. Moreover, the reach dimension of the RE-AIM framework was affected by a high proportion of non-eligible patients (44%). However, there was no correlation of the proportion of non-eligible patients with the incidence of adverse events, suggesting that a more flexible patient screening could be safely implemented. Nevertheless, the reach dimension was also severely disturbed by a high proportion of patients who refused IDE (36.1% among those eligible). Maintenance dimension was limited by a significant drop-out rate at one-year (57%), of which 52% were voluntary. Therefore, this dimension could be improved with strategies to prevent voluntary withdrawal. Nevertheless, for those patients that continued to exercise, the adherence rate was good (75±20%), though not enough to meet the UKKA aerobic PA recommendations for HD patients (3). For those who completed the one-year follow up, effectiveness was sustained in real-world conditions to improve physical function, body composition and Hb balance. Given the observational design of the study, these effectiveness outcomes should be carefully interpreted. Also, since the program was implemented by the existing dialysis staff, the implementation outcomes may have been limited by the absence of a dedicated exercise professional.

In Chapter 5, it was demonstrated a dose-dependent association of IDE with better mortality and hospitalization outcomes, being significant only for a group of patients with a higher exercise dose (110±16 minutes/week). Thus, a considerable exercise volume may be required and for many patients, this could not be achieved solely by IDE on its own. However, future RCTs are needed to fully clarify the impact of IDE on mortality and hospitalization of such a vulnerable population. Even so, these results advocate for a more comprehensive and personalized PA

intervention, which may include a home-based online exercise intervention (as observed in Chapter 6), that could be used to further complement IDE.

In Chapter 6, an implementation study was performed to an online exercise program settled during the COVID lockdown while the IDE was suspended. This intervention used a videoconferencing platform, and an implementation study was performed using the RE-AIM framework (as accomplished for IDE in Chapter 4). Implementation outcomes could have been limited by the challenging pandemic context, but as for IDE, some drawbacks were observed. Of all units invited, 33% did not adopt the intervention. Again, a high proportion of patients refused the intervention (73%) and 41% dropped out during the three-month follow up. Such as for IDE, those who completed the intervention had a good adherence rate (73%±19%). The intervention was safe and effective to improve physical function, depressive symptoms, and fatigue. This form of exercise has the potential to be used beyond the pandemic to complement the typical IDE intervention that on its own is not sufficient to allow patients to meet the UKKA PA recommendations for HD patients (3).

Despite being completely different exercise interventions, both the IDE and the online exercise had good adherence rates, which is indicative that those patients who accepted and continued to perform each of these interventions were effectively engaged. However, both exercise options also had similar drawbacks (high proportion of non-eligibility, refusals, and voluntary withdrawals), indicative that each single exercise intervention did not meet the needs or preferences of many patients. Accordingly, these limitations were shared and not specific of a particular exercise intervention. Thus, having a wider range of exercise options could effectively engage patients in the one(s) that meets their needs, convenience, and preferences.

Taken together, our data suggests that PA may be used to improve important endpoints in HD patients, as mortality and hospitalization. IDE is a convenient option but would not be the panacea for the challenging inactivity of all HD patients. On the other hand, the recommendation of 150 minutes/week of moderate aerobic exercise (3, 4) will hardly be achieved ignoring the substantial amount of time spent in HD. Moreover, using otherwise sedentary time, preventing myocardial stunning during HD (127, 128) and improving dialysis adequacy (77), IDE has specific advantages that are not shared by other exercise options and should be considered when implementing an exercise intervention for this population. Therefore, this thesis is in alignment with the UKKA recommendation that IDE “should be available in all units” and “once patients are familiar with exercising during dialysis, they should be encouraged to complete additional exercise on non-dialysis days” (3). This has also been suggested by previous authors that recommend moving for a more comprehensive exercise intervention (236), that could also include higher intensity interdialytic supervised exercise, home-based exercise, online exercise, and a behavior change intervention. It is not expected that a single intervention (regardless of what it may be) will meet all the needs and preferences of such a heterogenic population. Every stand-alone exercise intervention will have its limitations from a patients’ perspective. Thus, instead of arguing in favor of an intervention over another (324), the nephrology community should be advocating and testing a more comprehensive intervention that combines different options to exercise, so that patients could choose which one(s) best adapts to their routine.

Given the above-mentioned limitations, implementing sustainable exercise interventions is a key challenge in HD patients. Whatever the exercise option is, several key factors seem important and were proposed for chronic patients and older adults (308). Some of these factors include 1) individualization, 2) multidisciplinary team involvement, 3) supervision, 4) initial exploration of participant's characteristics, barriers, and facilitators, 5) participants education, adequate expectations, and knowledge about risks and benefits, 6) enjoyment, 7) integration in daily living, 8) social support and relatedness, 9) available progress information and monitoring, and 10) self-efficacy and competence (308). Each of these factors and its adequation for HD patients are individually discussed in the following paragraphs.

Individualization in terms of type, intensity, duration, frequency, but also in needs and interests, is crucial for adherence promotion to an exercise intervention. This would elicit superior results not only due to a better adjustment to physiological demands, but also enhancing patient perception towards the exercise program (308). This is particularly challenging when working with heterogeneous groups in terms of functional capacity, since exercise may be tailored for those with the lowest capacity, causing obvious limitations to an individualized exercise prescription. Thus, creating homogeneous groups regarding interests, needs and functionality will promote a better adjustment of exercise prescriptions to elicit a more robust physiological response. The two exercise protocols used in this thesis have a low variability between patients and may not be tailored for each patient´s functional capacity. This fact may have contributed for the considerable drop-out rate observed in IDE and in PEF_OnLine. Still about the need for more individualized exercise interventions, it is also critical to improve exercise prescriptions for HD patients, that have been failing to incorporate all the evidence-based exercise principles, especially in terms of progression (288). This demonstrates how exercise prescriptions do not consider individual adaptations to exercise, so that can be regularly updated based on periodic individual reassessments.

Another key factor for sustainable exercise interventions is multidisciplinary team involvement. Despite being the main responsible for exercise design and development, the exercise professional must evolve the multidisciplinary team. This is particularly important in HD patients, since they could be unfamiliar with the exercise professional and its role. However, a close and trust relationship should be already developed with the nephrologists and nurses who could be key players to increase patients' motivation. In this regard, we should not ignore that the dialysis staff could be either a barrier or a facilitator to exercise participation, depending on their attitudes towards exercise (66). This may explain the discrepancy on the implementation outcomes observed across different HD units. Thus, creating a multidisciplinary culture where exercise is a priority would be crucial for the success of any IDE program (325).

Supervision also contributes for a sustainable exercise intervention and involves a professional checking how the participant is performing the prescribed exercises, which could potentiate the exercise benefits and reduces the risks. Moreover, the supervision of an exercise professional would promote a trust relation, increasing patient´s knowledge and support, which may increase self-efficacy and reduce the discouraging feelings (308). The IDE program analyzed in this thesis had a low supervision, since it was implemented by the existing dialysis staff that still have to deal with other HD-related tasks. This factor may have precluded better implementation outcomes (previously discussed in Chapter 4). In fact, dedicated exercise professionals have

been advocated for sustainable exercise interventions in HD patients, contributing to safe, individually exercise regimens and thus, removing the pressure from busy HD staff who often consider exercise to be a low priority in their workload (168). Moreover, previous evidence demonstrated that the presence of an exercise professional increases the adherence to IDE (235). Typically, most IDE programs have been based on the goodwill and voluntarism of the dialysis staff. Future studies are needed to investigate if having dedicated exercise professionals would be decisive for better IDE implementation outcomes.

A comprehensive initial assessment should also promote a sustainable exercise participation. Assessing patients' barriers and facilitators should be performed and considered in the exercise prescription. As such, the stage of change is a known predictor of adherence to exercise in chronic patients (232). This concept emerged from the transtheoretical model, which defines a series of behavior change stages: pre-contemplation, contemplation, preparation, action and maintenance (233). Thus, a mismatch between the patient´s stage of change and an ambitious exercise prescription may lead to lower adherence and early drop-out (232). Moreover, common symptoms in HD patients as fatigue may reduce exercise participation (67) and should be addressed alongside the exercise initiation. Therefore, having a patient driven exercise prescription will enhance adherence, while allowing for an incremental exercise volume over time.

Another key factor for sustainable exercise interventions is participants education, adequate expectations, and knowledge about risks and benefits (308). In line with the health belief model, patients who are aware of what exercise can do for them usually show a higher participation in exercise programs (326). This could explain the higher adherence of some exercise programs. For instance, in fall prevention, the adherence is higher in programs designed to improve balance than in programs designed to improve flexibility (327). However, being aware of the benefits of exercise should not lead to unrealistic or overly optimistic expectations, since this is also a predictor of abandon (328). As such, this is a double-edged sword, and a balance should be achieved through an open discussion with the patient. Besides avoiding unrealistic expectations, risks should be discussed, and the occurrence of unpleasant feelings should be anticipated (e.g. muscle pain, dyspnea and fatigue during exercise) (329). There are some concerns that may preclude patients' participation in IDE (e.g., perception of having too medical conditions to exercise, aggravation of HD-related symptoms, increase staff workload, arteriovenous fistula) (66). Patients' education is of utmost importance to demystify these barriers, so that the exercise intervention could reach more patients.

The enjoyment obtained from the exercise program is also a key feature that improves the sustainability of exercise interventions. Enjoyment is an immediate reward that are closely associated with intrinsic motivation, leading to better persistence than delayed rewards (e.g. chronic health benefits) (330). As such, physical exercise programs for HD patients, regardless of whether they are IDE or not, should be experienced by the patient as an enjoyable activity. For instance, in a situation of having many patients performing IDE simultaneously and that are next to each other could promote an enjoyable environment and an entertaining discussion during the exercise sessions.

Integration in daily living is another key factor to sustain an exercise regimen. Transforming an IDE program into a lifestyle habit that goes beyond the dialysis period is crucial since, as reported earlier in this thesis, IDE *per se* may not be sufficient to achieve an effectively protective exercise dose. Many factors may affect this process, such as flexibility at work (331), intimidating gym environment and lack of confidence to manage gym equipment (332), however the background and the preferences of the patient are the most decisive ones (308). In this regard, a flexible timetable could be important for HD patients since time constraints are usually considered a barrier to exercise (68). As such, it has been suggested that in the long-term, people are more likely to adhere to a home-based exercise program (333) because they are easier to integrate in their daily life routines. This could be of particular interest for HD patients since home is their preferred location to exercise (65). In this context, VCTE interventions could become a promising tool to integrate exercise in the daily life of HD patients and could enhance the integration of exercise professionals for the adequate prescription and supervision of tailored exercise programs completed at home on non-dialysis days, further potentiating the positive adaptations induced by exercise.

Relatedness ("feeling of belonging to a group") and social support ("support accessible to an individual through social ties to other individuals, groups, and the larger community") are basic psychological needs to improve motivation that are also associated with exercise participation (308). For instance, creating a small competition among dialysis shifts (e.g., shift with the best adherence to IDE), would promote this sense of belonging to a group. Examples of social support could be provided from the exercise professional and from the dialysis staff (e.g., through active listening). Family involvement should also be a good source of social support and was already described as a facilitator to exercise participation in HD patients (66). In short, feelings of helplessness are common barriers to exercise in HD patients (68). Thus, positive social interactions with the staff and other participants may increase adherence to exercise. The social skills of the staff and the creation of homogeneous groups are key steps to achieve high levels of social support and relatedness (308).

Monitoring and feedback on patient outcomes are important key factors for exercise participation. As such, objective measures that the patient can understand and interpret would be valuable (308). Thus, a comprehensive baseline evaluation is mandatory to compare with future assessments. In the case of the IDE that was presented in this thesis, every three months feedback was provided on physical function and body composition outcomes. In the elderly, an underlying motivation to exercise seems to be the goal of maintaining their independence (334). Thus, regular feedback on physical function outcomes could be an extra motivation mainly for older HD patients.

Self-efficacy is one of the most widely known key factors to improve adherence among any kind of population (308). It is defined as the individuals´ belief in their own capacity to undertake a specific task and achieve the desired goal (335). This is particularly relevant in chronic patients as it reflects their perceptions about the possibility of control their own life and achieve goals (308). Results from this thesis show that both the IDE and the online exercise (explored in Chapters 4 and 6, respectively) had a high proportion of patients refusing the intervention. Moreover, it was observed that those who refused had a worst health condition. These results put into question whether the patients were in fact refusing or were afraid of not being able to

accomplish with the exercise prescription. If so, many patients may have refused due to low self-efficacy levels as it was already described in HD patients (234). Self-efficacy is closely associated with the levels of health literacy and so patient education could be decisive increasing the knowledge about what they can do and what they can change (308).

All these factors are proposed as important elements for exercise adherence in chronic diseases (308). Accordingly, the success of an exercise program for HD patients seems more dependent on how these factors are integrated during implementation than on what exercise option is adopted (IDE, home-based or supervised interdialytic exercise). This is not meant to say that all these factors are feasible in real-world. Nevertheless, for a better implementation, these factors should be contemplated as much as realistically possible. The association of IDE with mortality and hospitalization was dose-dependent. Thus, the results obtained on IDE implementation outcomes (Chapter 4) influenced its association with mortality and hospitalization (Chapter 5). Integrating the above-mentioned factors in IDE implementation would improve exercise dose and ultimately its effectiveness to improve hard clinical endpoints in this at-risk population.

The findings on hard endpoints observed in this thesis (Chapters 3 and 5) should be discussed in perspective with those from the general population. There is a commonplace that PA/exercise improves mortality both in HD patients (Chapters 3 and 5) and in the general population (191, 284). However, the amount of PA needed to improve mortality may be higher for HD patients. While on the general population, small amounts of PA (≈40min/week of moderate-to-vigorous PA) may be enough to improve mortality (191), this may not be the case in HD patients, since the low exercise group (<87min/week) that performed 63±19 min/week had no benefits on mortality (Chapter 5). This may partly be explained by the extra burden imposed by the non-traditional CV risk factors of HD patients (119). On the other hand, and as for the general population, PA levels below the recommendation of 150 min/week may improve mortality, since the high exercise group (≥87min/week) that performed 110±16 min/week had a significant improvement on mortality. Thus, the WHO recommendation for PA in the general population that “some is better than none” (4) may not be suited for HD patients and should be replaced by “some is better than none, but more is much better than some”.

In conclusion, this thesis provides compelling evidence that, in real-world-conditions, IDE is safe, feasible and has several health benefits for HD patients. However, this intervention does not solve every challenge of the complex inactivity in this population, since it does not meet the PA recommendations, and many patients were non-eligible, refused or voluntarily withdrew. Nevertheless, if a considerable exercise volume is achieved, IDE appears to be associated with better mortality and hospitalization outcomes. Moreover, an online exercise intervention has also been shown to be safe and feasible and can be used to complement the traditional IDE stand-alone exercise intervention delivered to HD patients. Future studies would be valuable to understand the implementation of a more personalized PA intervention and its impact on important endpoints as mortality and hospitalization.

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Appendices

Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	34
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	35
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	36
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	36
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	37
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	37
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	37
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	37
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	38

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	38
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	38
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	38
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	-
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	-

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	-
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	40
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	40
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	43
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	42,44
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	-
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	-
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	49
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	50
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	52
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	-

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Appendix 2: STARI checklist – Intradialytic exercise: a controlled nation-wide effectiveness-implementation study

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	53	Identification as an implementation study, and description of the methodology in the title and/or keywords		

Abstract	**2**	54	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	56	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**	28, 29	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).	56	The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).
Aims and objectives	**5**	56	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	57	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	57	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	57	The characteristics of the targeted 'site(s)' (e.g locations/personnel/resources etc.) for implementation and any eligibility criteria.	57	The population targeted by the intervention and any eligibility criteria.
Description	**9**	58	A description of the implementation strategy	58	A description of the intervention
Sub-groups	**10**	-	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					

Outcomes	**11**	58	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	58	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	-	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	-	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	-	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	-	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	59, 60	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	58, 59	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		
Results					
Characteristics	**17**	61-63	Proportion recruited and characteristics of the recipient population for the implementation strategy	61-63	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	-	Primary and other outcome(s) of the implementation strategy	61-75	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	-	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	-	Resource use, costs, economic outcomes and analysis for the implementation strategy	-	Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	-	Representativeness and outcomes of subgroups including those recruited to specific research tasks		

Fidelity/ adaptation	**22**	-	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	66-68	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	-	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	69-70	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	76-81	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	76	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)	76	Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	82	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		

Appendix 3: Pittsburgh Sleep Quality Index

Índice de qualidade do sono de Pittsburgh – versão Portugal (PSQI-PT)

Nome:_____ Idade:_____ Data:____/____/____

As questões a seguir são referentes à sua qualidade de sono apenas durante o mês passado. Sua resposta deve indicar a lembrança mais exata da maioria dos dias e noites do último mês. Por favor responda a todas as perguntas.

1) Durante o mês passado, a que horas você se deitou à noite, na maioria das vezes?
Horário de deitar:_____h_____min

2) Durante o mês passado, quanto tempo (em minutos) demorou para adormecer, na maioria das vezes?
Minutos demorou a adormecer: _____min

3) Durante o mês passado, a que horas você acordou (levantou) de manhã, na maioria das vezes?
Horário de acordar: _____h_____min

4) Durante o mês passado, quantas horas de sono por noite você dormiu? (pode ser diferente do número de horas que você ficou na cama).
Horas de noite de sono: _____h_____min

Para cada uma das questões seguintes, escolha uma única resposta, que você ache mais correta. Por favor, responda a todas as questões.

5) Durante o mês passado, quantas vezes você teve problema para dormir por causa de:

a) Demorar mais de 30 minutos para adormecer:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

b) Acordar ao meio da noite ou de manhã muito cedo:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

c) Levantar-se para ir à casa de banho:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

d) Ter dificuldade para respirar:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

e) Tossir ou ressonar alto:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

f) Sentir muito frio:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

g) Sentir muito calor:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

h) Ter sonhos maus ou pesadelos:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

i)Sentir dores:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

j) Outra razão, por favor, descreva: _____

_____

Quantas vezes você teve problemas para dormir por esta razão, durante o mês passado?

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

6) Durante o mês passado, como você classificaria a qualidade do seu sono?

( ) Muito boa	( ) Boa	( ) Má	( ) Muito Má

7) Durante o mês passado, você tomou algum medicamento para dormir, receitado pelo médico, ou indicado por outra pessoa (farmacêutico, amigo, familiar) ou mesmo por sua iniciativa?

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

8) **Durante o mês passado, teve problemas em ficar acordado durante as refeições, ou enquanto conduzia, ou enquanto participava nalguma atividade social?**

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

9) **Durante o mês passado, sentiu pouca vontade ou falta de entusiasmo para realizar as suas atividades diárias?**

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

10) Você vive com um(a) companheiro(a)?

( ) Não	( ) Sim, mas em outro quarto	( ) sim, no mesmo quarto mas, não na mesma cama	( ) sim, na mesma cama

Se você tem um(a) companheiro(a) de cama ou quarto, pergunte a ele (ela) se, no mês passado, você teve:

a) Ronco alto:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

b)Pausas longas na respiração durante o sono:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

c)Movimentos de pernas durante o sono:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

d)Episódios de desorientação ou confusão durante o sono:

( ) Nunca	( ) Menos de 1x/semana	( ) 1 ou 2x/semana	( ) 3x/semana ou mais

e)Outros sintomas na cama enquanto dorme, por favor, descreva:

_____

_____

Índice de qualidade do sono de Pittsburgh – versão Portugal (PSQI-PT)

(João, Becker, Jesus, & Martins, 2017)

Instruções de pontuação e referência

Referência

João, K. A. D. R., Becker, N. B., Jesus, S. N., & Martins, R. I. S. (2017). Validation of the Portugal version of the Pittsburgh Sleep Quality Index. *Psychiatry Research, 247*, 225–229.

Pontuações - reportadas em publicações

Componente 1 – Qualidade subjetiva do sono

Examine a **questão 6** e atribua a pontuação da seguinte maneira:

Resposta	Escore
Muito boa	0
Boa	1
Má	2
Muito má	3

Pontuação da componente 1:_____

Componente 2 – Latência do sono

1. Examine a **questão 2** e atribua a pontuação da seguinte maneira:

Resposta	Escore
< ou = 15 minutos	0
16 a 30 minutos	1
31 a 60 minutos	2
>60 minutos	3

2. Examine a **questão 5a** e atribua a pontuação da seguinte maneira:

Resposta	Escore
Nunca	0
Menos de 1x/semana	1
1 ou 2x/semana	2
3x/semana ou mais	3

3. Some a pontuação da **questão 2 e 5a**
4. Atribua a pontuação da Componente 2 da seguinte maneira:

Resposta	Escore
0	0
1 e 2	1
3 e 4	2
5 e 6	3

Pontuação da componente 2:_____

Componente 3 – Duração do sono

1. Examine a **questão 4** e atribua a pontuação da seguinte maneira:

Resposta	Escore
>7 horas	0
6 a 7 horas	1
5 a 6 horas	2
<5 horas	3

Pontuação da componente 3:_____

Componente 4 – Latência do sono

1. Atribua a pontuação da seguinte maneira:
   a) Escreva o número de horas dormidas (**questão 4**):_____
   b) Calcule o número de horas de leito: [horário de levantar (**questão 3**)] – [horário de deitar (**questão 1**)]
   c) Calcule a eficiência do sono: [nº de horas dormidas/nº de horas de leito] x 100 = eficiência do sono %
2. Atribua a pontuação da componente 4 da seguinte maneira:

Resposta	Escore
>85%	0
75% a 84%	1
65% a 74%	2
<65%	3

Pontuação da componente 4:_____

Componente 5 – Distúrbios do sono

1. Examine as **questões de 5b a 5j** e atribua pontuação da seguinte maneira:

Resposta	Escore
Nunca	0
Menos de 1x/semana	1
1 ou 2x/semana	2
3x/semana ou mais	3

2. Some a pontuação das **questões 5b a 5j**
3. Atribua a pontuação da componente 5 da seguinte maneira:

Resposta	Escore
0	0
1 a 9	1
10 a 18	2
19 a 27	3

Pontuação da componente 5:_____

Componente 6 – Uso de medicação para dormir

1. Examine a **questão 7** e atribua a pontuação da seguinte maneira:

Resposta	Escore
Nunca	0
Menos de 1x/semana	1
1 ou 2x/semana	2
3x/semana ou mais	3

Pontuação da componente 6:_____

Componente 7 – Sonolência diurna e distúrbios durante o dia

1. Examine a **questão 8** e atribua a pontuação da seguinte maneira:

Resposta	Escore
Nunca	0
Menos de 1x/semana	1
1 ou 2x/semana	2
3x/semana ou mais	3

2. Examine a **questão 9** e atribua a pontuação da seguinte maneira:

Resposta	Escore
Nunca	0
Menos de 1x/semana	1
1 ou 2x/semana	2
3x/semana ou mais	3

3. Some a pontuação das **questões 8 e 9**
4. Atribua a pontuação da componente 7 da seguinte maneira:

Resposta	Escore
0	0
1 e 2	1
3 e 4	2
5 e 6	3

Pontuação da componente 7:_____

Qualidade do sono – valor global

Some os escores das 7 componentes para obter o valor global do PSQI (Qualidade do sono).

A pontuação varia de 0 a 21.

<5 boa qualidade do sono

>5 pobre qualidade do sono

Appendix 4: Center of Epidemiologic Studies Depression Scale

Nº.....

CES-D

Encontra nesta página uma lista das maneiras como se pode ter sentido ou reagido. Indique com que frequência se sentiu dessa maneira **durante a semana passada** fazendo uma cruz no quadrado correspondente.

Use a seguinte chave:

- ☐ Nunca ou muito raramente (menos de 1 dia)
- ☐ Ocasionalmente (1 ou 2 dias)
- ☐ Com alguma frequência (3 ou 4 dias)
- ☐ Com muita frequência ou sempre (5 ou 7 dias)

Durante a semana passada:	Nunca ou muito raramente	Ocasional-mente	Com alguma frequência	Com muita frequência ou sempre
1. Fiquei aborrecido com coisas que habitualmente não me aborrecem	☐	☐	☐	☐
2. Não me apeteceu comer; estava sem apetite	☐	☐	☐	☐
3. Senti que não conseguia livrar-me da neura ou da tristeza, mesmo com a ajuda da família ou dos amigos	☐	☐	☐	☐
4. Senti que valia tanto como os outros	☐	☐	☐	☐
5. Tive dificuldade em manter-me concentrado no que estava a fazer	☐	☐	☐	☐
6. Senti-me deprimido	☐	☐	☐	☐
7. Senti que tudo o que fazia era um esforço	☐	☐	☐	☐
8. Senti-me confiante no futuro	☐	☐	☐	☐
9. Pensei que a minha vida tinha sido um fracasso	☐	☐	☐	☐
10. Senti-me com medo	☐	☐	☐	☐
11. Dormi mal	☐	☐	☐	☐
12. Senti-me feliz	☐	☐	☐	☐
13. Falei menos do que o costume	☐	☐	☐	☐
14. Senti-me sozinho	☐	☐	☐	☐
15. As pessoas foram desagradáveis ou pouco amigáveis comigo	☐	☐	☐	☐
16. Senti prazer ou gosto na vida	☐	☐	☐	☐
17. Tive ataques de choro	☐	☐	☐	☐
18. Senti-me triste	☐	☐	☐	☐
19. Senti que as pessoas não gostavam de mim	☐	☐	☐	☐
20. Senti falta de energia	☐	☐	☐	☐

T.Fagulha & B.Gonçalves, FPCE-UL. Versão para estudo. Circulação restrita.

Appendix 5: Functional Assessment of Chronic Illness Therapy – Fatigue Scale

Escala de Fadiga FACIT (Versão 4)

Nome: _____ Data: ___ / ___ / _____

Abaixo encontrará uma lista de afirmações que outras pessoas com a sua doença disseram ser importante. **Por favor, circunde ou marque um número em cada um das linhas para indicar a resposta que melhor corresponde ao seu estado durante os <u>últimos 7 dias</u>.**

	Nem um pouco	Um pouco	Mais ou menos	Muito	Muitíssimo
Sinto-me fatigado(a)	0	1	2	3	4
Sinto fraqueza generalizada	0	1	2	3	4
Sinto-me sem forças	0	1	2	3	4
Sinto-me cansado(a)	0	1	2	3	4
Tenho dificuldade em começar as coisas porque estou cansado(a)	0	1	2	3	4
Tenho dificuldade em terminar as coisas porque estou cansado(a)	0	1	2	3	4
Tenho energia	0	1	2	3	4
Sou capaz de fazer as minhas actividades normais	0	1	2	3	4
Preciso de dormir durante do dia	0	1	2	3	4
Estou cansado(a) demais para comer	0	1	2	3	4
Preciso de ajuda para as minhas actividades normais	0	1	2	3	4
Estou frustrado(a) por estar cansado(a) demais para fazer as coisas que quero	0	1	2	3	4
Tenho de limitar a minha vida social por estar cansado(a)	0	1	2	3	4

FACIT-Fatigue Subscale Scoring Guidelines (Version 4)

Instructions: * 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____=**Fatigue Subscale score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

Appendix 6: STARI checklist – Video conferencing telehealth exercise intervention: a controlled nation-wide effectiveness-implementation study

Standards for Reporting Implementation Studies: the StaRI checklist for completion

The StaRI standard should be referenced as: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths CJ, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor SJC for the StaRI Group. Standards for Reporting Implementation Studies (StaRI) statement. *BMJ* 2017;356:i6795

The detailed Explanation and Elaboration document, which provides the rationale and exemplar text for all these items is: Pinnock H, Barwick M, Carpenter C, Eldridge S, Grandes G, Griffiths C, Rycroft-Malone J, Meissner P, Murray E, Patel A, Sheikh A, Taylor S, for the StaRI group. Standards for Reporting Implementation Studies (StaRI). Explanation and Elaboration document. *BMJ Open* 2017 2017;7:e013318

Notes: A key concept of the StaRI standards is the dual strands of describing, on the one hand, the implementation strategy and, on the other, the clinical, healthcare, or public health intervention that is being implemented. These strands are represented as two columns in the checklist.

The primary focus of implementation science is the implementation strategy (column 1) and the expectation is that this will always be completed.	The evidence about the impact of the intervention on the targeted population should always be considered (column 2) and either health outcomes reported or robust evidence cited to support a known beneficial effect of the intervention on the health of individuals or populations.

The StaRI standardsrefers to the broad range of study designs employed in implementation science. Authors should refer to other reporting standards for advice on reporting specific methodological features. Conversely, whilst all items are worthy of consideration, not all items will be applicable to, or feasible within every study.

Checklist item		Reported on page #	Implementation Strategy	Reported on page #	Intervention
			"Implementation strategy" refers to how the intervention was implemented		"Intervention" refers to the healthcare or public health intervention that is being implemented.
Title and abstract					
Title	**1**	107	Identification as an implementation study, and description of the methodology in the title and/or keywords		

Abstract	**2**	108-109	Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.		
Introduction					
Introduction	**3**	110	Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.		
Rationale	**4**	110	The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).	110	The scientific background and rationale for the intervention being implemented (including evidence about its effectiveness and how it is expected to achieve its effects).
Aims and objectives	**5**	111	The aims of the study, differentiating between implementation objectives and any intervention objectives.		
Methods: description					
Design	**6**	112	The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons		
Context	**7**	112	The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).		
Targeted 'sites'	**8**	112, 113	The characteristics of the targeted 'site(s)' (e.g locations/personnel/resources etc.) for implementation and any eligibility criteria.	112, 113	The population targeted by the intervention and any eligibility criteria.
Description	**9**	113, 114	A description of the implementation strategy	114, 116	A description of the intervention
Sub-groups	**10**	-	Any sub-groups recruited for additional research tasks, and/or nested studies are described		
Methods: evaluation					

Outcomes	**11**	117	Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets	117	Defined pre-specified primary and other outcome(s) of the intervention (if assessed), and how they were assessed. Document any pre-determined targets
Process evaluation	**12**	-	Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work		
Economic evaluation	**13**	-	Methods for resource use, costs, economic outcomes and analysis for the implementation strategy	-	Methods for resource use, costs, economic outcomes and analysis for the intervention
Sample size	**14**	-	Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)		
Analysis	**15**	118	Methods of analysis (with reasons for that choice)		
Sub-group analyses	**16**	-	Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks		
Results					
Characteristics	**17**	119	Proportion recruited and characteristics of the recipient population for the implementation strategy	119	Proportion recruited and characteristics (if appropriate) of the recipient population for the intervention
Outcomes	**18**	-	Primary and other outcome(s) of the implementation strategy	119 - 131	Primary and other outcome(s) of the Intervention (if assessed)
Process outcomes	**19**	-	Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work		
Economic evaluation	**20**	-	Resource use, costs, economic outcomes and analysis for the implementation strategy		Resource use, costs, economic outcomes and analysis for the intervention
Sub-group analyses	**21**	-	Representativeness and outcomes of subgroups including those recruited to specific research tasks		

Fidelity/ adaptation	**22**	-	Fidelity to implementation strategy as planned and adaptation to suit context and preferences	123, 124	Fidelity to delivering the core components of intervention (where measured)
Contextual changes	**23**	-	Contextual changes (if any) which may have affected outcomes		
Harms	**24**	125, 126	All important harms or unintended effects in each group		
Discussion					
Structured discussion	**25**	132 - 136	Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications		
Implications	**26**	-	Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)	135	Discussion of policy, practice and/or research implications of the intervention (specifically including sustainability)
General					
Statements	**27**	137	Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest		