Università
degli Studi
di Ferrara

DOCTORAL COURSE IN
"ENVIRONMENTAL SUSTAINABILITY AND WELLBEING"

CYCLE XXXVI

COORDINATOR Prof. Spinozzi Paola

A MULTI-DISCIPLINARY APPROACH TO THE PHYSICAL, PSYCHOLOGICAL AND SOCIAL WELLBEING OF PEOPLE IN DIALYSIS CENTER

Scientific/Disciplinary Sector (SDS) M-EDF/01

Candidate
Dott. Piva Giovanni

Supervisor
Prof. Lamberti Nicola

Year 2020/2024

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1. AIM OF THE PROJECT

Chronic kidney disease (CKD) is a worldwide public health problem that affects millions of people. In the final stage of the disease, the kidneys cease to function, necessitating replacement treatment for the patient's survival. The most common treatment for kidney failure is dialysis, which can significantly affect a person's quality of life.

Physical activity is widely recommended as an effective intervention to improve patients' conditions. However, many barriers exist, such as the absence of a physical activity expert to whom patients can turn, which can force them into a sedentary lifestyle.

In order to spread the physical and psychological benefits to as many patients as possible, this PhD project aims to conduct a pragmatic, non-randomised trial with an exercise expert in the dialysis unit. His role was to contact each patient individually and propose four different exercise modalities, from which the patient could choose the one that best suited his/her availability. The patients underwent functional assessments and psychological questionnaires before the start of the exercise period and repeated the same measurements at the end of the planned three months of training. The objectives of the trial included determining which type of exercise was preferred by dialysis patients and whether there was a difference in effectiveness between the proposed programmes.

In order to increase the benefits of exercise on the mood of dialysis patients and staff, it was considered that the environment of the dialysis centre itself should be modified. Recognising the proven benefits of the natural environment on people's mood, the redesign of the dialysis centre's exterior and interior environment was designed to harness its effects to enhance the patients' experience of the treatment site.

CHAPTERS 2 – 3

2. CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) is a worldwide public health problem. The causes, consequences, and costs of kidney disease have implications for public health policy in all countries [1]. This condition occurs when the kidneys are damaged and can't filter blood the way they should. It is a noncommunicable disease with a progressively worsening course. From a clinical perspective, CKD is defined as a reduced eGFR (<60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), excess urinary albumin excretion (ACR ≥30 mg/g), or both [2]. The more common causes of CKD in adults are diabetes mellitus and hypertension. Other risk factors include cardiovascular disease (CVD), obesity, family history of CKD, kidney disorders, past damage to the kidneys, and age. However, in the early stages, it is possible to slow the progression of the disease through drug therapy, proper nutrition [3,4], and physical exercise [5]. In the final stage of the disease, called end-stage renal disease (ESRD), the kidneys are no longer able to perform their tasks. Hence, patients need replacement treatment to survive. Several replacement therapies exist, such as haemodialysis, peritoneal dialysis, or kidney transplantation [6]. Each substitution treatment has its strengths and weaknesses; nevertheless, they are all costly solutions for the health care system [7] and have a high environmental impact. In particular, the impact of dialysis on patients' quality of life (QoL) is devastating, as it pushes them toward a condition of progressive disability, resulting in loss of autonomy.

2.1 Epidemiology of CKD

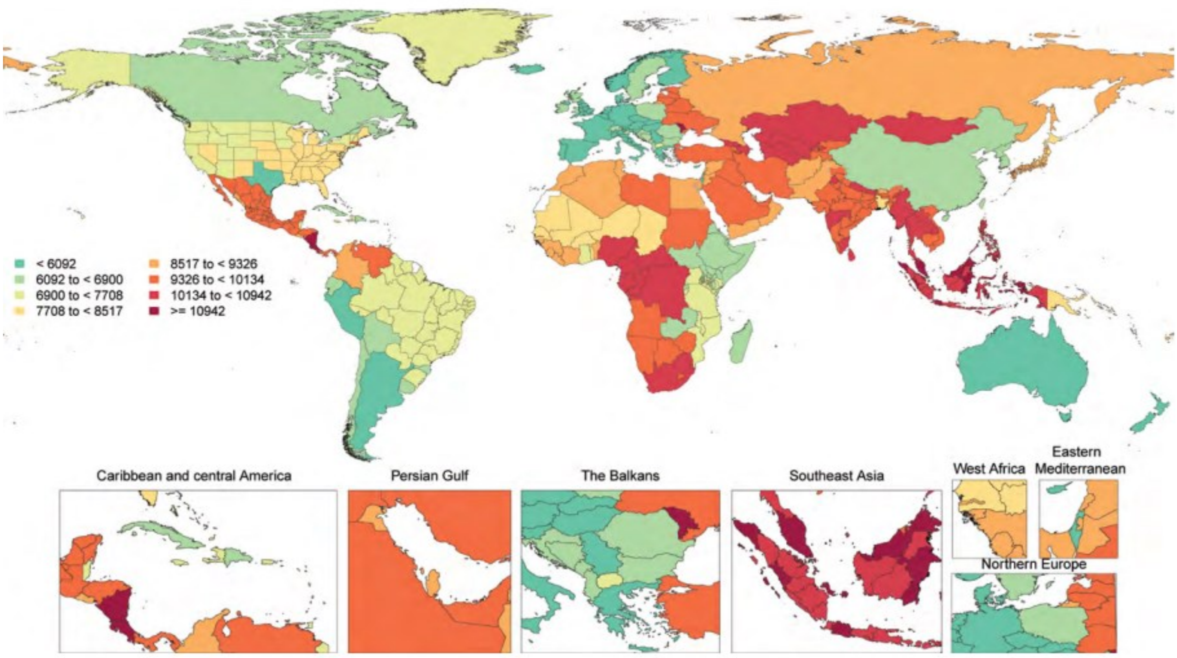
CKD is a condition that affects >10% of the general population worldwide, with >800 million individuals and a dramatic increasing trend. CKD has emerged as one of the leading causes of death worldwide [8]. Although it is a problem of worldwide concern and the presence of the disease is increasing worldwide, its distribution is not homogeneous.
The prevalence of CKD shows significant geographical differences between high-income countries and middle- or low-income countries. In general, in richer countries, the disease is present at slightly lower rates [9], and this difference is increasing. In particular, concerning the last stage of the disease, the most recent studies have shown that poverty is an independent cause that favors the presence of ESRD more than in the past. This is a major issue considering the high costs required to treat people with kidney failure.

Many risk factors for CKD, such as smoking and diabetes, are the same as those for CVD. Age is a risk factor for CKD. Although it is also prevalent in young adults, older people are more exposed. Indeed, CKD affects 6% of people aged 18–44 years and 12% of people aged 45–64 years; in people >65 years of age, it affects approximately 38% of the population [2]. In elderly individuals, the aggravation of the disease, with a consequent reduction in autonomy, pushes them toward the loss of independence, requiring the help of family members or other caregivers. Taking care of a patient with kidney failure requires a considerable amount of time and energy and greatly impacts the QoL of patients and caregivers [10].

Social factors play an important role in the prevalence of this disease. Socioeconomically disadvantaged populations show a disproportionate burden of CKD, often complicated by the unavailability of adequate medical care [11].

Gender and ethnicity also affect the prevalence of CKD. Regarding gender-related disparities, there is strong evidence in the literature that kidney disease is prevalent and evolves differently between males and females. The prevalence of CKD is greater in females, even though there is a greater incidence of ESRD in males [12]. Additionally, ethnicity affects the incidence, prevalence, and course of CKD. These disparities are also due to differences in healthcare access and health outcomes. It has been proven that people of different ethnicities who become minorities in the country to which they are migrating may have increased risk factors for CKD. Studies performed in the United States have shown that African Americans are more at risk of CKD and progress from earlier stages to ESRD faster than other populations [13,14].

Figure 1. Age-standardized global prevalence rates for CKD per 100,000 people of both sexes in 2020. [13]



2.2 Diagnosis of CKD

CKD is characterized by a gradual loss of kidney function over time. There are two methods for diagnosing and monitoring CKD:

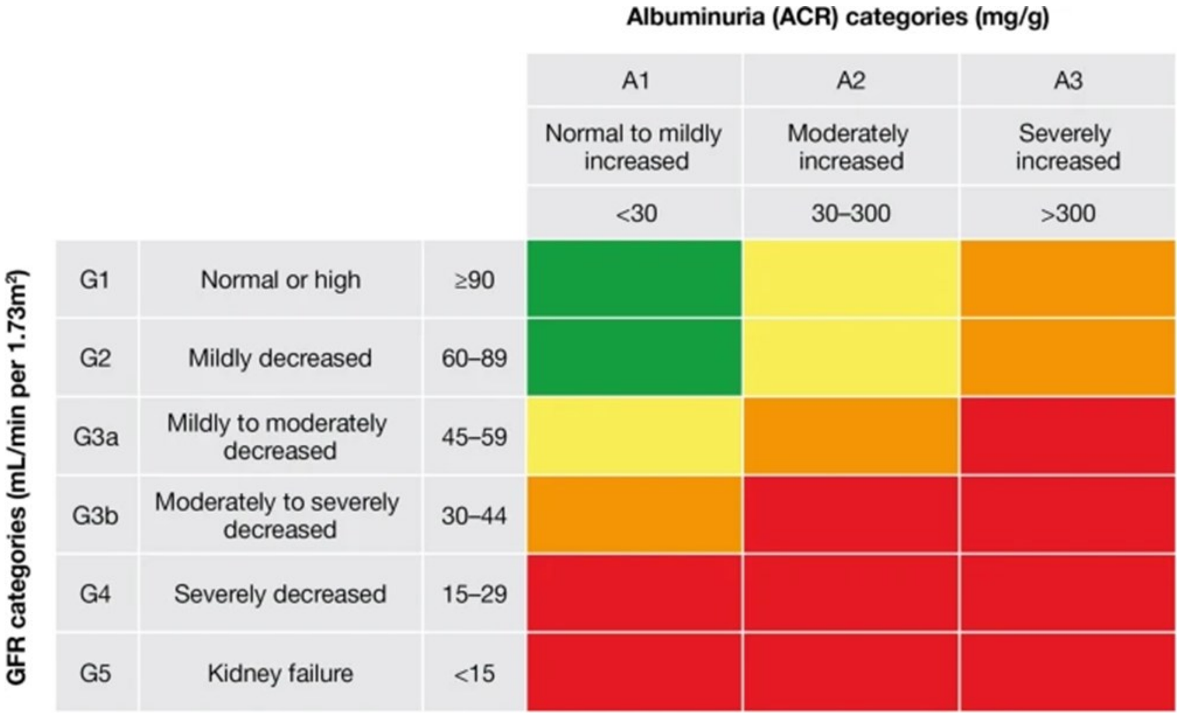
- A blood test, called Glomerular Filtration Rate (GFR), measures the effectiveness of the kidneys in filtering the blood, estimating how much blood passes through the glomeruli each minute. It is performed by obtaining creatinine levels in a blood sample, and it is a chemical waste product of creatine. In healthy kidneys, creatinine is removed from the blood, and as CKD worsens, creatinine levels increase. Afterward, the creatinine level was combined with other factors (age, ethnicity, gender, height, weight) to estimate the GFR (eGFR).
- A test to determine the presence of albumin in the urine. It is a protein that can pass into the urine when the kidneys are damaged; if it is detected, it is a sign of kidney injury.

These two values can be combined to identify the risk of worsening disease to which the patient is exposed (Figure 2). The same tests can be repeated over time to monitor the evolution of the disease. Although the GFR can't increase, it is important to slow deterioration as much as possible.

2.3 Progression of CKD

CKD was classified according to the eGFR and albuminuria level to stratify patients according to the degree of risk (Figure 2).

Figure 2. Prognosis of CKD by GFR and albuminuria categories [15]



Green: low risk of disease progression; Yellow: moderately increased risk of disease progression; Orange: high risk of disease progression; Red: very high risk.

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

Each stage of CKD can be associated with different symptoms:

- ***Stage 1***: The GFR is at a normal level (90 or more), and the kidney is slightly damaged and still functioning well. It is possible that there are no symptoms or that there may be other signs of kidney damage, such as proteinuria.
- ***Stage 2***: When the GFR is between 60 and 89, the kidneys are mildly damaged and continue to work well, and it is still possible that there are no visible signs or that there are minor symptoms.

- ***Stage 3***: The GFR decreases between 30 and 59, indicating moderate kidney damage. Stage 3 is divided into two substages based on the GFR: at stage 3a, the GFR is 45-59, and at stage 3B, it is 30-44. At this point, the kidneys no longer work as they should and cannot filter the extra fluid from the blood. Symptoms include hypertension, fatigue, and distal swelling in the lower and upper limbs. With appropriate medical therapy and a healthy lifestyle based on physical activity and a proper diet, many people can maintain their disease at stage 3.
- ***Stage 4***: The GFR is between 29-15, and renal damage is moderate-severe. Waste that the kidneys cannot filter continues to cause problems, including cardiovascular problems. is the last stage before renal failure, so it is essential to have regular nephrology follow-ups to plan the start of replacement treatment.
- ***Stage 5***: End-stage kidney disease (ESRD): The GFR is <15, renal damage is severe, and the kidneys can no longer perform their tasks. Under these conditions, replacement treatment is necessary for survival; the only options are renal transplantation or dialysis.

2.4 End-Stage Renal Disease

ESRD is defined as severe CKD requiring long-term kidney replacement therapy [6]. At this stage of the disease, individuals have a high risk of CVD morbidity and mortality, even though the death rate is declining [9]. As with the other stages of the disease, the prevalence of ESRD is also influenced by factors such as ethnicity and gender. Several studies have been conducted on this topic in the United States [13], but there is a lack of studies on these differences globally. In the US, in 2019, the prevalence of ESRD was highest in black adults, followed by Native American adults, Asian adults, and White adults [13].
With regard to the two countries where the PhD project was conducted, in Italy more than 40,000 people are affected by ERSD [16], while in Spain the number exceeds 60,000 [17].

2.5 Replacement treatments

Since the kidneys can no longer perform their functions, patients must undergo renal replacement treatment (RRT) to survive. RRT is defined as a therapy that replaces kidney function.

There are different types of RRT.

- ***Dialysis***: Dialysis is the process of removing waste products and excess fluid from the body. This operation can be performed in several ways.
    - ***Haemodialysis (HD)***: The patient is connected to a dialysis machine, which pumps blood from the patient's body, passes it through a filter called a dialyzer, and puts it back into the patient's circulation.
    - ***Peritoneal Dialysis (PD)***: removes waste and extra fluid through the blood vessels of the peritoneum, a membrane that covers the walls of the abdomen.
- ***Kidney Transplant (KT)***: Some people with ESRD may be able to receive, through surgical transplantation, a healthy kidney from a compatible donor. The new kidney performs the same function as the two old kidneys.

Both modalities have advantages and disadvantages. With respect to KT, in the case of successful surgery, the patient’s life expectancy and QoL can improve significantly [18] because stopping dialysis allows more time and energy for daily activities and travel, improves sex life, and reduces dietary restrictions. On the other hand, there are several risks associated with the procedure, both related to the surgery [19] and problems with the transplanted kidney, as well as the use of immunosuppressant medicines [20], which are necessary to prevent rejection. However, due to a critical shortage of available kidney grafts, the majority of people with ESRD do not have the opportunity to receive KT. Fewer than 20% of patients requiring HD undergo KT [21], despite attempts globally to increase this percentage, so dialysis treatment remains the only chance of survival for most of them.
This dependence on therapy seriously affects patients’ psychological and social well-being. Therefore, in addition to monitoring the medical aspect, psychosocial evaluation is relevant because RRT, especially HD, makes patients socially and emotionally vulnerable. It interrupts work and school routines and leisure activities; creates anger, frustration, tension, and guilt due to the dependence on caregivers (e.g., partners, relatives, friends) to which the frailest patients are forced; and alters body image [22] because of reduced physical energy, loss of or decrease in sexual desire and function [23], changes in body composition [24], changed appearance due to access surgery, dialysis catheter placement, needle marks, bone disease, or other physical deterioration. Some patients react to these feelings by nonadherence or by being uncooperative with the treatment team [25,26].

References

1. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ [Internet]. 2018 Jun 1;96(6):414-422D. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5996218/pdf/BLT.17.206441.pdf/
2. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis [Internet]. 2021 Apr;77(4):A7–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S027263862100024X
3. Jiang S, Fang J, Li W. Protein restriction for diabetic kidney disease. Cochrane Database Syst Rev [Internet]. 2023 Jan 3;2023(1). Available from: http://doi.wiley.com/10.1002/14651858.CD014906.pub2
4. Hodson EM, Cooper TE. Altered dietary salt intake for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev [Internet]. 2023 Jan 16;2023(1). Available from: http://doi.wiley.com/10.1002/14651858.CD006763.pub3
5. Zhang L, Wang Y, Xiong L, Luo Y, Huang Z, Yi B. Exercise therapy improves eGFR, and reduces blood pressure and BMI in non-dialysis CKD patients: evidence from a meta-analysis. BMC Nephrol [Internet]. 2019 Dec 29;20(1):398. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-019-1586-5
6. Levey AS, Eckardt K-U, Dorman NM, Christiansen SL, Hoorn EJ, Ingelfinger JR, et al. Nomenclature for kidney function and disease: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int [Internet]. 2020 Jun;97(6):1117–29. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253820302337
7. Johansen KL, Chertow GM, Gilbertson DT, Herzog CA, Ishani A, Israni AK, et al. US Renal Data System 2021 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis [Internet]. 2022 Apr;79(4):A8–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S027263862200453X
8. Rhee CM, Kovesdy CP. Spotlight on CKD deaths—increasing mortality worldwide. Nat Rev Nephrol [Internet]. 2015 Apr 3;11(4):199–200. Available from: https://www.nature.com/articles/nrneph.2015.25

9. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl [Internet]. 2022 Apr;12(1):7–11. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2157171621000666
10. Ebadi A, Sajadi SA, Moradian ST, Akbari R. Psychological consequences for family caregivers of patients receiving hemodialysis: threat or opportunity? BMC Psychol [Internet]. 2021 Dec 7;9(1):154. Available from: https://bmcpsychology.biomedcentral.com/articles/10.1186/s40359-021-00667-7
11. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic Disparities in Chronic Kidney Disease. Adv Chronic Kidney Dis [Internet]. 2015 Jan;22(1):6–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1548559514001086
12. Harris RC, Zhang M-Z. The role of gender disparities in kidney injury. Ann Transl Med [Internet]. 2020 Apr;8(7):514–514. Available from: http://atm.amegroups.com/article/view/37890/html
13. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, et al. Heart Disease and Stroke Statistics—2023 Update: A Report From the American Heart Association. Circulation [Internet]. 2023 Feb 21;147(8). Available from: https://www.ahajournals.org/doi/10.1161/CIR.0000000000001123
14. Correa-Rotter R, García-García G, Chávez-Iñiguez J, Ramírez-Sandoval JC. Ethnicity and Chronic Kidney Disease in Disadvantaged Populations—An International Perspective. In: Chronic Renal Disease [Internet]. Elsevier; 2020. p. 121–38. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780128158760000097
15. Murton M, Goff-Leggett D, Bobrowska A, Garcia Sanchez JJ, James G, Wittbrodt E, et al. Burden of Chronic Kidney Disease by KDIGO Categories of Glomerular Filtration Rate and Albuminuria: A Systematic Review. Adv Ther [Internet]. 2021 Jan 24;38(1):180–200. Available from: http://link.springer.com/10.1007/s12325-020-01568-8
16. Report 2010 – Ridt. https://ridt.sinitaly.org/2017/03/21/report-2010/. Accessed 22 Sept 2022
17. Mahillo B; on behalf of the Spanish Registry of Renal Patients (REER) : Dialysis and Transplant report 2018. Available at: www.senefro.org
18. Sarhan AL, Jarareh RH, Shraim M. Quality of life for kidney transplant recipients and hemodialysis patients in Palestine: a cross-sectional study. BMC Nephrol [Internet]. 2021 Dec 3;22(1):210. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-021-02412-z

19. Reyna-Sepúlveda F, Ponce-Escobedo A, Guevara-Charles A, Escobedo-Villarreal M, Pérez-Rodríguez E, Muñoz-Maldonado G, et al. Outcomes and Surgical Complications in Kidney Transplantation. Int J organ Transplant Med [Internet]. 2017;8(2):78–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28828167
20. Bauer AC, Franco RF, Manfro RC. Immunosuppression in Kidney Transplantation: State of the Art and Current Protocols. Curr Pharm Des [Internet]. 2020 Aug 31;26(28):3440–50. Available from: https://www.eurekaselect.com/182196/article
21. Vernooij RWM, Law W, Peters SAE, Canaud B, Davenport A, Grooteman MPC, et al. The probability of receiving a kidney transplantation in end-stage kidney disease patients who are treated with haemodiafiltration or haemodialysis: a pooled individual participant data from four randomised controlled trials. BMC Nephrol [Internet]. 2021 Dec 25;22(1):70. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-021-02265-6
22. Lev-Wiesel R, Sasson L, Scharf N, Abu Saleh Y, Glikman A, Hazan D, et al. "Losing Faith in My Body": Body Image in Individuals Diagnosed with End-Stage Renal Disease as Reflected in Drawings and Narratives. Int J Environ Res Public Health [Internet]. 2022 Aug 30;19(17):10777. Available from: https://www.mdpi.com/1660-4601/19/17/10777
23. Luo L, Xiao C, Xiang Q, Zhu Z, Liu Y, Wang J, et al. Significant Increase of Sexual Dysfunction in Patients with Renal Failure Receiving Renal Replacement Therapy: A Systematic Review and Meta-Analysis. J Sex Med [Internet]. 2020 Dec 1;17(12):2382–93. Available from: https://academic.oup.com/jsm/article/17/12/2382/6973802
24. Wang K, Zelnick LR, Chertow GM, Himmelfarb J, Bansal N. Body Composition Changes Following Dialysis Initiation and Cardiovascular and Mortality Outcomes in CRIC (Chronic Renal Insufficiency Cohort): A Bioimpedance Analysis Substudy. Kidney Med [Internet]. 2021 May;3(3):327-334.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2590059521000248
25. Clark S, Farrington K, Chilcot J. Nonadherence in Dialysis Patients: Prevalence, Measurement, Outcome, and Psychological Determinants. Semin Dial [Internet]. 2014 Jan 25;27(1):42–9. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12159
26. Ozen N, Cinar FI, Askin D, Mut D, Turker T. Nonadherence in Hemodialysis Patients and Related Factors: A Multicenter Study. J Nurs Res [Internet]. 2019

Aug;27(4):e36. Available from: https://journals.lww.com/00134372-201908000-00008

3. DIALYSIS

In the final stage of CKD, kidney function is compromised. Dialysis is a procedure for removing waste products and excess fluid from the blood when the kidneys stop working properly. During dialysis, the patient is required to be connected to a machine that performs the functions of the kidney, which is why it is also called an "artificial kidney."
There are two types of dialysis treatment: haemodialysis and peritoneal dialysis.

3.1 Haemodialysis

HD treatment requires the patient to be connected to a machine, which draws blood from the patient and runs it through a "dialyzer" filter, which removes waste and then returns it to circulation. It is an invasive procedure requiring the patient to remain attached to the machine for 3 to 5 hours. Although some patients are allowed to receive treatment at home, most are forced to go to the dialysis centre 2 to 4 times a week. This is necessary, as the prescribed procedure must be observed scrupulously at all times to avoid the risk of infection and other unfavourable events, which represent a real risk to patients [1].

Most infections originate from vascular access. Patients can be connected to the machine in two ways: through a catheter or through a fistula.

- ***Dialysis catheter***: an artificial indwelling transcutaneous conduit used to access the intravascular or intraperitoneal space for RRT. There are two broad types of dialysis catheters: those used for extracorporeal modes of RRT (such as HD) and those used for PD. HD catheters are essentially central venous lines that allow blood to be drawn and returned to the patient efficiently. In this way, the patient's blood can be temporarily removed from the body to be processed in a machine that can perform HD. Depending on the expected duration of therapy, the catheter may be inserted directly through the skin into the target vein or passed under the skin through a short subcutaneous tunnel before reaching the vein [2].
- ***Dialysis fistula***: a procedure performed for patients who require permanent vascular access for haemodialysis. An arteriovenous fistula is a surgical connection between an artery and a vein. Since veins can be perforated quite easily, the blood flow inside them is too low for HD treatment, while in arteries, blood flows with higher pressure.

Nevertheless, they are much harder to reach, and a new vessel is surgically created, combining the characteristics of both. During the "maturation" process, the diameter and thickness of the vessel wall increase, making it easier to insert the needle. This process takes 2-6 weeks. Arteriovenous fistulas are preferred because they have superior clinical and economic advantages [3]. The most common arteriovenous fistula techniques include radio cephalic fistula, brachiocephalic fistula, and transposed brachiobasilic fistula.

Figure 1. Arteriovenous fistula

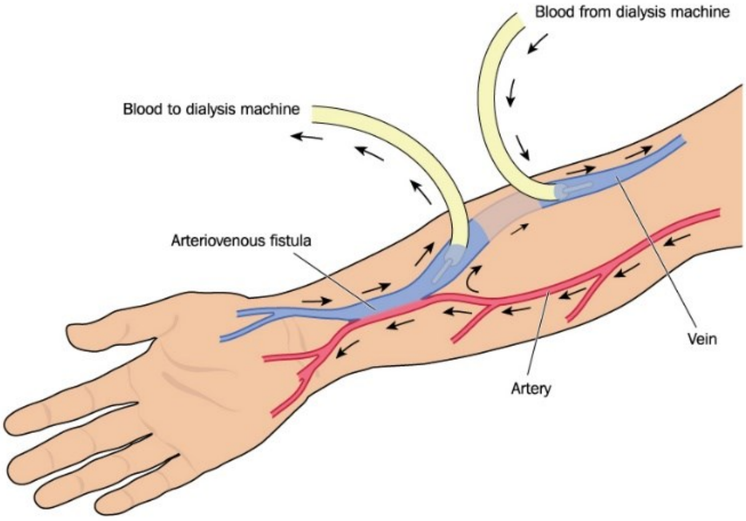
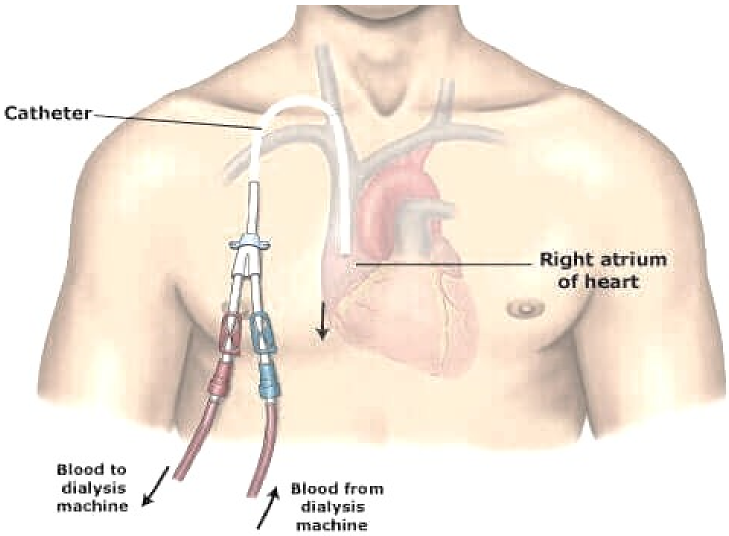


Figure 2. Dialysis catheter



3.2 Peritoneal dialysis

In contrast to HD, PD does not require a machine to purify the patient's blood; it uses a membrane, called the peritoneum, which works as a filter. A catheter was surgically placed in the patient's belly a few weeks before starting peritoneal dialysis. Dialysis solution is inserted through the catheter from a bag at the beginning of treatment. While inside the abdomen, the dialysis solution absorbs waste and extra bodily fluids. After a few hours, the solution and waste are drained from the belly into a second empty bag.

There are two types of PD:

- ***Continuous ambulatory peritoneal dialysis***: the patient manually performs the bag exchange in any sterilized place. The procedure took approximately 30-40 minutes, and the solution was kept in the belly for 4-6 hours. Activities such as reading, watching TV, etc., can be carried out during the exchange. It is necessary to repeat the operation at least four times/day and sleep with the solution in the belly at night.
- ***Automated peritoneal dialysis***: In this case, a machine, called a cycler, exchanges the dirty solution for the clean solution three to five times during the night while the patient sleeps. Afterward, the last solution can be left in the belly throughout the day, or an exchange can be performed manually during the day.

3.3 Dialysis-related issues

HD significantly impacts a patient’s quality of life, especially in the beginning. This is because patients' lives depend on a machine, and they are often forced to rely on the help of caregivers (e.g., partners, relatives, friends) because of a physical condition that worsens over time. This loss of independence, combined with the awareness that this new condition will last for the rest of their lives, except in the case of transplantation, can push patients toward depression.

3.3.1 Mortality

Patients on HD treatment have a greater risk of death than healthy people of the same age. In the United States, the 1-year mortality rate after dialysis initiation for people older than 65 years is approximately 30% [4], with a 5-year survival rate of approximately 50% [5]. Cardiovascular diseases are reportedly the leading causes of death among HD patients [6]; however, approximately a quarter of the deaths are attributed to unknown causes [5].

It is necessary to construct sustainable intervention models that extend the survival perspective of patients. In this regard, multiple observational studies have reported that increased physical activity levels are associated with decreased mortality among HD patients [7,8]. Including patients in specific exercise programs means increasing their chances of survival. Therefore, it is necessary to establish multidisciplinary teams, which include exercise experts, for the prescription of physical exercise in HD patients [9].

3.3.2 Hospitalization

When HD develops, patients are at high risk of hospitalization. During the first year of treatment, more than 80% of patients are hospitalized [10]. Younger patients are particularly affected by these adverse events (hospitalization and mortality) during the initial treatment period. In these patients, infections are the most common cause of hospitalization [11].

For these people, hospitalization is risky because it not only increases the risk of death but also exposes them to a period of forced sedentariness, which poses a danger to them and can lead to a deterioration in their health and quality of life.

One protective element is exercise, which has been shown to be effective in reducing the risk of hospitalisation. Mallamaci et al [8] analysed the effects after three years of a six-month walking programme and reported that the long-term risk of hospitalisation in the exercise group was 29-45% lower than in the control group, depending on adherence to the prescribed programme.

3.3.3 Sedentary lifestyle

The WHO recommends adopting an active lifestyle and reducing sedentary behaviours [12]. In healthy people, regular physical activity is associated with a reduced risk of mortality caused by cardiovascular disease, diabetes, obesity, and cancer [13]. Recent studies have confirmed that higher levels of physical activity are associated with reduced mortality, even in dialysis patients [7,14]. Nevertheless, patients on HD are less active than age-matched sedentary controls; consequently, they cannot benefit from the protective effect of exercise. In addition to the progressive deterioration of functional capacity induced by the disease, this inactivity forces patients into a vicious cycle, which exposes them to a greater risk of adverse events and worsens their quality of life (QoL).

Therefore, developing effective strategies to promote a physically active lifestyle is fundamental to improving HD patients' quality and length of life. However, despite the known benefits, engaging dialysis patients in exercise programs is a difficult challenge due to the existence of several barriers that limit adherence [15]. The researchers' goal then should be to develop simple and easily implemented intervention models so that as many people as possible can be involved.

3.3.4 Fatigue

Among the barriers to exercise, fatigue is defined as a condition marked by "*overall tiredness and inability to function due to a lack of energy*". It is one of the most commonly reported debilitating symptoms among HD patients, with a reported prevalence rate of 60-97% [16] and a profound negative impact on their QoL [17]. The consequences of fatigue are bodily depletion due to a vicious cycle of post-dialysis exhaustion, vigilance, and worry inhibiting rest, restricted life participation, diminishing capacities to fulfil relationship roles, and vulnerability to misunderstanding due to being criticized for the need to rest and fail to meet expectations [18]. Another issue related to fatigue is that it is the main cause of limited physical activity [19].

Although fatigue is one of the main causes of sedentary behaviour in this population, it has been proven that specific exercise programmes can counteract this trend. In fact, Grigoriu et al conducted a trial [20] of nine months of exercise, at the end of which participants reported less perceived fatigue, both at the end of the dialysis session and in general.

Considering the high prevalence of this condition in HD patients, it is essential that the proposed exercise programs take this into account and that they can be carried out even by individuals with low energy reserves.

3.3.5 Depression

Depression is defined as a "*mood disorder that causes a persistent feeling of sadness and loss of interest*". It is estimated that 5% of the global population suffers from this disorder, and it is the most common psychological problem for people with HD; approximately one-quarter meet the diagnostic criteria for major depression [21,22]. HD patients are associated with lower adherence to medical prescriptions [22,23], which may lead to poorer clinical outcomes [24]. Depression has also been associated with increased death [21,25,26] and increased risk of hospitalization in HD patients [27,28]. The main factors contributing to depressive symptoms are medications, reductions in physical function, and dietary restrictions [29].

To improve this aspect, a multidisciplinary approach is needed. Depression can be treated by both physical and psychosocial interventions [30]. However, sedentary behaviour is positively associated with depression [31]. The correlation between these two aspects (sedentariness and bad mood) represents a difficult issue to overcome when aiming to introduce patients to exercise. The care of HD patients must include these aspects, as active patient involvement is necessary to ensure adherence to the proposed treatment over time.

3.3.6 Social isolation

Social isolation is defined as a lack of social relationships and low levels of contact with family, friends, the community, and the general social environment [32]. It is significantly associated with a rapid decline in kidney function at all stages of the disease [33], worsening QoL, and a greater incidence of various psychological and physical disorders [34,35]. It is a common condition in patients with ESKD [36], particularly in the HD population, who, due to physical (fatigue) and psychological (depression) symptoms, often drastically reduce the time spent together with friends, relatives, etc., and thus spend considerable time at home.

In treating patients, this aspect must both be combined (to avert the negative outcomes with which it is associated) and respected because an approach that is too "invasive" could be perceived as a violation of privacy and could lead the patient to refuse the procedure.

3.4 Benefits

Despite complex situations due to several factors that negatively affect the condition of patients, several factors can improve the quality of life of these people. This is a crucial aspect. Improving health-related quality of life is often more important than just prolonging life for older people [37]. Considering the particularly frail condition and the limited resources, in terms of energy and time, that patients have, it is crucial to implement strategies that will bring definite benefits with very low risks.

3.4.1 Physical exercise

The WHO has highlighted the importance of exercise for the mental and physical well-being of people of all ages and abilities [12]. The benefits that physical activity can bring people on dialysis are well recognized. Exercise can improve depression and the capacity to perform activities and tasks. It may also improve fatigue, pain, and the physical aspects of QoL, improving the mental well-being of patients [38]. Moreover, people in HD need to engage in physical activity to reduce their level of sedentariness [39].

Although the benefits of exercise for dialysis patients are now recognized, this approach is relatively "young." Indeed, until a few decades ago, physical activity in frail people was limited or even discouraged for these individuals because of their condition. This type of prescription has proven to be counterproductive. By advising HD patients to further reduce their already low levels of physical activity, they were forced to remain prisoners of the vicious cycle of sedentariness. Fortunately, this approach has been abandoned, and scientific research is increasingly active in the search for effective and sustainable models of exercise that are effective in HD patients. Although exercise can benefit all dialysis patients, whether they are HD or PD patients, these patients are a very heterogeneous population, with the ability and limitations of exercise varying from one individual to another. Therefore, to propose effective protocols, knowing the specific person and structuring the program according to his or her needs is necessary.

Although research into the effects of exercise on dialysis patients is now at its peak, a recent meta-analysis [40] identified only 12 randomized controlled trials (RCTs) conducted in HD patients who can be considered significant. There is no uniformity in the mode, setting, or intensity of exercise proposed. Some researchers have experimented with exercise programs carried out during HD treatment, and others have proposed that patients train in the HD centre, but on non-dialysis days; alternatively, home-based exercise programs were proposed, which could be carried out by the patient independently at home. Of the 12 included studies, only the study by Manfredini et al. [41] was performed on a relevant number of patients (216), while all others had a small sample size.

3.4.2 Diet therapy

The nutritional aspect is fundamental for patients with CKD. Dietary interventions are crucial for slowing disease progression and optimizing dialysis effectiveness [42]. Considering that malnutrition is a hazardous risk factor that affects more than 30% of HD patients [43], it is clear that nutritional interventions are needed for patient well-being. For healthy individuals, it is important to base patients' diets on natural, unprocessed, low-protein products and monitor their intake of phosphates, salt, and red meat [44-46]. These aspects must also be evaluated on an individual case-by-case basis, as the assimilation and clearance capabilities of these products vary among individuals.

The synergy between diet therapy and exercise can be an effective multidisciplinary intervention modality. These two aspects can influence each other positively; indeed, nutritional interventions could favour the physical performance of CKD patients [47,48] through targeted nutritional strategies (e.g., protein supplementation) associated with specific types of exercise. In the literature, several randomized controlled trials [49-53] have explored the promising effects of this mixed mode of intervention on dialysis patients.

3.4.3 Psychosocial interventions

Psychosocial interventions can be defined as strategies that provide psychological, emotional, or social support without the use of pharmacological substances. These may include different techniques, which may vary in their mode of delivery, intensity, methodology, and level of contact with an individual therapist or support worker. Psychosocial interventions may help reduce distressing symptoms, increase coping strategies and social connectedness, assist in strategies to address specific disease-related problems and decrease anxiety and stress [30].

This approach is recommended, especially for individuals who are keen to isolate themselves and who reject the support that can come from social interaction. Because these individuals may have low compliance and have difficulty performing activities independently, psychosocial interventions can be effective tools for multidisciplinary teams. According to the literature, cognitive behavioural therapy, exercise or relaxation techniques are the most effective interventions for reducing depressive symptoms in HD patients [30].

3.4.4 Environmental benefits

In the search for possible sustainable interventions to improve patients' quality of life, attention has focused on the role that the environment in which patients live can play. It is well known that the natural environment has positive effects on the regulation of chronic disorders. Spending time in nature decreases anxiety and depression [54], improves chronic pain [55], and improves outcomes and biochemical intermediaries of chronic disease processes.

However, despite the recognized benefits, most HD patients do not spend time in nature. This is because they have to stay at the dialysis unit long enough to receive treatment, which must be added to the time to travel to and from the centre. In addition, fatigue, which is a symptom reported by more than 60% of patients, discourages them from reaching green places [56]. Frailty is also a barrier in this instance, as this condition often makes it objectively difficult for patients to reach suitable places.

3.5 Environmental impact of dialysis

Climate change is recognized as the greatest danger facing humanity. At the same time, the health system, which is concerned with preserving people's health, is one of the largest carbon polluters. In industrialized countries, carbon emissions constitute 25% of all public sector carbon emissions [57]. In particular, existing modes of treatment for kidney disease are among the most environmentally impactful. For example, by omitting the electricity needed to operate machinery, more than 2 million people require 160 billion litres of water for haemodialysis, which generates over 900,000 tons of predominantly plastic waste [57].

Certainly, reducing the overall burden of kidney disease will in turn be key to mitigating some of the environmental impacts of dialysis [58]. However, it is crucial to seek innovative strategies to reduce the impact of dialysis as early as possible. Clean and local production of dialysis materials, dialysis filter reprocessing, dialysis water reuse, solar-powered dialysis, and waterless dialysis are all promising strategies that could reduce the environmental footprint of dialysis and its costs [57]. Another aspect that can be worked on is people's lifestyles, as this would also mitigate dialysis costs.

References

1. Kumbar L, Yee J. Current Concepts in Hemodialysis Vascular Access Infections. Adv Chronic Kidney Dis [Internet]. 2019 Jan;26(1):16–22. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1548559518302180
2. Beecham GB, Aeddula NR. Dialysis Catheter [Internet]. StatPearls. 2024. Available from: http://www.ncbi.nlm.nih.gov/pubmed/0
3. Stolic R. Most Important Chronic Complications of Arteriovenous Fistulas for Hemodialysis. Med Princ Pract [Internet]. 2013;22(3):220–8. Available from: https://www.karger.com/Article/FullText/343669
4. Wachterman MW, O'Hare AM, Rahman O-K, Lorenz KA, Marcantonio ER, Alicante GK, et al. One-Year Mortality After Dialysis Initiation Among Older Adults. JAMA Intern Med [Internet]. 2019 Jul 1;179(7):987. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/jamainternmed.2019.0125
5. Saran R, Li Y, Robinson B, Abbott KC, Agodoa LYC, Ayanian J, et al. US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis [Internet]. 2016 Mar;67(3):A7–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638615014900
6. Bhandari SK, Zhou H, Shaw SF, Shi J, Tilluckdharry NS, Rhee CM, et al. Causes of Death in End-Stage Kidney Disease: Comparison between the United States Renal Data System and a Large Integrated Health Care System. Am J Nephrol [Internet]. 2022;53(1):32–40. Available from: https://karger.com/doi/10.1159/000520466
7. Zhang F, Wang H, Wang W, Zhang H. The Role of Physical Activity and Mortality in Hemodialysis Patients: A Review. Front Public Heal [Internet]. 2022 Feb 17;10. Available from: https://www.frontiersin.org/articles/10.3389/fpubh.2022.818921/full
8. Mallamaci F, D'Arrigo G, Tripepi G, Lamberti N, Torino C, Manfredini F, et al. Long-Term Effect of Physical Exercise on the Risk for Hospitalization and Death in Dialysis Patients. Clin J Am Soc Nephrol [Internet]. 2022 Aug;17(8):1176–82. Available from: https://journals.lww.com/10.2215/CJN.03160322
9. Martínez-Majolero V, Urosa B, Hernández-Sánchez S. Physical Exercise in People with Chronic Kidney Disease—Practices and Perception of the Knowledge of Health Professionals and Physical Activity and Sport Science Professionals about Their

Prescription. Int J Environ Res Public Health [Internet]. 2022 Jan 7;19(2):656. Available from: https://www.mdpi.com/1660-4601/19/2/656

10. Kolbrink B, Schüssel K, von Samson-Himmelstjerna FA, Esser G, Floege J, Kunzendorf U, et al. Patient-focused outcomes after initiation of dialysis for ESRD: mortality, hospitalization and functional impairment. Nephrol Dial Transplant [Internet]. 2023 Oct 31;38(11):2528–36. Available from: https://academic.oup.com/ndt/article/38/11/2528/7172141

11. Dalrymple LS, Johansen KL, Chertow GM, Cheng S-C, Grimes B, Gold EB, et al. Infection-Related Hospitalizations in Older Patients With ESRD. Am J Kidney Dis [Internet]. 2010 Sep;56(3):522–30. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638610009133

12. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med [Internet]. 2020 Dec;54(24):1451–62. Available from: https://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2020-102955

13. Mok A, Khaw K-T, Luben R, Wareham N, Brage S. Physical activity trajectories and mortality: population based cohort study. BMJ [Internet]. 2019 Jun 26;l2323. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.l2323

14. Martins P, Marques EA, Leal D V., Ferreira A, Wilund KR, Viana JL. Association between physical activity and mortality in end-stage kidney disease: a systematic review of observational studies. BMC Nephrol [Internet]. 2021 Dec 18;22(1):227. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-021-02407-w

15. Regolisti G, Maggiore U, Sabatino A, Gandolfini I, Pioli S, Torino C, et al. Interaction of healthcare staff's attitude with barriers to physical activity in hemodialysis patients: A quantitative assessment. PLoS One. 2018;13(4):1–15.

16. Ju A, Teixeira-Pinto A, Tong A, Smith AC, Unruh M, Davison SN, et al. Validation of a Core Patient-Reported Outcome Measure for Fatigue in Patients Receiving Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2020 Nov;15(11):1614–21. Available from: https://journals.lww.com/10.2215/CJN.05880420

17. Debnath S, Rueda R, Bansal S, Kasinath BS, Sharma K, Lorenzo C. Fatigue characteristics on dialysis and non-dialysis days in patients with chronic kidney failure on maintenance hemodialysis. BMC Nephrol [Internet]. 2021 Dec 27;22(1):112. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-021-02314-0

18. Jacobson J, Ju A, Baumgart A, Unruh M, O'Donoghue D, Obrador G, et al. Patient Perspectives on the Meaning and Impact of Fatigue in Hemodialysis: A Systematic Review and Thematic Analysis of Qualitative Studies. Am J Kidney Dis [Internet]. 2019 Aug;74(2):179–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638619301660
19. Fiaccadori E, Sabatino A, Schito F, Angella F, Malagoli M, Tucci M, et al. Barriers to Physical Activity in Chronic Hemodialysis Patients: A Single-Center Pilot Study in an Italian Dialysis Facility. Kidney Blood Press Res [Internet]. 2014;39(2–3):169–75. Available from: https://www.karger.com/Article/FullText/355793
20. Grigoriou, S. S., Krase, A. A., Karatzaferi, C., Giannaki, C. D., Lavdas, E., Mitrou, G. I., Bloxham, S., Stefanidis, I., & Sakkas, G. K. (2021). Long-term intradialytic hybrid exercise training on fatigue symptoms in patients receiving hemodialysis therapy. International urology and nephrology, 53(4), 771–784. https://doi.org/10.1007/s11255-020-02711-8
21. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int [Internet]. 2013 Jul;84(1):179–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815559279
22. Szeifert L, Bragg-Gresham JL, Thumma J, Gillespie BW, Mucsi I, Robinson BM, et al. Psychosocial variables are associated with being wait-listed, but not with receiving a kidney transplant in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant [Internet]. 2012 May 1;27(5):2107–13. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfr568
23. Kaveh K, Kimmel PL. Compliance in Hemodialysis Patients: Multidimensional Measures in Search of a Gold Standard. Am J Kidney Dis [Internet]. 2001 Feb;37(2):244–66. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638601990237
24. Chilcot J, Guirguis A, Friedli K, Almond M, Day C, Da Silva-Gane M, et al. Depression Symptoms in Haemodialysis Patients Predict All-Cause Mortality but Not Kidney Transplantation: A Cause-Specific Outcome Analysis. Ann Behav Med [Internet]. 2018 Jan 5;52(1):1–8. Available from: https://academic.oup.com/abm/article/52/1/1/4733476
25. Hedayati SS. Association Between Major Depressive Episodes in Patients With Chronic Kidney Disease and Initiation of Dialysis, Hospitalization, or Death. JAMA

[Internet]. 2010 May 19;303(19):1946. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2010.619

26. Weisbord SD, Mor MK, Sevick MA, Shields AM, Rollman BL, Palevsky PM, et al. Associations of Depressive Symptoms and Pain with Dialysis Adherence, Health Resource Utilization, and Mortality in Patients Receiving Chronic Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2014 Sep;9(9):1594–602. Available from: https://journals.lww.com/01277230-201409000-00015
27. Flythe JE, Hilbert J, Kshirsagar A V., Gilet CA. Psychosocial Factors and 30-Day Hospital Readmission among Individuals Receiving Maintenance Dialysis: A Prospective Study. Am J Nephrol [Internet]. 2017;45(5):400–8. Available from: https://www.karger.com/Article/FullText/470917
28. Lopes AA, Bragg J, Young E, Goodkin D, Mapes D, Combe C, et al. Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. Kidney Int [Internet]. 2002 Jul;62(1):199–207. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815485370
29. Farrokhi F, Abedi N, Beyene J, Kurdyak P, Jassal SV. Association Between Depression and Mortality in Patients Receiving Long-term Dialysis: A Systematic Review and Meta-analysis. Am J Kidney Dis [Internet]. 2014 Apr;63(4):623–35. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638613012195
30. Natale P, Palmer SC, Ruospo M, Saglimbene VM, Rabindranath KS, Strippoli GF. Psychosocial interventions for preventing and treating depression in dialysis patients. Cochrane Database Syst Rev [Internet]. 2019 Dec 2; Available from: https://doi.wiley.com/10.1002/14651858.CD004542.pub3
31. Jiang L, Cao Y, Ni S, Chen X, Shen M, Lv H, et al. Association of Sedentary Behavior With Anxiety, Depression, and Suicide Ideation in College Students. Front Psychiatry [Internet]. 2020 Dec 11;11. Available from: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.566098/full
32. Escalante E, Golden RL, Mason DJ. Social Isolation and Loneliness: Imperatives for Health Care in a Post-COVID World. JAMA [Internet]. 2021 Feb 9;325(6):520. Available from: https://jamanetwork.com/journals/jama/fullarticle/2776188
33. Zhou W, Li Y, Ning Y, Gong S, Song N, Zhu B, et al. Social Isolation Is Associated With Rapid Kidney Function Decline and the Development of Chronic Kidney Diseases in Middle-Aged and Elderly Adults: Findings From the China Health and Retirement Longitudinal Study (CHARLS). Front Med [Internet]. 2021 Dec 2;8. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2021.782624/full

34. Moreno-Tamayo K, Manrique-Espinoza B, Ramírez-García E, Sánchez-García S. Social isolation undermines quality of life in older adults. Int Psychogeriatrics [Internet]. 2020 Nov 1;32(11):1283–92. Available from: https://www.cambridge.org/core/product/identifier/S1041610219000310/type/journal_article
35. Cotterell N, Buffel T, Phillipson C. Preventing social isolation in older people. Maturitas [Internet]. 2018 Jul;113:80–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0378512218301634
36. Hejazi SS, Hosseini M, Ebadi A, Alavi Majd H. Components of quality of life in hemodialysis patients from family caregivers' perspective: a qualitative study. BMC Nephrol [Internet]. 2021 Dec 13;22(1):379. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-021-02584-8
37. de Rooij ENM, Meuleman Y, de Fijter JW, Le Cessie S, Jager KJ, Chesnaye NC, et al. Quality of Life before and after the Start of Dialysis in Older Patients. Clin J Am Soc Nephrol [Internet]. 2022 Aug;17(8):1159–67. Available from: https://journals.lww.com/10.2215/CJN.16371221
38. Bernier-Jean A, Beruni NA, Bondonno NP, Williams G, Teixeira-Pinto A, Craig JC, et al. Exercise training for adults undergoing maintenance dialysis. Cochrane database Syst Rev. 2022 Jan;1(1):CD014653.
39. Battaglia Y, Lamberti N, Piva G, Manfredini F, Storari A. [Physical exercise in chronic kidney disease: an empty narrative or an effective intervention?]. G Ital Nefrol [Internet]. 2021 Dec 16;38(6). Available from: http://www.ncbi.nlm.nih.gov/pubmed/34919791
40. Battaglia Y, Amicone M, Mantovani A, Combe C, Mitra S, Basile C. Home-based exercise in patients on maintenance dialysis: a systematic review and meta-analysis of randomized clinical trials. Nephrol Dial Transplant [Internet]. 2023 Oct 31;38(11):2550–61. Available from: https://academic.oup.com/ndt/article/38/11/2550/7172143
41. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2017 Apr;28(4):1259–68.
42. Cupisti A, Brunori G, Di Iorio BR, D'Alessandro C, Pasticci F, Cosola C, et al. [Nutritional diet therapy in the management of the patient with Chronic Kidney Disease in advanced phase to delay the beginning and reduce the frequency of dialysis. An option also in the pre-emptive transplant program]. G Ital Nefrol

[Internet]. 2018 Sep;35(5). Available from: http://www.ncbi.nlm.nih.gov/pubmed/30234228

43. Kopple JD. Effect of Nutrition on Morbidity and Mortality in Maintenance Dialysis Patients. Am J Kidney Dis [Internet]. 1994 Dec;24(6):1002–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638612810754
44. Ornish D. Holy Cow! What's Good for You Is Good for Our Planet. Arch Intern Med [Internet]. 2012 Apr 9;172(7):563. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2012.174
45. Etemadi A, Sinha R, Ward MH, Graubard BI, Inoue-Choi M, Dawsey SM, et al. Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population based cohort study. BMJ [Internet]. 2017 May 9;j1957. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.j1957
46. Wolk A. Potential health hazards of eating red meat. J Intern Med [Internet]. 2017 Feb 6;281(2):106–22. Available from: https://onlinelibrary.wiley.com/doi/10.1111/joim.12543
47. Cupisti A, D'Alessandro C, Fumagalli G, Vigo V, Meola M, Cianchi C, et al. Nutrition and Physical Activity in CKD patients. Kidney Blood Press Res [Internet]. 2014;39(2–3):107–13. Available from: https://www.karger.com/Article/FullText/355784
48. Ekramzadeh M, Santoro D, Kopple JD. The Effect of Nutrition and Exercise on Body Composition, Exercise Capacity, and Physical Functioning in Advanced CKD Patients. Nutrients [Internet]. 2022 May 20;14(10):2129. Available from: https://www.mdpi.com/2072-6643/14/10/2129
49. Dong J, Sundell MB, Pupim LB, Wu P, Shintani A, Ikizler TA. The Effect of Resistance Exercise to Augment Long-term Benefits of Intradialytic Oral Nutritional Supplementation in Chronic Hemodialysis Patients. J Ren Nutr [Internet]. 2011 Mar;21(2):149–59. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1051227610000750
50. Gamboa JL, Deger SM, Perkins BW, Mambungu C, Sha F, Mason OJ, et al. Effects of long-term intradialytic oral nutrition and exercise on muscle protein homeostasis and markers of mitochondrial content in patients on hemodialysis. Am J Physiol - Ren Physiol. 2020;319(5):F885–94.

51. Majchrzak KM, Pupim LB, Flakoll PJ, Ikizler TA. Resistance exercise augments the acute anabolic effects of intradialytic oral nutritional supplementation. Nephrol Dial Transplant. 2008;23(4):1362–9.
52. Martin-Alemañy G, Valdez-Ortiz R, Olvera-Soto G, Gomez-Guerrero I, Aguire-Esquivel G, Cantu-Quintanilla G, et al. The effects of resistance exercise and oral nutritional supplementation during hemodialysis on indicators of nutritional status and quality of life. Nephrol Dial Transplant. 2016;31(10):1712–20.
53. Martin-Alemañy G, Espinosa-Cuevas M de los Á, Pérez-Navarro M, Wilund KR, Miranda-Alatriste P, Cortés-Pérez M, et al. Effect of Oral Nutritional Supplementation With and Without Exercise on Nutritional Status and Physical Function of Adult Hemodialysis Patients: A Parallel Controlled Clinical Trial (AVANTE-HEMO Study). J Ren Nutr. 2020;30(2):126–36.
54. Capaldi CA, Dopko RL, Zelenski JM. The relationship between nature connectedness and happiness: a meta-analysis. Front Psychol [Internet]. 2014 Sep 8;5. Available from: http://journal.frontiersin.org/article/10.3389/fpsyg.2014.00976/abstract
55. Han J-W, Choi H, Jeon Y-H, Yoon C-H, Woo J-M, Kim W. The Effects of Forest Therapy on Coping with Chronic Widespread Pain: Physiological and Psychological Differences between Participants in a Forest Therapy Program and a Control Group. Int J Environ Res Public Health [Internet]. 2016 Feb 24;13(3):255. Available from: http://www.mdpi.com/1660-4601/13/3/255
56. Delgado C, Johansen KL. Barriers to exercise participation among dialysis patients. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2012 Mar;27(3):1152–7.
57. Agar JWM. Green Dialysis: The Environmental Challenges Ahead. Semin Dial [Internet]. 2015 Mar 30;28(2):186–92. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12324
58. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the sustainable development goals. Bull World Health Organ [Internet]. 2018 Jun 1;96(6):414-422D. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5996218/pdf/BLT.17.206441.pdf/

CHAPTERS 4 – 5 – 6 – 7 – 8

4. EXERCISE IN DIALYSIS

4.1 Effect of exercise on physical function

It is recognized that HD therapy forces patients into a sedentary condition [1] that exposes them to an even greater risk of clinically adverse events. A review conducted in 2022 by Zhang et al. [2] revealed that "regular physical activity is associated with a reduced risk of mortality caused by cardiovascular disease, diabetes, obesity, and cancer". A study published in the same year by Mallamaci et al. [3] revealed that patients who participated in a home walking program at the 36-month follow-up were 29% less likely to be hospitalized than those in the control group (even 45% less, in subjects with high exercise adherence). It is therefore clear that patients must remain physically active to have a stable clinical situation. In addition to providing greater clinical stability, exercise improves other factors relevant to patients' health [4].

Effective exercise programs can improve patients' functional capacity and strength, especially in the lower limbs. The functional ability, more specifically the walking autonomy, of HD patients is a crucial factor; indeed, it has been shown that the distance covered in the 6-minute walking test (6MWT), the most widely used test for assessing walking ability, is directly proportional to the survival probability of individuals with ESRD [5]. Regarding the effectiveness of training programs, Bohannon et al. [6] estimated the minimal clinically important difference measured in the 6MWT to range from 14.0 to 30.5 meters. For these reasons, it is important that the training offered includes specific aerobic exercises to improve patients' walking ability.

Effective training programs should also include resistance exercises to preserve muscle strength and prevent sarcopenia. This is defined as the "*progressive decline in muscle mass and strength upon aging*" [7] and is strongly correlated with long-term mortality and cardiovascular events in HD patients [8]. Therefore, this is another aspect relevant to patients' health that can be improved with exercise.

In addition to patients' functional abilities, the level of perceived fatigue, which is one of the major limitations reported by patients, is generally alleviated at the end of exercise interventions [9]. Performing specific exercises can also reduce the level of pain perceived by patients and help them achieve a better QoL [4].

4.2 Effect of exercise on other parameters

In addition to the previously described impacts, exercise can improve other measurable parameters. Despite the few studies on the subject, resistance exercises increased the muscle mass of the trained limbs. In contrast, there was no uniformity regarding the effect on body mass index (BMI) since fat mass decreased in some studies and increased in others [10].
Cycling exercise performed during HD sessions is effective at improving bone metabolism [11], while aerobic and resistance exercise programs improve systemic inflammation biomarkers [12].

4.3 Effects of exercise on quality of life

Patients on HD treatment are known to have a lower QoL than non-dialyzed patients [13]. This is due to several factors. One of the main symptoms is depression, which is a common symptom of chronic diseases [14] and is diagnosed in 25% of HD patients [15]. Certainly, the functional limitations and physical symptoms that result from a chronic disease such as CKD can cause depression [16,17]. However, the comorbid conditions of these individuals make it difficult to discern whether depression is caused by different symptoms or whether these symptoms result from depressive status [18]. Even in the absence of such conditions, poor functional capacity is sufficient to impair the ability to perform activities of daily living and reduce overall QoL [19].
Interestingly, the main factors reducing patients' QoL (fatigue and low mood) are also among the main causes of patients not exercising [20], and it is well known that a sedentary lifestyle leads to an increased risk of depression [21]. Thus, there is a vicious cycle in which patients are trapped, in which the synergy between low physical activity and poor mood progressively reduces people's QoL.
Thus, there is a vicious cycle in which patients are trapped, in which the synergy between low physical activity and poor mood progressively reduces people's QoL. An effective tool to help patients overcome this condition is exercise, which can positively influence causes and symptoms. Indeed, it can improve functional capacity and fatigue, depressive symptoms, and overall QoL in HD patients [4]. The positive effect of exercise is felt by the patients themselves [22]; however, the number of active patients is remarkably low. This implies that some factors limit physical activity, even in individuals who want to exercise.

4.4 Barriers to exercise

The issue of barriers is extremely relevant when it concerns bringing HD patients to exercise. "Barrier" is defined as something that makes it difficult to perform physical activity; this term includes both issues related to a person's physical health and those related to mental health, logistics, family, etc., aspects. Due to the different nature of the barriers, a multidisciplinary approach involving different figures (kinesiologists, nephrologists, nurses, caregivers) and the patient himself is necessary. In particular, the active involvement of healthcare staff is crucial to the effectiveness of the intervention, as a non-proactive attitude is a major barrier to exercise [20].

The limitations most reported by patients are physical restrictions, such as fatigue (64%) and pain (27%) on dialysis days, while a logistical problem is the lack of time on dialysis days (41%). The most reported psychological barriers are lack of motivation (41%), feeling of having too many medical problems (29%), sadness (29%), feeling of helplessness (28%), and fear of getting hurt (28%) [20].

Analyzing what patients themselves were reporting, it is evident that the day of dialysis is problematic due to various factors (fatigue, pain, lack of time). For an exercise program to be sustainable for the patient, this aspect should be considered. "Forcing" patients to exercise under conditions of fatigue or pain could discourage them and push them even further toward sedentariness. Similarly, it would be difficult for patients to sustain additional consistent effort on those days, and adherence to the exercise would probably be low.

The psychological aspect should also be taken care of carefully. Patients must engage in exercise because of the benefits it can bring to their mood [4,22]; however, it is necessary to propose programs adapted to their low functional capacity so that these are perceived as "feasible" and do not require an effort that exceeds their abilities.

All of these aspects must be taken into consideration by the kinesiologist when structuring exercise programs and should be discussed with other staff members, the patient, and caregivers [23]. It is important for everyone involved to be aware of the effectiveness of exercise in improving the well-being of HD patients so that everyone can contribute to helping patients stay compliant and adhere to the program. For this to be possible, it is crucial that the prescribed exercise is effective, has a low impact, and provides benefits that can be experienced by the patient in daily life in a medium to short time.

4.5 Different exercise programs

Despite the recognized benefits, it has not yet been demonstrated which type of exercise is best for improving patients’ well-being. This is also because not enough studies have been conducted thus far. Although the greatest efficacy is achieved by providing patients with programs that combine aerobic and resistance exercises, the best mode of administration is unclear.

Trials conducted thus far have used either the intradialytic exercise (IDE) formula, thus proposing workouts carried out during the HD session, or the interdialytic model, with training sessions carried out off the HD session at the patient's residence, or other locations (gyms, dialysis centers, etc.). At present, both modalities are considered to provide similar benefits to patients, with no evidence of the superiority of either training modality over the other [24].

4.5.1 Intradialytic exercise

It is exercise training performed during the HD session [25]. Depending on the equipment used, aerobic, resistance, and stretching exercises can be proposed to improve the physical and psychological health of patients. The number of randomized clinical trials (RCTs) that have tested this exercise setting is significantly greater than that in the HB setting, which is the most commonly applied exercise in cycling [26]. The two major trials that have used intradialytic exercise are DiaTT (Dialysis Training Therapy) [27] and PEDAL (PrEscription of intraDialytic exercise to improve quAlity of Life) [28], involving a total of more than 1,200 patients, and they produced different results. Indeed, while the DiaTT significantly improved lower limb strength, the PEDAL did not affect QoL or VO2max.

One of the advantages of IDE is that it takes advantage of therapy time to support exercise. This allows the exercise to be easily supervised, as neither patient nor staff time outside HD is needed. On the other hand, for patients to perform the exercise, the attendance of a staff member (kinesiologist, nurse, nephrologist) is necessary. This makes the costs of this intervention considerable (US$ 589-1,079 per participant per year for the PEDAL study [28], while it was calculated that the cost of DiaTT would be US$ 3,500 per year if IDE is anticipated for all dialysis sessions [27]), in addition to its uncertain effectiveness. Furthermore, concerning PEDAL, patients in the intervention group also showed poor compliance (48%) and very low adherence to exercise (19%) [28].

These results are not surprising, considering that the two biggest barriers to exercise are fatigue and perceived pain on HD days [20]. However, given the need to develop economically sustainable models with high adherence, it would probably be preferable to follow a different path to bypass the difficulties of HD days.

4.5.2 Interdialytic exercise

Interdialytic exercise is performed outside the HD session in a home-based (HB) setting. HB exercise is defined as exercise performed in various locations outside of a clinical setting [29]. Most HD patients train either at home or in gyms specialized in treating individuals with chronic diseases. A recent meta-analysis by Battaglia et al. [30] revealed that the number of RCTs on this type of treatment is low, and the sample size is often small. The only exception is the Excite [31] study, which included a sample of 286 subjects and provided evidence of the potential of HB exercise in HD patients. Despite the limited number of studies, the authors concluded that HB exercise interventions lasting 3–6 months are associated with significant improvements in physical performance [30].

At present, the superiority of either treatment over the other in improving patient function has not been identified, and both IDE and HB training can promote benefits for individuals undergoing HD [24]. However, regarding cost, the Excite study was the most cost-effective. The only tool needed for the exercise was a simple digital metronome (US$ 25), and the HB modality did not require the direct presence of any staff member, which was necessary only at the time of evaluation and prescription of the exercise program. Regarding exercise adherence, the HB program also proved superior, with 83% of scheduled sessions being completed during Excite [31]. Most likely, the opportunity to perform exercise at home helped patients overcome logistical barriers (time, transportation, etc.), and the indication to perform exercise on non-dialysis days was crucial in circumventing dialysis day difficulties, making exercise less "annoying."

References

1. Johansen KL, Chertow GM, Ng A V., Mulligan K, Carey S, Schoenfeld PY, et al. Physical activity levels in patients on hemodialysis and healthy sedentary controls. Kidney Int [Internet]. 2000 Jun;57(6):2564–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815470164
2. Zhang F, Wang H, Wang W, Zhang H. The Role of Physical Activity and Mortality in Hemodialysis Patients: A Review. Front Public Heal [Internet]. 2022 Feb 17;10. Available from: https://www.frontiersin.org/articles/10.3389/fpubh.2022.818921/full
3. Mallamaci F, D'Arrigo G, Tripepi G, Lamberti N, Torino C, Manfredini F, et al. Long-Term Effect of Physical Exercise on the Risk for Hospitalization and Death in Dialysis Patients. Clin J Am Soc Nephrol [Internet]. 2022 Aug;17(8):1176–82. Available from: https://journals.lww.com/10.2215/CJN.03160322
4. Bernier-Jean A, Beruni NA, Bondonno NP, Williams G, Teixeira-Pinto A, Craig JC, et al. Exercise training for adults undergoing maintenance dialysis. Cochrane database Syst Rev. 2022 Jan;1(1):CD014653.
5. de Moraes Kohl L, Signori LU, Ribeiro RA, Silva AMV, Moreira PR, Dipp T, et al. Prognostic value of the six-minute walk test in end-stage renal disease life expectancy: a prospective cohort study. Clinics [Internet]. 2012 Jun;67(6):581–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1807593222017914
6. Bohannon RW, Crouch R. Minimal clinically important difference for change in 6-minute walk test distance of adults with pathology: a systematic review. J Eval Clin Pract [Internet]. 2017 Apr 4;23(2):377–81. Available from: https://onlinelibrary.wiley.com/doi/10.1111/jep.12629
7. Metter EJ, Conwit R, Tobin J, Fozard JL. Age-Associated Loss of Power and Strength in the Upper Extremities in Women and Men. Journals Gerontol Ser A Biol Sci Med Sci [Internet]. 1997 Sep 1;52A(5):B267–76. Available from: https://academic.oup.com/biomedgerontology/article-lookup/doi/10.1093/gerona/52A.5.B267
8. Kim J-K, Kim SG, Oh J-E, Lee Y-K, Noh J-W, Kim HJ, et al. Impact of sarcopenia on long-term mortality and cardiovascular events in patients undergoing hemodialysis. Korean J Intern Med [Internet]. 2019 May 1;34(3):599–607. Available from: http://kjim.org/journal/view.php?doi=10.3904/kjim.2017.083

9. Song Y, Hu R, Diao Y, Chen L, Jiang X. Effects of Exercise Training on Restless Legs Syndrome, Depression, Sleep Quality, and Fatigue Among Hemodialysis Patients: A Systematic Review and Meta-analysis. J Pain Symptom Manage [Internet]. 2018 Apr;55(4):1184–95. Available from: https://linkinghub.elsevier.com/retrieve/pii/S088539241731223X
10. Ekramzadeh M, Santoro D, Kopple JD. The Effect of Nutrition and Exercise on Body Composition, Exercise Capacity, and Physical Functioning in Advanced CKD Patients. Nutrients [Internet]. 2022 May 20;14(10):2129. Available from: https://www.mdpi.com/2072-6643/14/10/2129
11. Elshinnawy HA, Mohamed AMBB, Farrag DAB, AbdElgawad MAE. Effect of intradialytic exercise on bone profile in hemodialysis patients. Egypt Rheumatol Rehabil [Internet]. 2021 Dec 6;48(1):24. Available from: https://erar.springeropen.com/articles/10.1186/s43166-021-00071-4
12. Meléndez Oliva E, Villafañe JH, Alonso Pérez JL, Alonso Sal A, Molinero Carlier G, Quevedo García A, et al. Effect of Exercise on Inflammation in Hemodialysis Patients: A Systematic Review. J Pers Med [Internet]. 2022 Jul 21;12(7):1188. Available from: https://www.mdpi.com/2075-4426/12/7/1188
13. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom Burden, Depression, and Quality of Life in Chronic and End-Stage Kidney Disease. Clin J Am Soc Nephrol [Internet]. 2009 Jun;4(6):1057–64. Available from: https://journals.lww.com/01277230-200906000-00007
14. Ingle V, Pandey I, Singh A, Pakhare A, Kumar S. Screening of patients with chronic medical disorders in the outpatient department for depression using handheld computers as interface and patient health questionnaire-9 as a tool. Int J Appl Basic Med Res [Internet]. 2017;7(2):129. Available from: https://journals.lww.com/10.4103/2229-516X.205809
15. Palmer S, Vecchio M, Craig JC, Tonelli M, Johnson DW, Nicolucci A, et al. Prevalence of depression in chronic kidney disease: systematic review and meta-analysis of observational studies. Kidney Int [Internet]. 2013 Jul;84(1):179–91. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815559279
16. Seidel UK, Gronewold J, Volsek M, Todica O, Kribben A, Bruck H, et al. Physical, Cognitive and Emotional Factors Contributing to Quality of Life, Functional Health and Participation in Community Dwelling in Chronic Kidney Disease. Kleinschnitz C, editor. PLoS One [Internet]. 2014 Mar 10;9(3):e91176. Available from: https://dx.plos.org/10.1371/journal.pone.0091176

17. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry [Internet]. 2003 Aug;54(3):216–26. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006322303002737
18. Shirazian S, Grant CD, Aina O, Mattana J, Khorassani F, Ricardo AC. Depression in Chronic Kidney Disease and End-Stage Renal Disease: Similarities and Differences in Diagnosis, Epidemiology, and Management. Kidney Int Reports [Internet]. 2017 Jan;2(1):94–107. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2468024916300845
19. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev. 2011;2011(10).
20. Regolisti G, Maggiore U, Sabatino A, Gandolfini I, Pioli S, Torino C, et al. Interaction of healthcare staff's attitude with barriers to physical activity in hemodialysis patients: A quantitative assessment. PLoS One. 2018;13(4):1–15.
21. Huang Y, Li L, Gan Y, Wang C, Jiang H, Cao S, et al. Sedentary behaviors and risk of depression: a meta-analysis of prospective studies. Transl Psychiatry [Internet]. 2020 Jan 22;10(1):26. Available from: https://www.nature.com/articles/s41398-020-0715-z
22. Ghafourifard M, Mehrizade B, Hassankhani H, Heidari M. Hemodialysis patients perceived exercise benefits and barriers: the association with health-related quality of life. BMC Nephrol. 2021;22(1):1–9.
23. Johansen KL, Sakkas GK, Doyle J, Shubert T, Adams Dudley R. Exercise counseling practices among nephrologists caring for patients on dialysis. Am J Kidney Dis [Internet]. 2003 Jan;41(1):171–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638603500221
24. Ferrari F, Andrade FP, Teixeira MS, Ziegelmann PK, Carvalho G, Bittencourt ESS, et al. Efficacy of six exercise-based interventions for individuals undergoing hemodialysis: a network meta-analysis of randomized clinical trials. Nephrol Dial Transplant [Internet]. 2023 Sep 29;38(10):2389–406. Available from: https://academic.oup.com/ndt/article/38/10/2389/7146837
25. Salhab N, Karavetian M, Kooman J, Fiaccadori E, El Khoury CF. Effects of intradialytic aerobic exercise on hemodialysis patients: a systematic review and meta-analysis. J Nephrol [Internet]. 2019 Aug 18;32(4):549–66. Available from: http://link.springer.com/10.1007/s40620-018-00565-z

26. Zoccali C, Manfredini F, Kanbay M, Mallamaci F. Intradialysis exercise in haemodialysis patients: effective but complex and costly. Nephrol Dial Transplant [Internet]. 2023 Dec 20;39(1):7–9. Available from: https://academic.oup.com/ndt/article/39/1/7/7240750
27. Anding-Rost K, von Gersdorff G, von Korn P, Ihorst G, Josef A, Kaufmann M, et al. Exercise during Hemodialysis in Patients with Chronic Kidney Failure. NEJM Evid. 2023;2(9).
28. Greenwood SA, Koufaki P, Macdonald JH, Bhandari S, Burton JO, Dasgupta I, et al. Randomized Trial—PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Hemodialysis. Kidney Int Reports [Internet]. 2021;6(8):2159–70. Available from: https://doi.org/10.1016/j.ekir.2021.05.034
29. Lopez C, McGarragle K, Pritlove C, Jones JM, Alibhai SMH, Lenton E, et al. Variability and limitations in home-based exercise program descriptions in oncology: a scoping review. Support Care Cancer [Internet]. 2020 Sep 16;28(9):4005–17. Available from: https://link.springer.com/10.1007/s00520-020-05453-6
30. Battaglia Y, Amicone M, Mantovani A, Combe C, Mitra S, Basile C. Home-based exercise in patients on maintenance dialysis: a systematic review and meta-analysis of randomized clinical trials. Nephrol Dial Transplant [Internet]. 2023 Oct 31;38(11):2550–61. Available from: https://academic.oup.com/ndt/article/38/11/2550/7172143
31. Manfredini F, Mallamaci F, D’Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2017 Apr;28(4):1259–68.

5. EXERCISE FACILITATORS

Several strategies have been used to increase patient adherence to exercise programs as much as possible. These are called "exercise facilitators," which means "*something that facilitates exercise practice*". Research on HD patients has focused more on barriers and less on facilitators than on other diseases (e.g., cancer). To identify which interventions were most palatable to patients, some studies asked them precisely what they thought would be most effective in supporting them in performing exercise [1]. Almost all respondents reported that the presence of an experienced exercise figure who was available to supervise and prescribe tailored programs would be important to them.

The presence of an exercise facilitator (EF) can be defined as a psychosocial intervention, as it is a strategy aimed at providing psychological and social support without the use of pharmacological substances, which can have important effects on patients' psychological well-being [2].

5.1 An exercise expert in the dialysis center

Including an EF in the HD center could be a turning point. As emphasized by patients, they must have specific exercise skills in patients on HD. Thus, he/she should be an experienced physiotherapist and/or qualified exercise specialist [3]. His/her activity should consist of active presence within the HD center to suggest exercise programs to patients and possibly supervise their training sessions.

The effectiveness of EF inclusion may derive from the fact that it would fill a current gap. In fact, despite the need to promote exercise, to date, there is no figure in the HD center staff with specific skills who can support patients in this respect. Patients are forced to refer to a nephrologist or nurses, but they lack the necessary knowledge and are unable to be helpful to them. For this reason, an experienced person who knows the barriers that patients have to overcome, who is familiar with which exercise programs are effective for the HD population who can tailor them to the needs of the individual patient, and who can advise and motivate would represent a key figure, complementing those already operating, improving patient care.

References

1. Blaney J, Lowe-Strong A, Rankin J, Campbell A, Allen J, Gracey J. The Cancer Rehabilitation Journey: Barriers to and Facilitators of Exercise Among Patients With Cancer-Related Fatigue. Phys Ther [Internet]. 2010 Aug 1;90(8):1135–47. Available from: https://academic.oup.com/ptj/article/90/8/1135/2737982
2. Natale P, Palmer SC, Ruospo M, Saglimbene VM, Rabindranath KS, Strippoli GF. Psychosocial interventions for preventing and treating depression in dialysis patients. Cochrane Database Syst Rev [Internet]. 2019 Dec 2; Available from: https://doi.wiley.com/10.1002/14651858.CD004542.pub3
3. Manfredini F, Lamberti N, Battaglia Y, Straudi S, Belvederi Murri M, Donadi M, et al. A Personalized Patient-Centered Intervention to Empower through Physical Activity the Patient in the Dialysis Center: Study Protocol for a Pragmatic Nonrandomized Clinical Trial. Methods Protoc [Internet]. 2020 Dec 6;3(4):83. Available from: https://www.mdpi.com/2409-9279/3/4/83

6. EXERCISE, DIALYSIS AND ENVIRONMENT

Two types of connections between HD and the environment can be identified. The first is the impact that HD treatment has on the environment in terms of the consumption of water, electricity, and energy and the production of potentially contaminated waste. Patients receiving standard dialytic therapy (three times a week for four hours) consume approximately 18,000 liters of water and 800-925 KWh per year. Thus, dialysis can be considered an extremely environmentally impactful treatment. Exercise is effective in the stages before ESRD because it enhances the recovery of renal function in patients with acute renal failure [1] and because physically active patients start HD later than sedentary individuals [2]. Despite these positive effects, it has not yet been demonstrated with certainty whether improved functional capacity is associated with the optimization of therapy in terms of reducing the duration and number of HD sessions. These aspects must be investigated, but exercise models should be tested and applied in the early stages of the disease.

The second interesting aspect is the analysis of how the surrounding environment can affect patients' well-being. Given the special nature of treatment, which forces patients to go to the care center often and for a lifetime, it can almost be considered the HD center as a "second home" because of the amount of time they spend there. Because the effects of the hospital environment on patients' mental and physical health were recognized as early as the last century, it is important to evaluate this topic in people with HD.

6.1 Can the care environment become part of care?

The positive effects of the environment on hospitalized patients were described by the German architect Roger S Ulrich, who found that patients who viewed natural scenes through their windows needed fewer analgesic drugs and had a shorter postoperative course than those who viewed other buildings [3]. Subsequently, the analysis of nature's effects on health has attracted increasing interest, and today, it is one of the most widely discussed topics.

The concept of "biophilia", the tendency of humans to be attracted to everything alive and vital, was defined in the 1960s by the German sociologist Erich Fromm. Building on this definition, the biophilic design was developed based on an attempt to transfer individuals' innate inclination toward nature into the construction of buildings. From this perspective, the hospital has become a place to highlight not only advances in medical knowledge but also changes in the relationships among humans, the built environment, and nature. Hospital design approaches the patients' perspective by also caring about the patient's psychosocial well-being, not just the physical well-being.

A review by Jimenez et al. [4] confirmed the positive effect of the natural environment on people's mental health; however, the HD center environment has some sanitation limitations, so it would be impossible to place real plant elements inside. Patients' contact with real plants could occur in common areas or outside the hospital. Activities such as green walking and gardening are effective at improving patients' psychological well-being; however, they are not effective in the HD unit. Fortunately, it has been shown that exposure to artificial nature (plants, panels, paintings, etc.) has effects similar to those of real nature [5]. This is an important point because the placement of artificial elements in the HD center reminiscent of the natural environment is allowed and would be effective in improving the well-being of patients and staff.

References

1. Asad A, Thomas A, Dungey M, Hull KL, March DS, Burton JO. Associations between physical activity levels and renal recovery following acute kidney injury stage 3: a feasibility study. BMC Nephrol [Internet]. 2022 Dec 11;23(1):140. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-022-02759-x
2. Izumi A, Kitamura M, P. Izawa K. Effects of Exercise Training on Delaying Disease Progression in Patients with Chronic Kidney Disease: a Review of the Literature. Rev Recent Clin Trials [Internet]. 2016 Oct 4;11(4):333–41. Available from: http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1574-8871&volume=11&issue=4&spage=333
3. Ulrich RS. View Through a Window May Influence Recovery from Surgery. Science (80-) [Internet]. 1984 Apr 27;224(4647):420–1. Available from: https://www.science.org/doi/10.1126/science.6143402
4. Jimenez MP, Deville N V, Elliott EG, Schiff JE, Wilt GE, Hart JE, et al. Associations between Nature Exposure and Health: A Review of the Evidence. Int J Environ Res Public Heal. 2021;18:4790.
5. Beukeboom CJ, Langeveld D, Tanja-Dijkstra K. Stress-reducing effects of real and artificial nature in a hospital waiting room. J Altern Complement Med. 2012;18(4):329–33.

7. BENEFITS OF EXERCISE IN THE NATURAL ENVIRONMENT

The setting of a biophilic environment in the HD centre would open up additional exercise-related possibilities. Indeed, the benefits of the natural environment include enhancing the effects of exercise. Shinrin-Yoku (or forest bathing or forest therapy) is a Japanese expression of the practice of performing activities in the forest to enjoy the full benefits of the forest. Interest in this activity has spread globally, and studies have shown its effectiveness in improving physiological parameters (e.g., blood pressure and cortisol levels) and mental health disorders, such as depression and anxiety. The positive effects of forest walking have also been found in elderly and frail populations, which include the majority of dialyzed individuals. Despite the fact that this practice is now known in European countries where it is practised in suitable areas (e.g. the Dolomites in Italy), no studies have yet been carried out in these countries, with the result that the only studies in the literature to date have been carried out on the Asian continent.

Recreating a natural, even if artificial, environment in the HD unit would also create a functional setting for carrying out exercises. If patients had the opportunity to exercise, perhaps close to HD sessions, within the centre itself, they could experience the benefits of exercise enhanced by a favourable environment and overcome barriers of time, transportation, etc., that would hinder them from exercising in other settings.

7.1 Effect of exercise in nature on physical and mental health

While studying the effects of exercise in the natural environment, we conducted a systematic review of the literature entitled "*Effects of forest walking on physical and mental health in elderly populations. A systematic review*" published in the journal Reviews on Environmental Health. Research has shown that walking in a natural environment (forest walking) provides measurable benefits to the mental and physical health of elderly people. This was a useful result because it had some implications for the development of the project.

7.2 Introduction

Population aging is a global phenomenon; there were 703 million persons aged 65 years or older in the world in 2019, and it is estimated that the number of older persons will double by 2050 [1]. In 2015–2020, a person aged 65 years was expected to live an additional 17 years, which could increase to 19 years by 2045–2050 [1]. The prevalence of multimorbidity in older people ranges between 55 and 98%, and it results in disability and functional decline, poor quality of life, and high healthcare costs for health systems [1], with related socioeconomic concerns [2].

For the prevention and regulation of age-related chronic disorders, there is growing interest in the role of the environment in human health. Environmental stressors such as air pollution and crowding in urban areas substantially increase stress. In contrast, the natural environment has positive health effects, and therefore, activities performed in nature are gaining attention as lifestyle-related interventions [1, 3]. In particular, forests and other similar natural environments are recognized as fundamental health resources and may play a role in disease prevention and treatment [4] by improving the physical and mental health of people [2]. Nonetheless, government, public, and private sectors are not making efforts the use the therapeutic function of forests as a contribution to the well-being of older adults in the aging society [5].

A forest is one of the most accessible ways to experience the natural environment, and forest therapy is gaining more recognition as a nature-based therapy [2, 3]. A forest is either defined as an "ecosystem dominated by trees and other woody vegetation" (MedLine MeSH term) or as "Land spanning more than 0.5 hectares with trees higher than 5 m and a canopy cover of more than 10 percent, or trees able to reach these thresholds in situ" (Food and Agriculture Organization of the United Nations). The term "forest therapy" has been used interchangeably with the more traditionally defined "forest bathing" or "Shinrin-yoku" [2]. This Japanese term depicts activities of recreation and relaxation in a forest. Shinrin-yoku specifically relates to the activity of forest bathing, staying and/or walking in the forest, and breathing in the volatile substances released by the trees [4]. In particular, it means taking in all of one's senses, the forest atmosphere combining walking in the woods, with the conscious and contemplative practice of being immersed in the sights, sounds, and smells of the forest. It was developed in Japan during the 1980s, and in 1982 Japan made this form of mobile meditation under the canopy of living forests a part of its national health program. Researchers, primarily in Japan and South Korea, have established a growing body of scientific literature on the diverse health benefits. Nowadays forest bathing is attracting

increasing attention due to its health-promotion effects in humans [6], moving towards a global phenomenon. Previous studies on this topic have mostly focused on the capacity of forest bathing to provide relaxation and
reduce stress for people living in urban areas [7]. Research has reported potential benefits in the management of psychological symptoms, including anxiety, depression, mood disorder, burnout syndrome, lifestyle-related stress, and overall quality of life. Studies investigating the effect of forest therapy on physiological well-being have also demonstrated a positive impact on cognitive function,
immune function, blood glucose levels in diabetic patients, hypertension, cardiovascular disease, cancer prevention, and pain [4, 8–13].

In the elderly population, only a few programs have been proposed, often in combination with walking, physical training, or cognitive interventions, with reported positive effects on physiological and psychological outcomes [1].

While previous literature suggests the effectiveness of forest walking and bathing in improving the physical and psychological health of elderly people, a systematic review of the literature is lacking, and this paper aims to fill this gap. Moreover, this manuscript aims to identify the type, duration, and frequency of an effective forest therapy intervention to provide directions for future research.

7.3 Methods

Search strategy

A literature search was undertaken using the following electronic databases: MEDLINE, EMBASE, ResearchGate, Google Scholar, and Web of Science. Grey literature was searched as well through internet-based platforms. Studies published from the inception of the database to December 2021 were searched.

The search terms used to identify literature included (“elderly” OR “older adults” OR “older people” OR “aged[MeSH]”) AND (“forest therapy” OR “forest walking” OR “forest bathing” OR “forest environment” OR “forest healing” OR “Shinrin-yoku” OR “green environment” OR “walking in the forest” OR “nature-based intervention”). The reference lists of the retrieved studies were also searched for possible additional relevant studies. Full-text studies were then retrieved and evaluated for eligibility. The inclusion criteria were: publications that reported the effects of forest therapy on health and well-being in elderly participants, with the full article published in the English language.

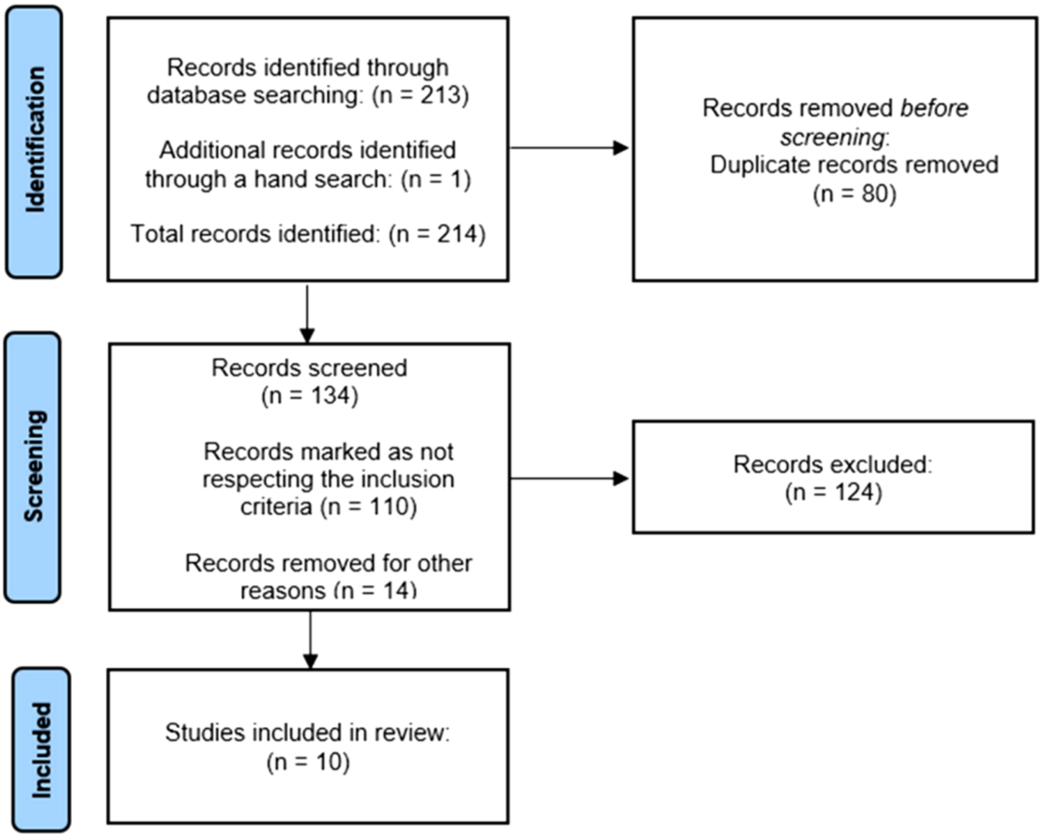
Selection criteria

The retrieved studies were screened based on the following inclusion criteria: subjects 60 years or older, intervention such as forest bathing (Shinrin-yoku), forest therapy, and walking in the forest carried out in a natural environment.

Study selection process

A total of 213 studies were identified from the literature search. One additional study was identified through a manual search of the reference lists of the included publications. Eighty studies were removed due to duplication. Two independent reviewers performed the screening of the articles (G.P. and L.C.) and a third reviewer (N.L.) solved any possible conflict. The titles and abstracts of the remaining 134 publications were screened, and 124 studies were excluded due to a lack of a natural environment (n=110) and a nonelderly population (n=14). Finally, 10 articles, all published in English, were analyzed (Figure 1).

Figure 1. Flow chart of the literature search process (PRISMA 2009)



Assessing the quality of the literature for risk of bias

Two reviewers independently appraised the 10 selected studies for risk of bias. The quality of the studies was rated using the Quality Assessment Tool for Studies with Diverse Designs (QATSDD) [14]. This tool consists of 16 criteria, with scores ranging from 0 to 3 for each. To use the tool, reviewers are required to award each research paper a score on a scale from 0 to 3 for each of the criteria: the higher the score is, the higher the quality of the item (Figure 2).

Figure 2. Assessment of risk of bias based on the quality assessment tool for studies with diverse designs. Legend for background color: Yellow: medium risk of bias; light-green: low risk of bias; Dark-green: very-low risk of bias.

Mao et al, 2018, China [6]	Wu et al, 2020, China [15]	Lee et al, 2014, Korea [3]	Lim et at, 2021, Korea [5]	Bing et al, 2016, China [16]	Yi et al, 2021, Korea [1]	Lee et al, 2018, Korea [17]	Mao et al, 2017, China [18]	Mao et al, 2012, China [7]	Yi et al, 2019, Korea [2]
32	**28**	**31**	**25**	**32**	**35**	**27**	**32**	**28**	**35**

7.4 Results

Data extraction

A summary of the 10 included articles were tabulated (Table 1) according to the study characteristics (authors, year of publication, country where the study was conducted), study design, sample size, participants' characteristics (age, sex), and the criteria for the inclusion of the participants; the type and the duration of the intervention.

Study characteristics

Of the included articles, half of the studies were conducted in Korea (n=5), and half were conducted in China (n=5). Six studies had an exploratory design [5, 6, 15–18], two were randomized controlled trials [3, 7] and two were nonrandomized controlled trials [1, 2].

A total of 487 participants were included, ranging from 18 to 88 participants for each study. All the participants were adults older than 60 years.

These studies included participants with chronic heart failure [6, 18], hypertension [7, 15], chronic obstructive pulmonary disease [16], cognitive decline [5], or elderly individuals without specified diseases or conditions [1–3, 17].

Types of forest bathing interventions

The concept of forest bathing has been actualized with different types of forest therapies. The modalities of forest interventions consisted of forest walking [3, 6, 7, 15, 16, 18], cardio and muscle-strengthening exercises [5], band gymnastic and physio-cognitive play, and active walking [1], forest walking and five senses meditation and traditional play [17], forest walking and muscle training with stretchable bands and guided breathing meditation [2].

Table 1. Characteristics of the included studies

Author, Year, Country	Study design	Sample size	Criteria for the inclusion of participants	Criteria for the exclusion of participants	Forest bathing interventions	Control/ Comparator	Duration of the intervention
Mao et al, 2018, China [6]	Exploratory study	N=33 (F=42%); IG=23 (F=48%); CG=10 (F=30%)	Age 65-80; Diagnosed CHF; BP <150/90; Class I–III cardiac function (criteria of AHA); ADL independent	Acute diseases two weeks prior or during the trial; Chronic diseases; AMI or CVA within six months; severe trauma or major surgery	Walking in the forest	Walking in the city	10 days
Wu et al, 2020, China [15]	Exploratory study	N=31 (F=39%); IG=20 (F=40%); CG=11 (F=36%)	Age 60-75; Diagnosed HTN; BP <180/110; Class I-II cardiac function (criteria of AHA); ADL independent	Acute diseases two weeks prior or during the trial; Chronic history; AMI or CVA within six months; severe trauma or major surgery	Walking in the forest	Walking in the city	Three days
Lee et al, 2014, Korea [3]	Randomized controlled trial	N=62 (F=100%); IG=43; CG=19	Age 60-80; Only females; BP <160/110	Chronic liver and renal disease; CAD; CVA; Cancer; Disability or pain when walking; P>160/110	Walking in the forest	Walking in the city	Eight days
Lim et at, 2021, Korea [5]	Exploratory study	N=60; IG=30; CG=26	Age >65; No restrictions on outdoor activities or walking; Able to understand the purpose of the study	Cognitive decline or dementia; Restrictions on outdoor activities or walking; Not ADL independent	Forest therapy activities, including forest walking	Usual life	Up to four months
Bing et al, 2016, China [16]	Exploratory study	N=18 (F=33%); IG=10 (F=30%); CG=8 (F=38%)	Age >60; Diagnosed COPD; HR <110; BP <160/90; FEV1 >35%; FEV1/FVC >30%; Class I-IV mMRC dyspnea scale	Acute exacerbation of COPD for at least 6 weeks	Walking in the forest	Walking in the city	Four days
Yi et al, 2021, Korea [1]	Nonrandomized controlled trial	N=74 (F=49%); IG=43 (F=60%); CG=31 (F=32%)	Age >65; Able to complete the surveys; Able to understand the purpose of the study	Cognitive impairment or dementia; Restrictions on outdoor activity for more than three hours	Forest therapy activities, including forest walking	Usual life	Up to two months
Lee et al, 2018, Korea [17]	Exploratory study	N=61; IG=30; CG=31	Age >65; No restrictions on physical activities in order to participate in the program	Sensory disturbance, cognitive disorder and mental disorder	Forest therapy activities, including forest walking	Usual life	Up to three months
Mao et al, 2017, China [18]	Exploratory study	N=33 (F=42%); IG=24 (F=49%); CG=12 (F=25%)	Age 65-80; Diagnosed CHF; BP <150/90; Class I–III cardiac function (criteria of AHA); ADL independent	Acute diseases two weeks prior or during the trial; Chronic history; AMI or CVA within six months; severe trauma or major surgery	Walking in the forest	Walking in the city	Five days
Mao et al, 2012, China [7]	Randomized controlled trial	N=24; IG=12; CG=12	Aged 60-75; Diagnosed HTN; BP <180/110; Class I-II cardiac function (criteria of AHA); ADL independent	Acute diseases two weeks prior or during the trial; Chronic history; AMI or CVA within six months; severe trauma or major surgery	Walking in the forest	Walking in the city	Eight days
Yi et al, 2019, Korea [2]	Non-randomized Controlled trial	N=88 (F=80%); IG=60 (F=83%); CG=28 (F=71%)	Age >65; Able to communicate and complete the surveys; Able to understand the purpose of the study and voluntarily sign the consent form	Cognitive impairment or dementia; Restrictions on outdoor activity for more than three hours	Forest therapy activities, including forest walking	Usual life	Up to three months

n: sample size; F: females; IG: intervention group; CG: control group; CHF: chronic heart failure; AHA: American Heart Association; ADL: autonomous in daily life; BP: blood pressure; AMI: acute myocardial infarction; CVD: cardiovascular diseases; HTN: hypertension; CLD: chronic liver disease; CAD: coronary artery disease; CVA: cerebrovascular accident; COPD: chronic obstructive pulmonary disease.

Forest walking

Six studies adopted forest walking only. Two studies by Mao et al. [6, 18] required the participants to walk in a forest for 1 h 30 min twice a day for four days [18] and to repeat a second time of the four-day forest bathing trip after four weeks [6]. The study by Wu et al. [15] required the patients to walk in the forest for 1 h 30 min in the morning and in the afternoon, with a 20 min rest during the walk, for three days. Lee et al. [3] asked the participants to walk at their usual pace for 1 h in the morning around a forest area. Bing et al. [16] required the patients to walk in a forest for 1 h 30 min in the morning and in the afternoon for three days. Finally, another study by Mao et al. [7] asked the participants to walk in a forest for 1 h 30 min in the morning and in the afternoon for seven consecutive days.

Other forest activities

Four studies combined forest walking with other forest therapy activities, and they were all conducted in Korea and published between 2018 and 2021. The study by Lim et al. [5] included clapping with fingers/back of the hands/ palms to help prevent cognitive decline, band exercises to
increase flexibility of the body and strengthen the muscles, and walking in the forest with adzuki beans fixed to the deepest depression of the sole [19]. The study by Yi et al. [1] proposed to the participant warm up exercises (body tapping), Qigong exercises (meridian relaxation and body scanning, body balancing and sensory attention, motion-coherent breathing techniques, and Taoin massage), band gymnastics (arm stretching and shoulder lifting), physio-cognitive play (various types of clapping, line dance, artwork with leaves and natural materials), and cool down exercises (light stroll and oil massage). The study by Lee et al. [17] included five senses meditation to induce
cognitive stimulation and relax emotions and traditional play that is effective for relaxing emotions and maintaining or promoting the remaining physical abilities of older adults by recalling the emotions and memories of childhood through traditional play using natural objects. Finally, the study by Yi et al. [2] proposed guided breathing meditation with

simultaneous stimulation of the cervical spine so that the cervical spine was aligned. This posture is known to activate the therapeutic Qi and blood flow through the meridian system in traditional Korean medicine [20] moreover, stimulation of the cervical spine is known to increase cerebral blood flow and reduce neuropathic upper limb pain [21, 22], among other health-promotion effects.

Outcome measure

The outcomes of forest therapy interventions in the ten included studies can be divided into physiological, neurochemical, and psychological parameters, as summarized in Table 2.

The physiological outcomes included blood pressure, brain natriuretic peptide, pulse oxygen saturation, heart rate, heart rate variability, cardio-ankle vascular index, pulmonary function, electroencephalography, and bioimpedance.

The neurochemical outcomes included interleukin-1β, interleukin-6, interleukin-8, tumor necrosis factor α, serum total SOD, malondialdehyde, C-reactive protein, natural killer cells, natural killer T cells, cytotoxic T cells, interferon-γ, pulmonary and activation-regulated chemokines, metalloproteinase-1, surfactant protein D, cortisol, epinephrine, endothelin-1, homocysteine, and renin-angiotensin system constituents.

The physiological outcomes included tension and anxiety, depression, anger and hostility, vigor and activity, fatigue, confusion, stress, and quality of life.

Table 2. Outcome measures of the forest interventions

Author, Year, Country	Sample size, Study population	Intervention group Control group	Physiological and neurochemical outcomes	Psychological outcomes
Mao et al, 2018, China (6)	Age 65-80; N=36; Elderly patients with CHF	IG =24; CG =12	BNP; IL-6; TNF-α; T-SOD; MDA	*NA*
Wu et al, 2020, China (15)	Age 60-85; N=31; Elderly patients with HTN	IG =20; CG =11	BP; HR; HRV; CRP; SpO2%	POMS
Lee et al, 2014, Korea (3)	Age 60-80; N=70; Elderly females	IG =50; CG =20	BP; CAVI; FEV1; FEV6	*NA*
Lim et at, 2021, Korea (5)	Age >65; N=60; Elderly patients with cognitive decline	IG =30; CG =30	HR; HRV; EEG	K-GDS
Bing et al, 2016, China (16)	Age 60-70; N=18; Elderly patients with COPD	IG =10; CG =8	IL-1β; IL-6; IL-8; TNF-α; CRP; NK; NKT; D8+Tcells; IFN-γ; RAC/CCL-18; TIMP-1; SP-D; EPI; Cortisol	POMS
Yi et al, 2021, Korea (1)	Age >65; N=74; Elderly individuals	IG =43 (QP =25; WP =18); CG =31	HRV; EEG; BIA	K-MoCA; K-GDS; EQ-5D
Lee et al, 2018, Korea (17)	Age >65; N=61; Low-income elderly living alone	IG =30; CG =31	BIA; Weight; BMI	SRI; K-BDI-II
Mao et al, 2017, China (18)	Age 65-80; N=36; Elderly patients with CHF	IG =24; CG =12	BNP; IL-6; TNF-α; T-SOD; MDA; CRP; ET-1; Renin; AGT; Ang II; AT1; AT2	POMS
Mao et al, 2012, China (7)	Age 60-75; N=24; Elderly patients with HTN	IG =12; CG =12	BP; HR; IL-6; TNF-α; ET-1; Hcy; Renin; AGT; Ang II; AT1; AT2;	POMS
Yi et al, 2019, Korea (2)	Age >65; N=88; Elderly individuals	IG =60 (BP =29; WP =31); CG =28	HR; HRV; EEG; BIA	*NA*

N: sample size; CHF: chronic heart failure; IG: intervention group; CG: control group; BNP: brain natriuretic peptide; IL-6: interleukin-6; TNF-α: necrosis factor α; T-SOD: activities of serum total SOD; MDA: lipid peroxidation reflected by malondialdehyde; NA: not available; HTN: hypertension; BP: blood pressure; HR: heart rate; HRV: heart rate variability; CRP: C-reactive protein; SpO2%: pulse oxygen saturation; POMS: profile of mood states; CAVI: cardio-ankle vascular index; FEV1: forced expiratory volume in the 1st second; FEV6: forced expiratory volume in six seconds; EEG: electroencephalography; K-GDS: Korean Form of Geriatric Depression Scale; COPD: chronic obstructive pulmonary disease; IL-1β: interleukin-1β; IL-8: interleukin-8; NK: Natural killer cells; NKT: Natural killer T cells; CD8+T: cytotoxic T cell; IFN-γ: interferon-γ; RAC/CCL-18: pulmonary and activation-regulated chemokine; TIMP-1: tissue inhibitor of metalloproteinase-1; SP-D: surfactant protein D; EPI: epinephrine; BIA: bioimpedance analysis; K-MoCA: Korean Form of Montreal Cognitive Assessment; EQ-5D: quality of life; BMI: body mass index; SRI: Stress Response Inventory; K-BDI-II: Korean Beck Depression Inventory-II; ET-1:

endothelin-1; AGT: angiotensinogen; Ang II: angiotensin II; AT1: angiotensin II type 1 receptor; AT2: angiotensin II type 2 receptor; Hcy: homocysteine

Physiological parameters

Three studies measured blood pressure [3, 7, 15], and all of them reported a marked decrease in diastolic blood pressure (approximately 10 mmHg), while systolic blood pressure decreased in only two studies (from 5 to 10 mmHg) [3, 7]. No variations in pulse pressure have been noticed.

Both studies [6, 18] measuring brain natriuretic peptide reported a significant decrease (from 350 to 500 pg/mL). The only study [15] that analyzed pulse oxygen saturation reported an increase of 1%.

Concerning heart rate, trivial changes were reported in four studies [1, 2, 5, 15], with favorable variations reported in heart rate variability [15]. The only study [3] that measured cardio-ankle vascular index and pulmonary function highlighted a significant improvement in both outcomes.

Three studies employed electroencephalography as an outcome measure [1, 2, 5]. One trial [5] detected an increase in peak frequency; concerning median frequency, one study [1] reported an increase, while another [2] reported a decrease. Variations were also registered in α band power, β band power and alpha/theta ratio [1, 2, 5].

Three studies analyzed bioimpedance [1, 2, 17] with conflicting results. One study reduced weight, body mass index and fat mass [17]; another did not report any significant variations in these parameters [2], while the remaining study showed a decrease in fat-free mass and an increase in fat mass [17].

Two studies analyzing reactance measured variations in the reactance of both arms (between −0.86 and −6.32 Ω) and the decrease in the reactance of both legs (between +1.84 and + 2.15 Ω) [2, 17].

The analysis of the physiological parameters is shown in Table 3a.

Table 3a. Changes in the physiological outcome measures after the forest interventions

Outcome measured	Sample size	Exercise protocol	Outcome changes after intervention		Ref
Blood pressure (mmHg)			1		
	IG =20; CG =11	Single day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−10	DBP	(15)
				SBP	
	IG =43; CG =19	1 h of FW at usual pace, for 1 day	−10	DBP	(3)
			−10	SBP	
	IG =12; CG =12	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−10	DBP	(7)
			−5	SBP	
				Pulse pressure	
Brain natriuretic peptide (pg/ml)			50		
	IG =24; CG =12	Two 4-day trips, 1.5 h of FW in the morning and 1.5 h in the afternoon	−500		(6)
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−350		(18)
Pulse oxygen saturation (%)			0,5		
	IG =20; CG =11	Single day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−1		(15)
Heart rate (bpm)			0.25		
	IG =20; CG =11	Single day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon			(15)
	IG =30; CG =30	11 sessions, once a week, of forest therapy activities: FW, band gymnastic, rhythmic gymnastic			(5)
	IG =12; CG =12	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon			(7)
	BP =29; WP =31; CG =28	11 sessions, once a week. WP: FW. BP: guided-breathing meditation, FW, muscle training	+0.73	BP	(2)
				WP	
Heart rate variability (m/s2)			1		
	IG =20;		−5	Low frequency	(15)

	CG =11	Single day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	+1.2	High frequency	
			−0.2	LF/HF ratio	
	IG =30; CG =30	11 sessions, once a week, of forest therapy activities: FW, band gymnastic, rhythmic gymnastic	+0.396	High frequency	(5)
	QP =25; WP =18; CG =31	12 sessions, twice a week. QP: body tapping, Qigong exercises, band gymnastics, physio-cognitive play, light stroll. WP: body tapping, band gymnastics, FW, physio-cognitive play, oil massage		Low frequency – QP and WP	(1)
				High frequency – QP and WP	
				% low frequency – QP and WP	
				Total power – QP and WP	
	BP =29; WP =31; CG =28	11 sessions, once a week. WP: FW. BP: guided-breathing meditation, FW, muscle training	−0.46	High frequency – BP	(2)
				High frequency - WP	
				High frequency – BP and WP	
				% low frequency – BP and WP	
				Total power – BP and WP	
Cardio-ankle vascular index			0.1		
	IG =43; CG =19	1 h of FW at usual pace, for 1 day	−0.42		(3)
Pulmonary function			0.05		
	IG =43; CG =19	1 h of FW at usual pace, for 1 day	+0.19	FEV1	(3)
			+0.22	FEV6	
Electroencephalography			0.1		
	IG =43; CG =19	11 sessions, once a week, of forest therapy activities: FW, band gymnastic, rhythmic gymnastic	+0.227 Hz	Peak frequency	(5)
	QP =25; WP =18; CG =31	12 sessions, twice a week. QP: body tapping, Qigong exercises, band gymnastics, physio-cognitive play, light stroll. WP: body tapping, band gymnastics, FW, physio-cognitive play, oil massage	+0.22 Hz	Median frequency -QP	(1)
			+0.17 Hz	Median frequency -WP	
			−0.28 μV2	α band power - QP	
			+0.33 μV2	α band power -WP	
			-0.39 μV2	β band power – QP	
				β band power – WP	
				Alpha/theta ratio – QP	
				Alpha/theta ratio – WP	

	BP =29; WP =31; CG =28	11 sessions, once a week. WP: FW. BP: guided-breathing meditation, FW, muscle training		Median frequency - BP	(2)
			−0.4	Median frequency -WP	
				Alpha/theta ratio - BP	
			−0.15	Alpha/theta ratio - WP	
Bioimpedance			0.5		
	QP =25; WP =18; CG =31	12 sessions, twice a week. QP: body tapping, Qigong exercises, band gymnastics, physio-cognitive play, light stroll. WP: body tapping, band gymnastics, FW, physio-cognitive play, oil massage	−0.68 kg	Fat free mass – QP	(1)
			−1.5 kg	Fat free mass – WP	
				Body fat mass – QP and WP	
			+0.46%	% body fat – QP	
			+0.48%	% body fat – WP	
			−0.86 Ω	Reactance avg both arms – QP	
			−2.09 Ω	Reactance avg both arms – WP	
			+1.84 Ω	Reactance avg both legs – QP	
			+2.15 Ω	Reactance avg both legs – WP	
	IG =30; CG =31	9 session, once a week: FW, five senses meditation, traditional play	−0.58 kg	Weight	(17)
			−0.22	Body mass index	
			−0.61 kg	Fat mass	
				Muscle mass	
	BP =29; WP =31; CG =28	11 sessions, once a week. WP: FW. BP: guided-breathing meditation, FW, muscle training		Fat free mass – WP and BP	(2)
				Body fat mass – WP and BP	
				% body fat – WP and BP	
			+1.30°	Phase angle of whole body - BP	
			+0.44°	Phase angle of whole body - WP	
			+0.87°	Phase angle of both arms - BP	
				Phase angle of both arms – WP	
				Phase angle of both legs – BP	
			+0.6°	Phase angle of both legs – WP	
			+ 6.32 Ω	Reactance avg both arms – BP	

	Reactance avg both arms – WP
	Reactance avg both legs – BP
+2.25 Ω	Reactance avg both legs – WP

IG: intervention group; *CG*: control group; *DBP*: diastolic blood pressure; *SBP*: systolic blood pressure; *FW*: forest walking; *BP*: breathing program; *WP*: walking program; *LF*: low frequency; *HF*: high frequency; *QP*: Qigong program; *FEV1*: forced expiratory volume in the 1st second; *FEV6*: forced expiratory volume in six seconds

Neurochemical response

Four studies [6, 7, 16, 18] measured IL-6, and three of them [7, 16, 18] identified a decrease (from −2 to −60 pg/L). Four studies investigated TNF-α with a significant reduction (from −5 to −20 ng/mL) detected in two of them [16, 18].

Two studies measured serum total SOD and malondialdehyde (MDA): one of them detected a decrease inMDA levels (−2 nmol/L) [6], and the other noted an increase in T-SOD (+10.000 U/mL) [18].

One study measured IL-1β and IL-8, detecting a significant decrease in both of the parameters (−0.5 ng/L in IL-1β and −110 pg/L in IL-8) and the percentage of natural killer cells, natural killer T cells and cytotoxic T cells, measuring a general increase (approximately 35, 30 and 3%) [16]. The same study also investigated the levels of interferon-γ, pulmonary and activation-regulated chemokine, metalloproteinase-1, surfactant protein D, cortisol and epinephrine, detecting a decrease in all the parameters. Two studies measured renin-angiotensin system constituents, noting no significant variations [7, 18]. The analysis of the neurochemical parameters is shown in Table 3b.

Table 3b. Changes in the neurochemical outcome measures after the forest interventions

Outcome measured	Sample size	Exercise protocol	Outcome changes after intervention	Ref
Interleukin-1β (ng/l)			0.1	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−0.5	(16)
Interleukin-6 (pg/l)			5	
	IG =24; CG =12	Two 4-day trips, 1.5 h of FW in the morning and 1.5 h in the afternoon	After 1st trip After 2nd trip	(6)
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−60	(16)
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−2	(18)
	IG =12; CG =12	1.5 h of FW in the morning and 1.5 h in the afternoon, for 7 days	−15	(7)
Interleukin-8 (ng/l)			20	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon		(16)
Tumor necrosis factor α (ng/ml)			2,5	
	IG =24; CG =12	Two 4-day trips, 1.5 h of FW in the morning and 1.5 h in the afternoon	After 1st trip −5 After 2nd trip	(6)
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−20	(16)
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon		(18)
	IG =12; CG =12	1.5 h of FW in the morning and 1.5 h in the afternoon, for 7 days		(7)
Serum total SOD (U/ml)			1,000	
	IG =24; CG =12	Two 4-day trips, 1.5 h of FW in the morning and 1.5 h in the afternoon	After 1st trip After 2nd trip	(6)
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	+ 10,000	(18)
Malondialdehyde (nmol/l)			0.5	
	IG =24;		− 2 After 1st trip	(6)

	CG =12	Two 4-day trips, 1.5 h of FW in the morning and 1.5 h in the afternoon	− 2	After 2nd trip
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon		(18)
C-reactive protein (mg/l)			0.25	
	IG =20; CG =11	Single day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−1.4	(15)
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−3	(16)
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon		(18)
Natural killer cells (%)			5%	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−35%	(16)
Natural killer T cells (%)			5%	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−30%	(16)
Cytotoxic T-cell (%)			0.5	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−3%	(16)
Interferon-γ (ng/l)			50	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−350	(16)
Pulmonary and activation-regulated chemokine (ng/ml)			5	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−25	(16)
Metalloproteinase-1 (ng/ml)			5	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−50	(16)
Surfactant protein D (ng/ml)			0,1	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−0.9	(16)
Cortisol (ng/ml)			5	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−20	(16)

Epinephrine (ng/ml)			1	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−10	(16)
Endothelin-1 (pg/ml)			2.5	
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon		(18)
	IG =12; CG =12	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−12	(7)
Homocysteine (μM)			0.5	
	IG =12; CG =12	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	−2	(7)
Renin-angiotensin system constituents (pg/ml)			1	
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	Renin Angiotensinogen Angiotensin II Angiotensin II type 1 receptor Angiotensin II type 2 receptor	(18)
	IG =12; CG =12	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	Renin Angiotensinogen Angiotensin II Angiotensin II type 1 receptor Angiotensin II type 2 receptor	(7)

IG: intervention group; *CG*: control group; *FW*: forest walking; *BP*: breathing program; *WP*: walking program; *QP*: Qigong program

Psychological response

Four studies submitted to the participants the profile of mood state questionnaire, showing an improvement of all the analyzed parameters [7, 15, 16, 18]. Two studies used the Korean form of the geriatric depression scale to estimate depression levels, and both detected a decrease in depression levels [1, 5].

One study [1] measured cognitive impairment with the K-MoCA and quality of life with the EQ-5D and found a significant decrease in cognitive impairment and a significant improvement in life quality.

One study evaluated stress and depression levels using SRI and K-BDI-II and detected a significant reduction of both stress and depression [17]. The analysis of the psychological parameters is shown in Table 3c.

Table 3c. Improvements in the psychological outcome measures after the forest interventions

Outcome measured	Sample size	Exercise protocol	Outcome changes after intervention		Ref
Profile of mood state			1		
	IG =20; CG =11	Single day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	+2	Tension-anxiety	(15)
			+3	Depression	
			+1	Anger-hostility	
			+5	Vigor-activity	
			+1	Fatigue	
			+2	Confusion	
	IG =10; CG =8	7-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	+2	Tension-anxiety	(16)
			+5	Depression	
			+5	Anger-hostility	
			+2	Vigor-activity	
			+3	Fatigue	
			+3	Confusion	
	IG =24; CG =12	4-day trip, 1.5 h of FW in the morning and 1.5 h in the afternoon	+4	Tension-anxiety	(18)
			+7.5	Depression	
			+6.5	Anger-hostility	
				Vigor-activity	
			+3	Fatigue	
			+3.5	Confusion	
	IG =12; CG =12	1.5 h of FW in the morning and 1.5 h in the afternoon, for 7 days	+1	Tension-anxiety	(7)
			+4.5	Depression	
			+5	Anger-hostility	
			+3.5	Vigor-activity	
			+3	Fatigue	
			+3	Confusion	
Korean Form of Geriatric Depression Scale			1		
	IG =43; CG =19	11 sessions, once a week, of forest therapy activities: FW, band gymnastic, rhythmic gymnastic	−3.267		(5)
	QP =25; WP =18; CG =31	12 sessions, twice a week. QP: body tapping, Qigong exercises, band gymnastics, physio-cognitive play, light stroll. WP: body tapping, band gymnastics, FW, physio-cognitive play, oil massage	−2.23	QP	(1)
				WP	
Korean Form of Montreal Cognitive Assessment			1		

	QP =25; WP =18; CG =31	12 sessions, twice a week. QP: body tapping, Qigong exercises, band gymnastics, physio-cognitive play, light stroll. WP: body tapping, band gymnastics, FW, physio-cognitive play, oil massage	+2.22 QP +3.46 WP	(1)
EQ-5D			0.01	
	QP =25; WP =18; CG =31	12 sessions, twice a week. QP: body tapping, Qigong exercises, band gymnastics, physio-cognitive play, light stroll. WP: body tapping, band gymnastics, FW, physio-cognitive play, oil massage	+0.05	(1)
Stress response inventory			5	
	IG =30; CG =31	9 session, once a week: FW, five senses meditation, traditional play	−23.9	(17)
Korean Beck Depression Inventory – II			1	
	IG =30; CG =31	9 session, once a week: FW, five senses meditation, traditional play	−6.87	(17)

IG: intervention group; *CG*: control group; *FW*: forest walking; *BP*: breathing program; *WP*: walking program; *QP*: Qigong program

7.5 Discussion

The positive effects that exposure to nature plays on human health have been established. Numerous observational or randomized trials that included forest intervention reported positive outcomes among the participants who spent time in a forest, and some benefits were shown to be derived even with simply viewing natural environments [4, 8, 23–26]. To provide additional information, the aim of this review was to focus on the possible physiological and psychological benefits derived from exercise interventions performed in the natural environment in the elderly population to possibly suggest guidelines or directions for future research on forest bathing interventions.

To the best of our knowledge, no previous literature reviews have focused on forest therapy interventions in the population aged more than 60 years old. This fact sounds surprising since the global aging population is increasing [1] and exercise therapy is effective and warranted in the elderly [27–29]. The possible combination of exercise training with the positive effects derived from forest therapy in young and middle-aged people [13, 25, 30, 31] can further enhance the impact on physical and psychological wellbeing in this population. Several studies recently reviewed [32], highlighted the effectiveness of different natural interventions in different ages, with beneficial effects of both psychological and physical health equally observed among young and adults.

At first, it should be discussed that due to the high heterogeneity of interventions, a meta-analysis to determine the estimated total effects of forest therapy cannot be performed. This is mainly due to the lack of high-quality randomized trials, as already reported [8], and the lack of control groups in the majority of the studies analyzed.

Focusing on the interventions proposed, this review identified different types of exercise training, including forest walking [3, 6, 7, 15, 16, 18] and several musculoskeletal or cardio fitness exercises in addition to walking, in four other trials [1, 2, 5, 17]. In all the studies analyzed, the duration and speed of walking training were only occasionally reported, and large variability needs to be accounted for, particularly when a “comfortable” walking speed was required to the patients. This fact opens a possible discussion on the direct impact of forest interventions on measurable physiological outcomes, such as blood pressure. Indeed, despite the evidence provided by some papers reviewed here [3, 7, 15], the training factors in terms of duration, frequency and intensity are extensively known to be responsible for different changes in blood pressure response [28] in older patients [29]. This means that forest interventions cannot directly claim that the positive effects registered on the majority of functional parameters rely only on their interventions, but the physiological effects of any kind of physical activity need to be considered. Otherwise, the psychological effects recorded in several papers [1, 7, 9, 15–18, 24, 30, 33–35] may be reliable, since several studies suggest that exposure to a green environment is associated with a positive impact on psychological wellbeing, including recovery from illness and even decreased mortality [36–38]. The studies reviewed here specifically highlighted an improvement in the levels of cognitive functions, as well a reduction in stress and depression levels [1, 5, 7, 15–18]. From the neurochemical point of view, a general anti-inflammatory effect with a reduction in the expression of interleukins and other proinflammatory markers has been reported. However, it is impossible to make a comparison since a much higher number of different proteins and molecules have been measured in different studies. In addition, a direct comparison between forest therapy and simply outdoor exercise should not be directly performed, since no trials compared the same physical intervention carried out in different settings. To this end, while the combination of nature and therapy seems to be beneficial, the knowledge within forest therapies to date remains a conditional basis for effect inferences [39]. Indeed, most studies are based on qualitative or quantitative analysis of evidence-based medical research, lacking basic theoretical insights of forestry [32]. A comprehensive analysis of the forest combined with the monitoring of key factors of the therapeutic process are important to understand the multidimensional health benefits of forest therapy when compared to outdoor exercise [40]. Finally, another aspect to be discussed is the total absence of adverse events or re-actions that occurred during the >8,000 forest walking sessions examined. On the one hand, this fact may be due to poor quality in reporting this outcome, but on the other hand, it may suggest the safety of these forest interventions in the older population, when a higher risk is expected.

Recommendations for future research

Evidence-based guidelines on forest interventions, including walking or other forms of exercise, should be developed. High-quality trials should be conducted on forest walking or forest therapy programs as a health promotion in elderly patients to establish strong evidence of their clinical effects. For further studies, we recommend that researchers clearly set forest walking interventions according to the frequency, intensity, time parameters, since we believe that different adjustments of these factors may lead to dissimilar responses. In addition, we advise collecting physiological outcomes in standard conditions (e.g., blood pressure) to make possible a comparison between the studies. Moreover, considering psychological outcomes, it is necessary to identify scales and questionnaires globally, and not only regionally, used. Finally, we encourage countries other than Korea and China to perform these kinds of studies to promote forest interventions in the older populations outside Asian countries.

From a qualitative point of view, we encourage researchers to describe in details the different forestry contexts, since so far city parks have been classified as forest therapy as centuries-old forests, creating a possible bias in the results interpretation, considering also that different trees impact on psychological health [41]. Therefore, the existing evidence on the therapeutic effects of forest therapy is still insufficient to establish clinical guidelines on its use in the elderly population as a health promotion strategy or disease prevention activity.

Limitations

Although it was observed in this review that forest bathing had positive effects on the elderly population, there are several limitations to this review. First, only studies on forest therapy interventions published in English were examined; those in other languages were not identified. A number of papers on forest bathing have been published in Chinese and Japanese, leading to a possible language bias. The review, although limited to a "special" population, was not registered in the PROSPERO database. Finally, a comparison between different forests could not be performed due to the limited information provided in the analyzed manuscripts.

7.6 Conclusion

The evidence presented in the studies that were reviewed here indicated that forest therapy interventions were effective in improving physiological, neurochemical and biological parameters, and psychological wellbeing. A minimum duration of these interventions to obtain significant benefits cannot be identified yet due to the high heterogeneity of the protocols proposed and their conduction in only a few countries in the world. More observational, exploratory or randomized controlled trials are therefore warranted to establish the effectiveness of forest interventions on physiological and psychological parameters in the elderly population.

References

1. Yi J, Kim SG, Khil T, Shin M, You JH, Jeon S, et al. Psychoelectrophysiological benefits of forest therapies focused on qigong and walking with elderly individuals. Int J Environ Res Publ Health 2021;18:1–16.
2. Yi J, Ku B, Kim SG, Khil T, Lim Y, Shin M, et al. Traditional Korean medicine-based forest therapy programs providing electrophysiological benefits for elderly individuals. Int J Environ Res Publ Health 2019;16:4325.
3. Lee JY, Lee DC. Cardiac and pulmonary benefits of forest walking versus city walking in elderly women: a randomised, controlled, open-label trial. Eur J Integr Med 2014;6:5–11.
4. Oh B, Lee KJ, Zaslawski C, Yeung A, Rosenthal D, Larkey L, et al. Health and well-being benefits of spending time in forests: systematic review. Environ Health Prev Med 2017;22:1–11.
5. Lim YS, Kim J, Khil T, Yi J, Kim DJ. Effects of the forest healing program on depression, cognition, and the autonomic nervous system in the elderly with cognitive decline. J People Plants Environ 2021;24:107–17.
6. Mao GX, Cao YB, Yang Y, Chen ZM, Dong JH, Chen SS, et al. Additive benefits of twice forest bathing trips in elderly patients with chronic heart failure. Biomed Environ Sci 2018;31:159–62.
7. Mao GX, Cao YB, Lan XG, He ZH, Chen ZM, Wang YZ, et al. Therapeutic effect of forest bathing on human hypertension in the elderly. J Cardiol 2012;60:495–502.
8. Kaplan S. The restorative benefits of nature: toward an integrative framework. J Environ Psychol 1995;15:169–82.
9. Morita E, Fukuda S, Nagano J, Hamajima N, Yamamoto H, Iwai Y, et al. Psychological effects of forest environments on healthy adults: shinrin-yoku (forest-air bathing, walking) as a possible method of stress reduction. Publ Health 2007;121:54–63.
10. Sung J, Woo JM, Kim W, Lim SK, Chung EJ. The effect of cognitive behavior therapy-based “forest therapy” program on blood pressure, salivary cortisol level, and quality of life in elderly hypertensive patients. Clin Exp Hypertens 2012;34:1–7.
11. Li Q, Morimoto IK, Kobayashi M, Inagaki H, KatsumataM, Hirata Y, et al. Visiting a forest, but not a city, increases human natural killer activity and expression of anti-cancer proteins. Int J Immunopathol Pharmacol 2008;21:117–27.

12. Ohtsuka Y, Yabunaka N, Takayama S. Shinrin-yoku (forest-air bathing and walking) effectively decreases blood glucose levels in diabetic patients. Int J Biometeorol 1998;41:125–7.
13. Mao GX, Lan XG, Cao YB, Chen ZM, He ZH, Lv YD, et al. Effects of short-term forest bathing on human health in a broad-leaved evergreen forest in Zhejiang Province, China. Biomed Environ Sci 2012;25:317–24.
14. Sirriyeh R, Lawton R, Gardner P, Armitage G. Reviewing studies with diverse designs: the development and evaluation of a new tool. Eval Clin Pract 2012;18:746–52.
15. Wu Q, Ye B, Lv X, Mao G, Wang S, Chen Z, et al. Adjunctive therapeutic effects of cinnamomum camphora forest environment on elderly patients with hypertension. Int J Gerontol 2020;14:327–31.
16. Jia BB, Yang ZX,Mao GX, Lyu YD,Wen XL, XuWH, et al. Health effect of forest bathing trip on elderly patients with chronic obstructive pulmonary disease. Biomed Environ Sci 2016;29:212–8.
17. Lee HJ, Son SA. Psychological and physical effects of 10 weeks urban forest therapy program on dementia prevention in low-income elderly living alone. J People Plants Environ 2018;21: 557–64.
18. Mao G, Cao Y, Wang B, Wang S, Chen Z, Wang J, et al. The salutary influence of forest bathing on elderly patients with chronic heart failure. Int J Environ Res Publ Health 2017;14. https://doi.org/10. 3390/ijerph14040368.
19. Kim I, Koo C. A study of walking, Viewing and fragrance-based forest therapy programs effect on living alone adults' dementia prevention. Korean J Environ Ecol 2019;33:107–15.
20. Shang C. Emerging paradigms in mind-body medicine. J Alternative Compl Med 2001;7:83–91.
21. Visocchi M. Spinal cord stimulation and cerebral haemodynamics. Acta Neurochir Suppl 2006;99:111–6.
22. Wolter T, Winkelmüller M. Continuous versus intermittent spinal cord stimulation: an analysis of factors influencing clinical efficacy. Neuromodulation 2012;15:13–20.
23. Yau KKY, Loke AY. Effects of forest bathing on pre-hypertensive and hypertensive adults: a review of the literature. Environ Health Prev Med 2020;25:1–17.
24. Elsadek M, Shao Y, Liu B. Benefits of indirect contact with nature on the physiopsychological well-being of elderly people. HERD 2021;14:227–41.

25. Bowler DE, Buyung-Ali LM, Knight TM, Pullin AS. A systematic review of evidence for the added benefits to health of exposure to natural environments. BMC Publ Health 2010;10:456.
26. Jimenez MP, Deville NV, Elliott EG, Schiff JE, Wilt GE, Hart JE, et al. Associations between nature exposure and health: a review of the evidence. Int J Environ Res Publ Health 2021;18:4790.
27. Frankel JE, Bean JF, Frontera WR. Exercise in the elderly: research and clinical practice. Clin Geriatr Med 2006;22:239–56.
28. Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. Med Sci Sports Exerc 2001;33(6 Suppl):S484–92.
29. Pinto E. Blood pressure and ageing. Postgrad Med2007;83:109–14.
30. Lee J, ParkBJ, Tsunetsugu Y,Ohira T, Kagawa T,Miyazaki Y. Effect of forest bathing on physiological and psychological responses in young Japanese male subjects. Publ Health 2011;125:93–100.
31. Hansen MM, Jones R, Tocchini K. Shinrin-yoku (forest bathing) and nature therapy: a state-of-the-art review. Int J Environ Res Publ Health 2017;14:851.
32. Harper NJ, Fernee CR, Gabrielsen LE. Nature's role in outdoor therapies: an umbrella review. Int J Environ Res Publ Health 2021; 18:5117.
33. Antonelli M, Donelli D, Carlone L, Maggini V, Firenzuoli F, Bedeschi E. Effects of forest bathing (shinrin-yoku) on individual well-being: an umbrella review. Int J Environ Health Res 2022;32: 1842–67.
34. Ae JP, Ae YT, Kasetani T, Takahide AE, Ae K, Miyazaki Y. The physiological effects of shinrin-yoku (taking in the forest atmosphere or forest bathing): evidence from field experiments in 24 forests across Japan. Environ Health Prev Med 2010;15:18–26.
35. Meneguzzo F, Albanese L, Antonelli M, Baraldi R, Becheri FR, Centritto F, et al. Short-term effects of forest therapy on mood states: a pilot study. Int J Environ Res Public Health 2021;18:9509. Erratum in: Int J Environ Res Public Health 2022;19.
36. Ulrich RS. View through a window may influence recovery from surgery. Science 1984;224:420–1.
37. Park SH, Mattson RH. Ornamental indoor plants in hospital rooms enhanced health outcomes of patients recovering from surgery. J Altern Complement Med 2009;15:975–80.
38. Cervinka R, Röderer K, Hefler E. Are nature lovers happy? On various indicators of well-being and connectedness with nature. J Health Psychol 2012;17:379–88.

39. Mygind L, Kjeldsted E, Hartmeyer RD, Mygind E, Bølling M, Bentsen P. Immersive nature-experiences as health promotion interventions for healthy, vulnerable, and sick populations? A systematic review and appraisal of controlled studies. Front Psychol 2019;10:943.
40. Wen Y, Yan Q, Pan Y, Gu X, Liu Y. Medical empirical research on forest bathing (Shinrin-yoku): a systematic review. Environ Health Prev Med 2019;24:70.
41. Astell-Burt T, Feng X. Association of urban green space with mental health and general health among adults in Australia. JAMA Netw Open 2019;2:e198209.

8. ECOLOGICAL ASPECTS OF EXERCISE IN DIALYSIS

Given the high environmental impact of the healthcare system and, in particular, the high cost of dialysis treatment, we analysed how an approach based on the synergy of exercise, diet, and the environment could be effective in improving the wellbeing of people with CKD. We have written a narrative review on this topic, which is currently in the submission stage for possible publication.

8.1 Introduction

The World Health Organization (WHO) defines Sustainable Healthcare (SH) as "*a system that improves, maintains, or restores health while minimizing negative impacts on the environment and leveraging opportunities to restore and improve it, to the benefit of the health and well-being of current and future generations*" [1].
There is clear evidence suggesting that the activities of any healthcare system significantly impact and pressurize the environment. These impact agents include generations of hazardous and conventional garbage, significant water consumption and greenhouse gas emissions, and the high consumption of energy. Fortunately, technological advances in healthcare have shown the potential to provide health benefits while safeguarding the environment. Effective, efficient, resilient healthcare models designed with environmental awareness and patient involvement are fundamental for SHs, as are sustainable transversal models specific to the treatment of chronic diseases.
Among these, chronic kidney disease (CKD) calls for a sustainable model, or perhaps more different models, considering the peculiar characteristics of patients at different stages of the disease. In particular, for patients at the final stage, when dialysis treatment is life-saving while waiting whenever possible for kidney transplantation, ethical issues [2] and critical aspects have been highlighted [3]. Among those, the high cardiovascular morbidity and mortality, reduced quality of life (QoL), costs related to management and transport to the dialysis centre, and overall global disparities are notable due to the increasing demand and insufficient availability of the treatment itself.

In addition, the dramatic environmental impact of haemodialysis, in particular, is also reported, considering that for each dialysis session, a waste production of between 1.5 and 8 kg (including approximately 30% of hazardous trash) and a water consumption of 500 litres are reported.

Bearing in mind all the premises, there is a need to identify specific strategies to be implemented for CKD patients and their families. Among these strategies, physical exercise has been recognized as a useful tool to counteract the hazards derived from the sedentary behaviour of CKD patients.

This narrative review aims to provide an overview of the potential of physical exercise as an effective tool for improving the psychophysical well-being of patients on dialysis from an ecological perspective.

8.2 Exercise and End-Stage Kidney Disease

Poor physical functioning is probably the most pervasive and disabling disturbance in patients at the final stage of kidney disease [4]. When patients reach the last stage of the disease and start hemodialysis (HD) treatment, their physical activity levels decrease to approximately 25% of those recorded in age-matched sedentary healthy individuals. In addition, one out of three HD patients is unable to perform activities of daily living without assistance [5]. This triggers a vicious and potentially dangerous cycle for the health of patients, with an increased risk of morbidity and mortality. People undergoing HD treatment are at greater risk of cardiovascular disease and depression and have a lower QoL and limited survival than the general population [5].

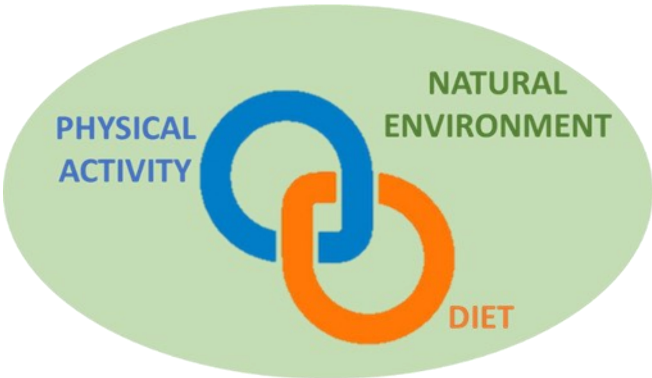
Physical activity represents an effective tool to overcome this vicious cycle, with reported beneficial effects on physical fitness, walking capacity, health-related QoL, and other parameters [6]. For these reasons, the National Kidney Foundation KDOQI Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients report that patients should be counseled and encouraged to increase their level of physical activity. However, exercise is still not prescribed regularly as part of usual care [5] due to several barriers, including a reported attitude of non-proactive staff toward encouraging patients to participate in exercise programs [7].

A behavioral change in patients' attitudes toward a more active and healthy lifestyle could represent a type of "ecological" intervention for its impact on QoL and mental and physical wellbeing [8] but also on environmental harmony. These interconnected aspects, potentially improvable through physical exercise [8], are perceived by patients [9-11] beyond the currently available scientific evidence [12]. Indeed, patients request effective interventions to prevent cardiovascular diseases, improve mobility and slow physical decline after dialysis treatment, improve debilitating physical (fatigue, insomnia, and cramps) and mood symptoms (depression, anxiety, and frustration) [13], maintain good QoL with the possibility of traveling [14,15], maintain mobility and the ability to work, have dialysis-free time, and reduce the impact of dialysis on family and/or friends [2,16-18].

The majority of these aspects are still unaddressed, or the scientific literature struggles to find wide-ranging solutions that are not limited to specific interventions (e.g., a clinical trial). The everyday reality and routine nature of renal care address the limited availability of effective programs offering physical function assessment and/or exercise training, which positively influence the trajectory of renal care [12,19,20], or crushes on the reported patients' and nephrologists' barriers in understanding the importance of exercise interventions [21].

Considering this scenario, it is important to describe the existing connections among the environment, diet, and exercise to make the latter a policy priority, to improve the physical and mental health of patients, and to reduce the impact of dialysis.

Figure 1. Visual conceptualization of the study



8.3 Exercise and dietary interventions

To favor an ecological strategy aimed at counteracting the negative effects of sedentariness and lack of exercise in patients with CKD [22], various key elements should be considered. At first, the importance of diet in protecting against the unfavorable evolution of renal disease [23,24] and the management of dialysis treatment [24] through a comprehensive nutritional approach based on natural foods and low protein, phosphate, or salt, red meat [25-28] and adequate fluid management [12] is well known.

The nutritional approach, on the one hand, may provide a synergistic effect with exercise, improving patients' well-being; on the other hand, the effects of nutritional interventions [29] could favor the physical performance of CKD patients [30] through targeted nutritional strategies (e.g., protein supplementation) associated with different types of exercise. However, based on the trials available in the literature, the results of the combination of exercise and supplementation are partly conflicting (Table 1). Finally, malnutrition should also be avoided and possibly prevented with simple screening tools [31].

Table 1. Effects of combined exercise and diet interventions in dialysis patients

Author	Journal	Year	Study design	Sample size	Age (years)	Intervention	Outcomes	Results
Martin-Alemañy et al [32]	J Ren Nutr	2019	Parallel controlled clinical trial	N =45 (F =24)	29 ± 9	AE+ONS (n =15) RE+ONS (n =15) ONS (n =15)	Physiological Psychological	Exercise and ONS had larger effects on PF than ONS alone
Gamboa et al [33]	Am J Physiol Renal Physiol	2020	Prospective, randomized, open-label, parallel-arm clinical trial	N =12 (F =2)	41 (30-50)	RE+ONS (n =6) ONS (n =6)	Neurochemical	IPS increases protein balance, fat cross-sectional area of the thigh, and markers of mitochondrial content
Majchrzak et al [34]	Nephrol Dial Transplant	2008	Randomized, prospective, crossover study	N = 8 (F =2)	38 ± 11	RE+ONS	Neurochemical	RE improves protein anabolic effects of intradialytic ONS
Dong et al [35]	J Ren Nutr	2011	Randomized controlled trial	32 (F =11)	43 ± 13	RE+ONS	Physiological	The addition of RE to ONS didn't show any extra effects on muscle protein accretion
Martin-Alemañy et al [36]	Nephrol Dial Transplant	2016	Randomized clinical trial	44	44 (24-43)	RE+ONS (n =22) ONS (n =22)	Psychological Neurochemical	ONS during HD improves NS. The addition of RE didn't show better effects

F: female; AE: aerobic exercise; ONS: oral nutritional supplementation; RE: resistance exercise; PF: physical function; IPS: intradialytic protein supplementation; HD: hemodialysis; NS: nutritional status

8.4 Exercise-environment synergy

In addition to nutrition, the synergy between exercise and the natural environment can also be exploited. According to Lewy, "*patients are less likely to exhibit signs of depression, especially where access to natural light and opportunities for physical exercise are present*" [37]. Indeed, it is believed that spending time in nature can promote and encourage physical activity and that a natural environment combined with exercise may improve mood [38,39,48,49,40–47] and functioning [50], as well as social cohesion and positive social relations between people.

These positive effects of the natural environment should also be pursued in CKD patients and particularly in HD patients, where the ecological model acquires a double meaning, considering that the Greek word “oikos” means “home”, or “place to live”. Considering that HD therapy involves a prolonged daily presence in the place of care, the creation of a favorable ecosystem (e.g., by rethinking the care environment itself) could foster a model of psychological and social interactions, with benefits not only for patients but also for the healthcare team.

In this sense, the inclusion of nature, or natural elements, in the dialysis center may be obtained through the exploitation of the principles of biophilic design. Its related aspects, such as environmental features, natural shape and forms, natural patterns, light, and space [51], could represent an effective tool to promote the empowerment of patients and improve psychological equilibrium and physical well-being. Visual contact with nature has been associated with improved health outcomes in patients [52-60], reduced duration of hospitalization and recovery time following surgery, lower perception of pain with reduced use of drugs, favorable physiological adaptations in the activity of the parasympathetic nervous system, lower levels of anxiety and fatigue stress, and a general sense of well-being. Positive effects in response to biophilic design may also be observed in visitors and caregivers as well as staff members in terms of stress, fatigue, productivity, organizational skills, job satisfaction, and attention levels. As a further favorable aspect, interventions to modify the environment of care with natural elements do not necessarily require structural solutions but can also be achieved through one of the three possible modes of interaction with nature [51] envisaged by biophilic design. Indeed, the biophilic experience may derive from direct and real contact or an indirect experience of nature through images or the use of perspectives, as well as from the virtual connection with nature, considering that visual, acoustic, olfactory, and tactile stimuli have a multisensory impact on the person.

The connection between exercise and the environment is a well-known concept. The Japanese term Shinrin-Yoku is an expression of the practice of performing activities in the forest to enjoy the full benefits of the forest and enhance the effects of the exercise. This activity has also recently become a field of interest in Western countries, and its beneficial effects on physiological (e.g., salivary cortisol levels, heart rate, blood pressure) and psychological (e.g., stress) parameters have been recognized.

Table 2. Systematic reviews of the effects of exercise in nature

Author	Journal	Year	Studies included	Intervention	Outcomes	Results
Antonelli et al [61]	Int J Biometeorol	2019	8	Forest walking	Psychological	Forest bathing can reduce stress levels
Brito et al [62]	Environ. Sci. Technol	2022	24	Green exercise	Physiological Psychological	Green exercise is associated with greater benefits than indoor exercise
Hansen et al [63]	Int. J. Environ. Res. Public Health	2017	64	Forest walking	Physiological Psychological	Forest walking reduces HR and BP, and increases relaxation
Ideno et al [64]	BMC Complement Altern Med	2017	20	Forest walking	Physiological	Forest walking can significantly reduce BP
Ka-Yin Yau et al [65]	Environ. Health Prev. Med.	2020	14	Forest walking	Physiological Neurochemical Psychological	Forest walking has physiologically and psychologically relaxing effects on people with pre-HTN and HTN
Lahart et al [66]	Int. J. Environ. Res. Public Health	2019	28	Green exercise	Physiological Psychological	Limited evidence that green exercise offers superior benefits than indoor exercise
Marini et al [67]	Int. J. Environ. Res. Public Health	2022	6	Green exercise	Physiological Psychological	Green exercise can have a positive impact on the healthy population
Park et al [68]	Int. J. Environ. Res. Public Health	2022	32	Forest walking Green exercise	Physiological Psychological	Forest walking can improve physiological and psychological outcomes
Piva et al [69]	Rev Environ Health	2022	10	Forest walking	Physiological Neurochemical psychological	Forest walking can improve physiological, neurochemical, and psychological parameters
Wicks et al [70]	Appl Psychol Health Well-Being	2022	24	Green exercise	Psychological	Exercise in nature improves psychological outcomes better than exercise in urban environment

SCL: salivary cortisol levels; HR: heart rate; BP: blood pressure; HTN: hypertension

8.5 Effects of exercise on the quality of life of people with CKD

The promotion of physical activity in patients with CKD thus represents both an ecological strategy and a necessary “replacement therapy”, since spontaneous activity measured or reported in these persons is markedly reduced in comparison with the elderly population and age-matched peers [12,71,72].

This sedentary behavior is associated with progressive deconditioning, skeletal muscle atrophy, dysfunction, and chronic fatigue, leading to a progressive reduction in exercise capacity, frailty, and disability [5,22,73]. In the course of this unfavorable progression, an inadequate lifestyle is associated with poor control of risk factors (e.g., blood pressure), low health-related QoL, psychological discomfort, depression, and lack of motivation [74]. Moreover, reduced physical activity and impaired mobility, as well as low measured physical function, are associated with poor clinical outcomes among the CKD population in general [75], with higher cardiovascular morbidity and all-cause mortality, particularly among patients on HD [76,77].

On the other hand, the benefits of regular exercise across the trajectory of renal care, from the early stages of CKD to kidney transplant recipients, have been reported [8,78]. Exercise has a positive impact on the cardiovascular system, walking capacity, and aerobic fitness, as well as on health-related QoL and mood. Even minimal weekly doses were reported to be associated with better clinical outcomes [4].

Table 3. Systematic reviews of the effects of exercise on QoL in dialysis patients

Author	Journal	Year	Studies included	Intervention	Outcomes	Results
Cai et al. [79]	Ann Palliat Med	2022	7	AE, RE	Urea clearance index; PF; Mental health	AE+RE can improve the urea clearance index, mental health, social functioning, and HRQoL
Bernier-Jean et al. [8]	CDSR	2022	89	AE, RE	Death; Fatigue; HRQoL; Depression; 6MWT; STS; BP; VO_2 max; ALB, Blood lipids; Body composition; BMI; Ca; CRP; KT/V; Energy intake; Hb; LVEF; LVMI; HR; Muscle strength; Phosphate; K; Protein intake; PTH; RHR; TUG	There is no certainty about the effects of AE or RE on the mental component of HRQoL
Hargrove et al. [80]	CJASN	2021	15	AE	RLS; Sleep disturbance; Anxiety; Depression; Muscle cramps; Fatigue	IDAE and EDAE can be therapeutic options for RLS, depression, muscle cramps and fatigue
Hu et al. [81]	Qual. Life Res.	2022	33	AE, RE	SF-36; KDQOL-SF; KDQOL-36; SF-12; RAND-36	AE can improve HRQoL. IDE can enhance the PCS and PF but not the MCS and BP
Huang et al. [82]	Am J Nephrol	2019	20	AE, RE	KT/V; SBP; DBP; VO_2 max; 6MWT; HRQoL	AE or AE+RE can be beneficial for exercise capacity, walking capacity and QoL
Mosted et al. [83]	Dan Med J	2019	8	RE	LBM; Muscle strength; FFM; HRQoL; PF	RE can improve self-reported physical function and the Physical Component of SF-36
Salhab et al. [84]	J. Nephrol.	2019	22	AE	SF-36; KDQOL-SF; WHO-QOL26; KDQOL	IDAE has positive effect on the Physical and Mental Component of SF-36
Song et al. [85]	J. Pain Manag	2018	15	AE, RE	RLS; Depression; Sleep quality; Fatigue	AE and RE may reduce the severity of RLS, depression, and fatigue
Zhang et al. [86]	Nurs. Open	2018	14	RE	6MWT; STS; HG; Nutrient intake; HRQoL	IDRE may give benefits in physical function, however there is no difference in the SF-36

AE: aerobic exercise; RE: resistance exercise; PF: physical functioning; HRQoL: health-related quality-of-life; 6MWT: 6-minute walking test; STS: sit-to-stand test; SBP: systolic blood pressure; DBP: diastolic blood pressure; ALB: albumin; BMI: body mass index; Ca: calcium; CRP: C-reactive protein; KT/V: dialysis efficacy; Hb: hemoglobin; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; HR: heart rate; K: potassium; PTH: parathyroid hormone; RHR: resting heart rate; TUG: Timed up-and-go test; RLS: restless legs syndrome; IDAE: intradialytic aerobic exercise; EDAE: extra-dialytic aerobic exercise; SF-36: Short Form Health Survey; KDOQOL-SF: Kidney Disease Quality of Life Short Form; KDQOL-36: Kidney Disease Quality of Life Instrument; SF-12: Short Form Health Survey; IDE: intradialytic aerobic exercise; PCS: physical component summary; MCS: mental component summary; BP: bodily pain; LBM: lean body mass; FFM: fat-free mass; eGFR: kidney function; IDRE: intra-dialytic resistance exercise;

8.6 Effects of exercise on CKD progression

Among the clinical outcomes related to the ecological approach to exercise in CKD patients, there is the possibility of positively interfering with renal function and renal disease progression through patients' physical empowerment. Stable values of kidney function parameters have been observed among physically active older subjects [87] compared to inactive ones [88], as well as a slower rate of eGFR loss and in persons with CKD [20,71,89-92], as well as in persons at a higher level of fitness [71,91,92] or a favorable or even small effect on eGFR after physical training, without effects of exercise on proteinuria [93,94].

The deceleration of CKD progression may be related to the favorable effects of physical activity and exercise [95] on blood pressure control [96] and vascular stiffness, although the results are controversial [97]. In CKD patients with concomitant PAD and claudication, walking as a form of exercise rehabilitation may lead to a lower rate of peripheral revascularization, with a lower need for kidney-invasive diagnostics (e.g., angiographic procedures) employing contrast agents [98]. However, the overall quality of the reported trials is low, and the potential ability of exercise to delay the initiation of dialysis treatment needs to be verified in prospective high-quality studies.

In the dialyzed patient (both HD and PD), the effects of physical exercise on dialysis treatment efficiency have been reported [99], with benefits observed in terms of improved hemodialysis adequacy, exercise capacity, depression, and quality of life of patients.

8.7 An ecological model for the care of dialysis patients

The demonstrated wide range of clinical benefits and patient requests [71] indicate the need for effective exercise-based interventions, which have been proposed and validated by researchers in the field [2,12]. However, despite the evidence in recent literature [19], it is difficult to believe that a single exercise-based intervention, even the most effective, can be widely disseminated and accepted by the majority of the scientific community.

The creation of sustainable, feasible, and broadly inclusive models of exercise and the incorporation of these activities into patients' daily routine is a necessary objective to pursue, despite its complexity.

Moving toward an ecological framework of the patient's engagement in physical activity, the interaction between the subjective and the environmental factors that influence, positively or negatively, patients' behaviour needs to be taken into consideration [100,101]. According to Sallis and Owen, these interventions should operate on multiple levels and should be designed considering the four domains of physical activity, namely, active recreation, household activities, occupational activities, and active transportation, which contribute to defining "active living" [101,102].

For CKD patients in particular, different models should be designed, paying special attention to the most fragile subgroup of this population or those at the final stage of disease. These four domains are mainly limited by the impact of the dialytic treatment, which occupies a significant part of the patient's day and causes him/her to experience fatigue and limited residual energy.

In this scenario, various exercise-based interventions should be tested in real-life models, taking into account the complex characteristics of these patients, including skills, limitations, and preferences. An expert in exercise training may offer group-based or individualized training solutions by assessing the subject's domains [101] and acting as a connector between the person, the environment, the family, and the nephrology staff. Customization should consider several related aspects to be integrated into the ecological model, such as patient-related factors (family context, age, disability status, income) [101], needs, and preferences about "where when, and how" to exercise.

The expert should also properly manage the exercise intervention and its determining factors. If we know sufficiently well "why exercise?" It is important to define other aspects—where when, and how much [71] exercise is recommended for patients—to design the model.

The location at which exercise training is performed is a crucial factor, according to the individual preferences of a single patient. This aspect, only partly investigated, shows the preference of patients for home-based exercise [9,71], including low-cost tele-rehabilitative therapies that are considered to be effective [2]. However, the choice of the home environment, or natural or outdoor environment, may be dependent on the patients' degree of fitness, age, knowledge, skills and abilities, neighbourhood or environmental surroundings, and related safety (e.g., access to sidewalks) [40,41] or autonomy of transport [101]. Training activities at home can be facilitated by technology and controlled by wearable or remote systems, and they can be carried out individually, organized (e.g., walking groups), or structured through the use of precise home-based programs.

The choice of an extra-home environment may take into account supervised community-based programs, which, on the other hand, are limited by the availability of fitness facilities, distances from patients' homes, the possibility of transportation, and the costs and affordability for patients.

As a final alternative, a limited number of patients may prefer the hospital environment, or more specifically, the dialysis unit [9,71]. Here, it may be implemented with the presence of an exercise specialist to carry out different unstructured or structured training interventions [103].

After the setting, a second crucial parameter is the exercise modality. The scientific literature offers a wide range of recommendations in terms of the intensity, duration, and frequency of aerobic and/or resistance training [104]. In general, despite low functioning and high cardiovascular risk, no side effects related to exercise were reported, leading to a lack of evidence for exercise restrictions [6,105]. However, the main issue remains encouraging people with comorbidities and disabilities [21] to engage in physical activity and exercise; therefore, safe and inclusive approaches need to be fully considered.

Exercise protocols should be designed to require a few preparticipation visits for the selected patients at a proper intensity to be safe for people with different capabilities [21,22] and to minimize exercise-limiting symptoms. For example, in patients with peripheral artery disease (PAD), who represent a high percentage of CKD patients, low levels of pain during exercise, which often represent a barrier to training [106], favour good adherence. The guidelines for chronic diseases recommend performing at least 150 minutes of moderate-intensity aerobic physical activity a week or 75 minutes of vigorous-intensity activity [107]; however, even lower doses of exercise can provide documented benefits [108].

In elderly individuals, a modest increase in physical activity has been associated with improved renal function over time while still keeping the patient in the considered sedentary range. Low-intensity programs carried out for short periods (8-15 min per day) were associated with benefits in strength, HRQoL, clinical outcomes, and hospitalization in CKD and ESKD patients [4] and may reduce post-dialysis fatigue and symptoms such as restless legs, cramps, with a legacy effect [109]. According to the Dialysis Outcomes and Practice Patterns Study, an exercise frequency of more than one session per week was associated with a lower mortality risk [110]. Effective protocols should be based on simple exercises (walking, pedalling, lightweight or bands), possibly structured [4]. Finally, the program should be well accepted and potentially chosen from various options to involve persons in their care and even flexible [111].

In terms of duration, training programs ranging from 4 to 6 months are generally reported, but will it also be possible for the ESRD patient to train for shorter repeatable cycles? Most likely, training periodization should be favoured over a foreseeable amount of time, and the high risk of morbidity and drop-outs should be considered.

In general, “ecological exercise” programs should be aimed at increasing physical activity and favouring socialization. However, in this direction, protocols should aim to be the least expensive possible (or free of charge) and to limit the requirements of transportation, tools, and resources (electricity, pollution, etc.). Moreover, they should have training goals that may be reached to avoid frustration and possible abandonment. Finally, exercise interventions could also be combined with physical or psychological complementary activities such as laughter therapy [112] and behavioural interventions such as mindfulness treatments, relaxation, narrative and storytelling, and cinema [113].

Therefore, it is necessary to define who can carry out this synthesis and provide the ideal exercise accompaniment for each subject, considering the reported positive effects of counselling [71]. In our opinion, a specific healthcare professional should be at the patient’s side. Considering the several limitations of physical activity conducted by nephrological nurses [114-118], as well as the poor experience of nephrologists [114], the presence of health and fitness professionals has a crucial role in creating multiprofessional teams in dialysis units [119]. These figures may address organizational and logistic issues and patient counselling in terms of exercise, based on the experience progressively gained [120].

Furthermore, this role is crucial considering the importance of integration with personnel engaged in the health care of patients (doctors, nurses, etc.) to disseminate the possible benefits derived from exercise and increased physical activity, considering the reported low rates of exercise counselling among nephrologists [7].

Finally, the changes in the individual ecological approach can occur according to local [101] or general availabilities of community facilities, rehabilitative services in the hospital, changes in exercise and physical activity policy barrier domains, and novel strategies in kidney care, which could facilitate health services to increase physical activity levels in CKD and ESKD patients [21].

Approaches to maximizing functional and social rehabilitation are also important in patients with kidney failure. In addition to the abovementioned symptoms, Tong et al. identified the ability to travel, the ability to work, dialysis-free time, the impact of dialysis on family and/or friends, and mobility as important middle-tier outcomes [16]. These authors also identified

life participation as one of five core outcomes and identified impact on family and/or friends and mobility as other outcomes that are important to patients [121].
Given the importance of these outcomes to patients and stakeholders, researchers in the field of nephrology must develop tools to enable valid and consistent measurement of these outcomes and identify interventions that could favourably modify them.

8.8 Conclusion

Researchers are currently attempting to hypothesize and test safe, sustainable, and effective interventions to improve patients' mobility and attitudes toward exercise in real-world environments.
On this basis, feasible models that overcome as many barriers as possible with ease of application may be derived and implemented in nephrology centres in any country. When possible, multidisciplinary interventions promoting exercise training, dietary improvements, and behavioural and environmental modifications should be designed. Multidisciplinary models that are sufficiently effective and cost-efficient and based on simple concepts, if shared without preconceptions by stakeholders, could be welcomed by persons on haemodialysis, with a positive impact on patient-centred outcomes and with wide dissemination.
These steps could favour “global and local policy reform to address funding, service provision, legislation, regulations, guidelines, environmental aspects, and communication and marketing to maintain physical activity and a high quality of life of people living with kidney disease” [21]. However, in addition to top-down interventions, bottom-up efforts from patients and researchers are necessary [2].

References

1. WHO Team. Environmentally sustainable health systems: a strategic document [Internet]. World Health Organization. Regional Office for Europe; 2017. 28 p. Available from: WHO/EURO:2017-2241-41996-57723
2. Himmelfarb J, Vanholder R, Mehrotra R, Tonelli M. The current and future landscape of dialysis. Nat Rev Nephrol [Internet]. 2020 Oct 30;16(10):573–85. Available from: https://www.nature.com/articles/s41581-020-0315-4
3. Piccoli GB, Cupisti A, Aucella F, Regolisti G, Lomonte C, Ferraresi M, et al. Green nephrology and eco-dialysis: a position statement by the Italian Society of Nephrology. J Nephrol [Internet]. 2020;33(4):681–98. Available from: https://doi.org/10.1007/s40620-020-00734-z
4. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2017 Apr;28(4):1259–68.
5. Kirkman DL, Edwards DG, Lennon-Edwards S. Exercise as an Adjunct Therapy In Chronic Kidney Disease. Ren Nutr forum [Internet]. 2014;33(4):1–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26069463
6. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. Cochrane Database Syst Rev. 2011;2011(10).
7. Regolisti G, Maggiore U, Sabatino A, Gandolfini I, Pioli S, Torino C, et al. Interaction of healthcare staff's attitude with barriers to physical activity in hemodialysis patients: A quantitative assessment. PLoS One. 2018;13(4):1–15.
8. Bernier-Jean A, Beruni NA, Bondonno NP, Williams G, Teixeira-Pinto A, Craig JC, et al. Exercise training for adults undergoing maintenance dialysis. Cochrane database Syst Rev. 2022 Jan;1(1):CD014653.
9. Moorman D, Suri R, Hiremath S, Jegatheswaran J, Kumar T, Bugeja A, et al. Benefits and Barriers to and Desired Outcomes with Exercise in Patients with ESKD. Clin J Am Soc Nephrol [Internet]. 2019 Feb;14(2):268–76. Available from: https://journals.lww.com/01277230-201902000-00016
10. Delgado C, Johansen KL. Barriers to exercise participation among dialysis patients. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2012 Mar;27(3):1152–7.

11. Bakker EA, Zoccali C, Dekker FW, Eijsvogels TMH, Jager KJ. Assessing physical activity and function in patients with chronic kidney disease: A narrative review. Clin Kidney J. 2021;14(3):768–79.
12. Wilund K, Thompson S, Bennett PN. A Global Approach to Increasing Physical Activity and Exercise in Kidney Care: The International Society of Renal Nutrition and Metabolism Global Renal Exercise Group. J Ren Nutr. 2019;29(6):467–70.
13. Flythe JE, Hilliard T, Castillo G, Ikeler K, Orazi J, Abdel-Rahman E, et al. Symptom Prioritization among Adults Receiving In-Center Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2018 May;13(5):735–45. Available from: https://journals.lww.com/01277230-201805000-00012
14. Manera KE, Johnson DW, Craig JC, Shen JI, Ruiz L, Wang AY-M, et al. Patient and Caregiver Priorities for Outcomes in Peritoneal Dialysis. Clin J Am Soc Nephrol [Internet]. 2019 Jan;14(1):74–83. Available from: https://journals.lww.com/01277230-201901000-00013
15. Manera KE, Tong A, Craig JC, Shen J, Jesudason S, Cho Y, et al. An international Delphi survey helped develop consensus-based core outcome domains for trials in peritoneal dialysis. Kidney Int [Internet]. 2019 Sep;96(3):699–710. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253819303400
16. Tong A, Manns B, Hemmelgarn B, Wheeler DC, Evangelidis N, Tugwell P, et al. Establishing Core Outcome Domains in Hemodialysis: Report of the Standardized Outcomes in Nephrology–Hemodialysis (SONG-HD) Consensus Workshop. Am J Kidney Dis [Internet]. 2017 Jan;69(1):97–107. Available from: http://dx.doi.org/10.1038/s41581-020-0315-4
17. Evangelidis N, Tong A, Manns B, Hemmelgarn B, Wheeler DC, Tugwell P, et al. Developing a Set of Core Outcomes for Trials in Hemodialysis: An International Delphi Survey. Am J Kidney Dis [Internet]. 2017;70(4):464–75. Available from: http://dx.doi.org/10.1053/j.ajkd.2016.11.029
18. Bello AK, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, et al. Epidemiology of haemodialysis outcomes. Nat Rev Nephrol. 2022;18(6):378–95.
19. Kim H, Ko MJ, Lim C-Y, Bae E, Hyun YY, Chung S, et al. Association between physical activity and risk of renal function decline and mortality in community-dwelling older adults: a nationwide population-based cohort study. BMC Geriatr [Internet]. 2022 Dec 17;22(1):973. Available from: https://bmcgeriatr.biomedcentral.com/articles/10.1186/s12877-022-03693-1

20. Piva G, Crepaldi A, Lamberti N, Caruso L, Rinaldo N, Manfredini R, et al. Home-Based Exercise in Elderly Patients with Claudication and Chronic Kidney Disease Is Associated with Lower Progressive Renal Function Worsening: A 5-Year Retrospective Study. Metabolites [Internet]. 2022 Dec 30;13(1):56. Available from: https://www.mdpi.com/2218-1989/13/1/56
21. Bennett PN, Kohzuki M, Bohm C, Roshanravan B, Bakker SJL, Viana JL, et al. Global Policy Barriers and Enablers to Exercise and Physical Activity in Kidney Care. J Ren Nutr [Internet]. 2022 Jul;32(4):441–9. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1051227621001655
22. JOHANSEN KL. Exercise and dialysis. Hemodial Int [Internet]. 2008 Jul 8;12(3):290–300. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1542-4758.2008.00269.x
23. Cupisti A, Brunori G, Di Iorio BR, D'Alessandro C, Pasticci F, Cosola C, et al. Nutritional treatment of advanced CKD: twenty consensus statements. J Nephrol [Internet]. 2018 Aug 24;31(4):457–73. Available from: http://link.springer.com/10.1007/s40620-018-0497-z
24. Cupisti A, Brunori G, Di Iorio BR, D'Alessandro C, Pasticci F, Cosola C, et al. [Nutritional diet therapy in the management of the patient with Chronic Kidney Disease in advanced phase to delay the beginning and reduce the frequency of dialysis. An option also in the pre-emptive transplant program]. G Ital Nefrol [Internet]. 2018 Sep;35(5). Available from: http://www.ncbi.nlm.nih.gov/pubmed/30234228
25. Ornish D. Holy Cow! What's Good for You Is Good for Our Planet. Arch Intern Med [Internet]. 2012 Apr 9;172(7):563. Available from: http://archinte.jamanetwork.com/article.aspx?doi=10.1001/archinternmed.2012.174
26. Etemadi A, Sinha R, Ward MH, Graubard BI, Inoue-Choi M, Dawsey SM, et al. Mortality from different causes associated with meat, heme iron, nitrates, and nitrites in the NIH-AARP Diet and Health Study: population based cohort study. BMJ [Internet]. 2017 May 9;j1957. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.j1957
27. Wolk A. Potential health hazards of eating red meat. J Intern Med [Internet]. 2017 Feb 6;281(2):106–22. Available from: https://onlinelibrary.wiley.com/doi/10.1111/joim.12543
28. Anderson JE, Boivin MR, Hatchett L. Effect of Exercise Training on Interdialytic Ambulatory and Treatment-Related Blood Pressure in Hemodialysis Patients. Ren

Fail [Internet]. 2004 Jan 7;26(5):539–44. Available from: http://www.tandfonline.com/doi/full/10.1081/JDI-200031735

29. Cupisti A, D'Alessandro C, Fumagalli G, Vigo V, Meola M, Cianchi C, et al. Nutrition and Physical Activity in CKD patients. Kidney Blood Press Res [Internet]. 2014;39(2–3):107–13. Available from: https://www.karger.com/Article/FullText/355784

30. Ekramzadeh M, Santoro D, Kopple JD. The Effect of Nutrition and Exercise on Body Composition, Exercise Capacity, and Physical Functioning in Advanced CKD Patients. Nutrients [Internet]. 2022 May 20;14(10):2129. Available from: https://www.mdpi.com/2072-6643/14/10/2129

31. Holvoet E, Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W, Eloot S. The screening score of Mini Nutritional Assessment (MNA) is a useful routine screening tool for malnutrition risk in patients on maintenance dialysis. Bulduk S, editor. PLoS One [Internet]. 2020 Mar 4;15(3):e0229722. Available from: https://dx.plos.org/10.1371/journal.pone.0229722

32. Martin-Alemañy G, Espinosa-Cuevas M de los Á, Pérez-Navarro M, Wilund KR, Miranda-Alatriste P, Cortés-Pérez M, et al. Effect of Oral Nutritional Supplementation With and Without Exercise on Nutritional Status and Physical Function of Adult Hemodialysis Patients: A Parallel Controlled Clinical Trial (AVANTE-HEMO Study). J Ren Nutr. 2020;30(2):126–36.

33. Gamboa JL, Deger SM, Perkins BW, Mambungu C, Sha F, Mason OJ, et al. Effects of long-term intradialytic oral nutrition and exercise on muscle protein homeostasis and markers of mitochondrial content in patients on hemodialysis. Am J Physiol - Ren Physiol. 2020;319(5):F885–94.

34. Majchrzak KM, Pupim LB, Flakoll PJ, Ikizler TA. Resistance exercise augments the acute anabolic effects of intradialytic oral nutritional supplementation. Nephrol Dial Transplant. 2008;23(4):1362–9.

35. Dong J, Sundell MB, Pupim LB, Wu P, Shintani A, Ikizler TA. The Effect of Resistance Exercise to Augment Long-term Benefits of Intradialytic Oral Nutritional Supplementation in Chronic Hemodialysis Patients. J Ren Nutr [Internet]. 2011 Mar;21(2):149–59. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1051227610000750

36. Martin-Alemañy G, Valdez-Ortiz R, Olvera-Soto G, Gomez-Guerrero I, Aguire-Esquivel G, Cantu-Quintanilla G, et al. The effects of resistance exercise and oral

nutritional supplementation during hemodialysis on indicators of nutritional status and quality of life. Nephrol Dial Transplant. 2016;31(10):1712–20.

37. Lewy AJ, Bauer VK, Cutler NL, Sack RL, Ahmed S, Thomas KH, et al. Morning vs Evening Light Treatment of Patients With Winter Depression. Arch Gen Psychiatry [Internet]. 1998 Oct 1;55(10):890. Available from: http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.55.10.890

38. Repke MA, Berry MS, Conway LG, Metcalf A, Hensen RM, Phelan C. How does nature exposure make people healthier?: Evidence for the role of impulsivity and expanded space perception. PLoS One. 2018;13(8):1–20.

39. de Vries S, van Dillen SME, Groenewegen PP, Spreeuwenberg P. Streetscape greenery and health: Stress, social cohesion and physical activity as mediators. Soc Sci Med [Internet]. 2013 Oct;94:26–33. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0277953613003742

40. Ellaway A, Macintyre S, Bonnefoy X. Graffiti, greenery, and obesity in adults: secondary analysis of European cross sectional survey. BMJ [Internet]. 2005 Sep 17;331(7517):611–2. Available from: https://www.bmj.com/lookup/doi/10.1136/bmj.38575.664549.F7

41. McGinn AP, Evenson KR, Herring AH, Huston SL. The relationship between leisure, walking, and transportation activity with the natural environment. Heal Place. 2007;13(3):588–602.

42. Song C, Ikei H, Miyazaki Y. Physiological Effects of Nature Therapy: A Review of the Research in Japan. Int J Environ Res Public Health [Internet]. 2016 Aug 3;13(8):781. Available from: http://www.mdpi.com/1660-4601/13/8/781

43. Hartig T, Mitchell R, de Vries S, Frumkin H. Nature and Health. Annu Rev Public Health [Internet]. 2014 Mar 18;35(1):207–28. Available from: https://www.annualreviews.org/doi/10.1146/annurev-publhealth-032013-182443

44. Keskinen KE, Rantakokko M, Suomi K, Rantanen T, Portegijs E. Nature as a facilitator for physical activity: Defining relationships between the objective and perceived environment and physical activity among community-dwelling older people. Heal Place [Internet]. 2018;49(January):111–9. Available from: https://doi.org/10.1016/j.healthplace.2017.12.003

45. Astell-Burt T, Feng X. Association of Urban Green Space With Mental Health and General Health Among Adults in Australia. JAMA Netw Open [Internet]. 2019 Jul 26;2(7):e198209. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2739050

46. Hunter MR, Gillespie BW, Chen SY-P. Urban Nature Experiences Reduce Stress in the Context of Daily Life Based on Salivary Biomarkers. Front Psychol [Internet]. 2019 Apr 4;10. Available from: https://www.frontiersin.org/article/10.3389/fpsyg.2019.00722/full
47. Barton J, Griffin M, Pretty J. Exercise-, nature- and socially interactive-based initiatives improve mood and self-esteem in the clinical population. Perspect Public Health [Internet]. 2012 Mar 7;132(2):89–96. Available from: http://journals.sagepub.com/doi/10.1177/1757913910393862
48. Pretty J, Peacock J, Sellens M, Griffin M. The mental and physical health outcomes of green exercise. Int J Environ Health Res [Internet]. 2005 Oct;15(5):319–37. Available from: http://www.tandfonline.com/doi/abs/10.1080/09603120500155963
49. Mygind L, Kjeldsted E, Hartmeyer RD, Mygind E, Bølling M, Bentsen P. Immersive Nature-Experiences as Health Promotion Interventions for Healthy, Vulnerable, and Sick Populations? A Systematic Review and Appraisal of Controlled Studies. Front Psychol [Internet]. 2019 May 3;10. Available from: https://www.frontiersin.org/article/10.3389/fpsyg.2019.00943/full
50. Piva G, Caruso L, Gómez AC, Calzolari M, Visintin EP, Davoli P, et al. Effects of forest walking on physical and mental health in elderly populations: a systematic review. Rev Environ Health. 2022;1–16.
51. Totaforti S. Applying the benefits of biophilic theory to hospital design. City, Territ Archit [Internet]. 2018 Dec 2;5(1):1. Available from: https://cityterritoryarchitecture.springeropen.com/articles/10.1186/s40410-018-0077-5
52. Ulrich RS. View Through a Window May Influence Recovery from Surgery. Science (80-) [Internet]. 1984 Apr 27;224(4647):420–1. Available from: https://www.science.org/doi/10.1126/science.6143402
53. Park S-H, Mattson RH. Effects of Flowering and Foliage Plants in Hospital Rooms on Patients Recovering from Abdominal Surgery. Horttechnology [Internet]. 2008 Jan;18(4):563–8. Available from: https://journals.ashs.org/view/journals/horttech/18/4/article-p563.xml
54. Matsunaga K, Park B-J, Kobayashi H, Miyazaki Y. Physiologically Relaxing Effect of a Hospital Rooftop Forest on Older Women Requiring Care. J Am Geriatr Soc [Internet]. 2011 Nov;59(11):2162–3. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2011.03651.x

55. Biederman I, Vessel E. Perceptual Pleasure and the Brain. Am Sci [Internet]. 2006;94(3):247. Available from: https://www.americanscientist.org/article/perceptual-pleasure-and-the-brain
56. Walch JM, Rabin BS, Day R, Williams JN, Choi K, Kang JD. The Effect of Sunlight on Postoperative Analgesic Medication Use: A Prospective Study of Patients Undergoing Spinal Surgery. Psychosom Med [Internet]. 2005 Jan;67(1):156–63. Available from: http://journals.lww.com/00006842-200501000-00022
57. Liu L, Marler MR, Parker BA, Jones V, Johnson S, Cohen-Zion M, et al. The relationship between fatigue and light exposure during chemotherapy. Support Care Cancer [Internet]. 2005 Dec 29;13(12):1010–7. Available from: http://link.springer.com/10.1007/s00520-005-0824-5
58. Tsunetsugu Y, Lee J, Park B-J, Tyrväinen L, Kagawa T, Miyazaki Y. Physiological and psychological effects of viewing urban forest landscapes assessed by multiple measurements. Landsc Urban Plan [Internet]. 2013 May;113:90–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0169204613000212
59. Li Q. Effect of forest bathing trips on human immune function. Environ Health Prev Med [Internet]. 2010 Jan 25;15(1):9–17. Available from: http://link.springer.com/10.1007/s12199-008-0068-3
60. McCoy JM, Evans GW. The Potential Role of the Physical Environment in Fostering Creativity. Creat Res J [Internet]. 2002 Oct;14(3–4):409–26. Available from: http://www.tandfonline.com/doi/abs/10.1207/S15326934CRJ1434_11
61. Antonelli M, Donelli D, Carlone L, Maggini V, Firenzuoli F, Bedeschi E. Effects of forest bathing (shinrin-yoku) on individual well-being: an umbrella review. Int J Environ Health Res [Internet]. 2021 [cited 2022 Mar 18]; Available from: https://pubmed.ncbi.nlm.nih.gov/33910423/
62. Brito HS, Carraça E V., Palmeira AL, Ferreira JP, Vleck V, Araújo D. Benefits to Performance and Well-Being of Nature-Based Exercise: A Critical Systematic Review and Meta-Analysis. Environ Sci Technol [Internet]. 2022 Jan 4;56(1):62–77. Available from: https://pubs.acs.org/doi/10.1021/acs.est.1c05151
63. Hansen MM, Jones R, Tocchini K. Shinrin-Yoku (Forest Bathing) and Nature Therapy: A State-of-the-Art Review. Int J Environ Res Public Heal [Internet]. 2017;14:851. Available from: www.mdpi.com/journal/ijerph
64. Ideno Y, Hayashi K, Abe Y, Ueda K, Iso H, Noda M, et al. Blood pressure-lowering effect of Shinrin-yoku (Forest bathing): a systematic review and meta-analysis. BMC Complement Altern Med [Internet]. 2017 Dec 16;17(1):409. Available from:

http://bmccomplementalternmed.biomedcentral.com/articles/10.1186/s12906-017-1912-z

65. Yau KK-Y, Loke AY. Effects of forest bathing on pre-hypertensive and hypertensive adults: a review of the literature. Environ Health Prev Med [Internet]. 2020 Dec 22;25(1):23. Available from: https://environhealthprevmed.biomedcentral.com/articles/10.1186/s12199-020-00856-7

66. Lahart I, Darcy P, Gidlow C, Calogiuri G. The Effects of Green Exercise on Physical and Mental Wellbeing: A Systematic Review. Int J Environ Res Public Health [Internet]. 2019 Apr 15;16(8):1352. Available from: https://www.mdpi.com/1660-4601/16/8/1352

67. Marini S, Mauro M, Grigoletto A, Toselli S, Maietta Latessa P. The Effect of Physical Activity Interventions Carried Out in Outdoor Natural Blue and Green Spaces on Health Outcomes: A Systematic Review. Int J Environ Res Public Health [Internet]. 2022 Sep 30;19(19):12482. Available from: https://www.mdpi.com/1660-4601/19/19/12482

68. Park S, Kim E, Kim G, Kim S, Choi Y, Paek D. What Activities in Forests Are Beneficial for Human Health? A Systematic Review. Int J Environ Res Public Health [Internet]. 2022 Feb 25;19(5):2692. Available from: https://www.mdpi.com/1660-4601/19/5/2692

69. Piva G, Caruso L, Gómez AC, Calzolari M, Visintin EP, Davoli P, et al. Effects of forest walking on physical and mental health in elderly populations: a systematic review. Rev Environ Health [Internet]. 2022 Oct 17; Available from: https://www.degruyter.com/document/doi/10.1515/reveh-2022-0093/html

70. Wicks C, Barton J, Orbell S, Andrews L. Psychological benefits of outdoor physical activity in natural versus urban environments: A systematic review and meta-analysis of experimental studies. Appl Psychol Heal Well-Being [Internet]. 2022 Aug 8;14(3):1037–61. Available from: https://iaap-journals.onlinelibrary.wiley.com/doi/10.1111/aphw.12353

71. Clyne N, Anding-Rost K. Exercise training in chronic kidney disease-effects, expectations and adherence. Clin Kidney J. 2021 Apr;14(Suppl 2):ii3–14.

72. Beddhu S, Baird BC, Zitterkoph J, Neilson J, Greene T. Physical Activity and Mortality in Chronic Kidney Disease (NHANES III). Clin J Am Soc Nephrol [Internet]. 2009 Dec;4(12):1901–6. Available from: https://journals.lww.com/01277230-200912000-00007

73. Tentori F, Elder SJ, Thumma J, Pisoni RL, Bommer J, Fissell RB, et al. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. Nephrol Dial Transplant [Internet]. 2010 Sep 1;25(9):3050–62. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfq138
74. Jassal SV, Karaboyas A, Comment LA, Bieber BA, Morgenstern H, Sen A, et al. Functional Dependence and Mortality in the International Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis [Internet]. 2016 Feb;67(2):283–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638615012561
75. MacKinnon HJ, Wilkinson TJ, Clarke AL, Gould DW, O'Sullivan TF, Xenophontos S, et al. The association of physical function and physical activity with all-cause mortality and adverse clinical outcomes in nondialysis chronic kidney disease: a systematic review. Ther Adv Chronic Dis [Internet]. 2018 Nov 4;9(11):209–26. Available from: http://journals.sagepub.com/doi/10.1177/2040622318785575
76. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: Effects on muscle strength, muscle quality, and physical function. Kidney Int [Internet]. 2003 Jan;63(1):291–7. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815488714
77. Johansen KL, Chertow GM, Kutner NG, Dalrymple LS, Grimes BA, Kaysen GA. Low level of self-reported physical activity in ambulatory patients new to dialysis. Kidney Int [Internet]. 2010 Dec;78(11):1164–70. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0085253815544402
78. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. Am J kidney Dis Off J Natl Kidney Found. 2014 Sep;64(3):383–93.
79. Cai X, Zeng D, Deng J. A systematic review and meta-analysis of the efficacy of aerobic exercise combined with resistance training on maintenance hemodialysis patients. Ann Palliat Med [Internet]. 2022 Apr;11(4):1360–8. Available from: https://apm.amegroups.com/article/view/92923/html
80. Hargrove N, El Tobgy N, Zhou O, Pinder M, Plant B, Askin N, et al. Effect of Aerobic Exercise on Dialysis-Related Symptoms in Individuals Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2021 Apr;16(4):560–74. Available from: https://journals.lww.com/10.2215/CJN.15080920

81. Hu H, Liu X, Chau PH, Choi EPH. Effects of intradialytic exercise on health-related quality of life in patients undergoing maintenance haemodialysis: a systematic review and meta-analysis. Qual Life Res [Internet]. 2022 Jul 3;31(7):1915–32. Available from: https://link.springer.com/10.1007/s11136-021-03025-7
82. Huang M, Lv A, Wang J, Xu N, Ma G, Zhai Z, et al. Exercise Training and Outcomes in Hemodialysis Patients: Systematic Review and Meta-Analysis. Am J Nephrol [Internet]. 2019;50(4):240–54. Available from: https://www.karger.com/Article/FullText/502447
83. Molsted S, Bjørkman ASD, Lundstrøm LH. Effects of strength training to patients undergoing dialysis: a systematic review. Dan Med J [Internet]. 2019 Jan;66(1). Available from: http://www.ncbi.nlm.nih.gov/pubmed/30573007
84. Salhab N, Karavetian M, Kooman J, Fiaccadori E, El Khoury CF. Effects of intradialytic aerobic exercise on hemodialysis patients: a systematic review and meta-analysis. J Nephrol [Internet]. 2019 Aug 18;32(4):549–66. Available from: http://link.springer.com/10.1007/s40620-018-00565-z
85. Song Y, Hu R, Diao Y, Chen L, Jiang X. Effects of Exercise Training on Restless Legs Syndrome, Depression, Sleep Quality, and Fatigue Among Hemodialysis Patients: A Systematic Review and Meta-analysis. J Pain Symptom Manage [Internet]. 2018 Apr;55(4):1184–95. Available from: https://linkinghub.elsevier.com/retrieve/pii/S088539241731223X
86. Zhang F, Zhou W, Sun Q, Zhai Y, Zhang Y, Su H, et al. Effects of intradialytic resistance exercises on physical performance, nutrient intake and quality of life among haemodialysis people: A systematic review and meta-analysis. Nurs Open [Internet]. 2021 Mar 30;8(2):529–38. Available from: https://onlinelibrary.wiley.com/doi/10.1002/nop2.274
87. Shlipak MG, Sheshadri A, Hsu F-C, Chen S-H, Jotwani V, Tranah G, et al. Effect of Structured, Moderate Exercise on Kidney Function Decline in Sedentary Older Adults. JAMA Intern Med [Internet]. 2022 Jun 1;182(6):650. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2791340
88. Toyama K, Sugiyama S, Oka H, Sumida H, Ogawa H. Exercise therapy correlates with improving renal function through modifying lipid metabolism in patients with cardiovascular disease and chronic kidney disease. J Cardiol [Internet]. 2010 Sep;56(2):142–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0914508710001334

89. Chen I-R, Wang S-M, Liang C-C, Kuo H-L, Chang C-T, Liu J-H, et al. Association of Walking with Survival and RRT Among Patients with CKD Stages 3–5. Clin J Am Soc Nephrol [Internet]. 2014 Jul;9(7):1183–9. Available from: https://journals.lww.com/01277230-201407000-00008
90. Robinson-Cohen C, Littman AJ, Duncan GE, Weiss NS, Sachs MC, Ruzinski J, et al. Physical Activity and Change in Estimated GFR among Persons with CKD. J Am Soc Nephrol [Internet]. 2014 Feb;25(2):399–406. Available from: https://journals.lww.com/00001751-201402000-00023
91. Kokkinos P, Faselis C, Myers J, Sui X, Zhang J, Tsimploulis A, et al. Exercise Capacity and Risk of Chronic Kidney Disease in US Veterans: A Cohort Study. Mayo Clin Proc [Internet]. 2015 Apr;90(4):461–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0025619615000749
92. Tsai Y-C, Chen H-M, Hsiao S-M, Chen C-S, Lin M-Y, Chiu Y-W, et al. Association of physical activity with cardiovascular and renal outcomes and quality of life in chronic kidney disease. Aguilera AI, editor. PLoS One [Internet]. 2017 Aug 23;12(8):e0183642. Available from: https://dx.plos.org/10.1371/journal.pone.0183642
93. Vanden Wyngaert K, Van Craenenbroeck AH, Van Biesen W, Dhondt A, Tanghe A, Van Ginckel A, et al. The effects of aerobic exercise on eGFR, blood pressure and VO2peak in patients with chronic kidney disease stages 3-4: A systematic review and meta-analysis. Cheungpasitporn W, editor. PLoS One [Internet]. 2018 Sep 11;13(9):e0203662. Available from: https://dx.plos.org/10.1371/journal.pone.0203662
94. Yang L, Wu X, Wang Y, Wang C, Hu R, Wu Y. Effects of exercise training on proteinuria in adult patients with chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol [Internet]. 2020 Dec 11;21(1):172. Available from: https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-020-01816-7
95. Emfietzoglou M, Terentes-Printzios D, Kotronias RA, Marin F, Montalto C, De Maria GL, et al. The spectrum and systemic associations of microvascular dysfunction in the heart and other organs. Nat Cardiovasc Res [Internet]. 2022 Apr 13;1(4):298–311. Available from: https://www.nature.com/articles/s44161-022-00045-5
96. MOREAU KL, DEGARMO R, LANGLEY J, MCMAHON C, HOWLEY ET, BASSETT DR, et al. Increasing daily walking lowers blood pressure in

postmenopausal women. Med Sci Sports Exerc [Internet]. 2001 Nov;33(11):1825–31. Available from: http://journals.lww.com/00005768-200111000-00005

97. Tanaka H, DeSouza CA, Seals DR. Absence of Age-Related Increase in Central Arterial Stiffness in Physically Active Women. Arterioscler Thromb Vasc Biol [Internet]. 1998 Jan;18(1):127–32. Available from: https://www.ahajournals.org/doi/10.1161/01.ATV.18.1.127

98. Sigterman TA, Bolt LJJ, Krasznai AG, Snoeijs MG, Heijboer R, Schurink GWH, et al. Loss of Kidney Function after Endovascular Treatment of Peripheral Arterial Disease. Ann Vasc Surg [Internet]. 2017 Apr;40:231–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0890509616312560

99. Pu J, Jiang Z, Wu W, Li L, Zhang L, Li Y, et al. Efficacy and safety of intradialytic exercise in haemodialysis patients: a systematic review and meta-analysis. BMJ Open [Internet]. 2019 Jan;9(1):e020633. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2017-020633

100. McLeroy KR, Bibeau D, Steckler A, Glanz K. An Ecological Perspective on Health Promotion Programs. Health Educ Q [Internet]. 1988 Dec 4;15(4):351–77. Available from: http://journals.sagepub.com/doi/10.1177/109019818801500401

101. King KM, Gonzalez GB. Increasing Physical Activity Using An Ecological Model. ACSMs Health Fit J [Internet]. 2018 Jul;22(4):29–32. Available from: https://journals.lww.com/00135124-201807000-00012

102. Sallis JF, Cervero RB, Ascher W, Henderson KA, Kraft MK, Kerr J. AN ECOLOGICAL APPROACH TO CREATING ACTIVE LIVING COMMUNITIES. Annu Rev Public Health [Internet]. 2006 Apr 1;27(1):297–322. Available from: https://www.annualreviews.org/doi/10.1146/annurev.publhealth.27.021405.102100

103. Bulckaen M, Capitanini A, Lange S, Caciula A, Giuntoli F, Cupisti A. Implementation of exercise training programs in a hemodialysis unit: effects on physical performance. J Nephrol [Internet]. 2011;24(6):790–7. Available from: http://www.jnephrol.com/Navigator.action?cmd=navigate&urlkey=Abstract&t=JN&UidArticle=53F0175D-D037-4CBF-8187-4ACECDE27F93

104. Lambert K, Lightfoot CJ, Jegatheesan DK, Gabrys I, Bennett PN. Physical activity and exercise recommendations for people receiving dialysis: A scoping review. Delanaye P, editor. PLoS One [Internet]. 2022 Apr 28;17(4):e0267290. Available from: https://dx.plos.org/10.1371/journal.pone.0267290

105. Wilund KR, Jeong JH, Greenwood SA. Addressing myths about exercise in hemodialysis patients. Semin Dial [Internet]. 2019 Jul 25;32(4):297–302. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12815
106. Cavalcante BR, Farah BQ, Barbosa JP dos A, Cucato GG, Chehuen M da R, Santana F da S, et al. Are the Barriers for Physical Activity Practice Equal for All Peripheral Artery Disease Patients? Arch Phys Med Rehabil [Internet]. 2015 Feb;96(2):248–52. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0003999314011150
107. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans From the US Department of Health and Human Services. Circ Cardiovasc Qual Outcomes [Internet]. 2018 Nov;11(11). Available from: https://www.ahajournals.org/doi/10.1161/CIRCOUTCOMES.118.005263
108. Manfredini F, Mallamaci F, Catizone L, Zoccali C. The burden of physical inactivity in chronic kidney disease: is there an exit strategy? Nephrol Dial Transplant [Internet]. 2012 Jun 1;27(6):2143–5. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfs120
109. Manfredini F, D'arrigo G, Lamberti N, Torino C, Tripepi G, Mallamaci F, et al. The legacy effect of a home walking exercise programme in kidney failure patients on dialysis. Nephrol Dial Transplant [Internet]. 2022 Sep 22;37(10):1974–81. Available from: https://academic.oup.com/ndt/article/37/10/1974/6596293
110. Pisoni RL, Gillespie BW, Dickinson DM, Chen K, Kutner MH, Wolfe RA. The Dialysis Outcomes and Practice Patterns Study (DOPPS): Design, data elements, and methodology. Am J Kidney Dis [Internet]. 2004 Nov;44:7–15. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638604010996
111. Parsons TL, Bohm C, Poser K. "A Learned Soul to Guide Me": The Voices of Those Living with Kidney Disease Inform Physical Activity Programming. Physiother Canada [Internet]. 2018 Aug;70(3):289–95. Available from: https://utpjournals.press/doi/10.3138/ptc.2017-01.ep
112. Bennett PN, Parsons T, Ben-Moshe R, Weinberg M, Neal M, Gilbert K, et al. Laughter and Humor Therapy in Dialysis. Semin Dial [Internet]. 2014 Sep 28;27(5):488–93. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12194
113. Morais EM, Moreira PR, Winkelmann ER. Movie watching during dialysis sessions reduces depression and anxiety and improves quality of life: A randomized clinical trial. Complement Ther Med [Internet]. 2020 Aug;52:102488. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0965229919317728

114. Delgado C, Johansen KL. Deficient Counseling on Physical Activity among Nephrologists. Nephron Clin Pract [Internet]. 2010 Jul 28;116(4):c330–6. Available from: https://www.karger.com/Article/FullText/319593
115. Bennett PN, Peter J, Wang W, Street M. Attitudes of Nephrology Nurses Toward Patient Exercise During Hemodialysis. Nephrol Nurs J [Internet]. 2016;43(4):331–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30550060
116. Bennett PN, Dewald G. Patient Care Technicians Managing Hemodialysis Central Venous Catheter Care: Pro and Con. Nephrol Nurs J [Internet]. 2017;44(5):449–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29160979
117. Bennett PN. Satellite dialysis nursing: technology, caring and power. J Adv Nurs [Internet]. 2011 Jan;67(1):149–57. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2648.2010.05474.x
118. Bennett PN, Capdarest-Arest N, Parker K. The physical deterioration of dialysis patients—Ignored, ill-reported, and ill-treated. Semin Dial [Internet]. 2017 Sep 5;30(5):409–12. Available from: https://onlinelibrary.wiley.com/doi/10.1111/sdi.12610
119. Capitanini A, Lange S, D'Alessandro C, Salotti E, Tavolaro A, Baronti ME, et al. Dialysis Exercise Team: The Way to Sustain Exercise Programs in Hemodialysis Patients. Kidney Blood Press Res [Internet]. 2014;39(2–3):129–33. Available from: https://www.karger.com/Article/FullText/355787
120. Manfredini F, Lamberti N, Battaglia Y, Straudi S, Belvederi Murri M, Donadi M, et al. A Personalized Patient-Centered Intervention to Empower through Physical Activity the Patient in the Dialysis Center: Study Protocol for a Pragmatic Nonrandomized Clinical Trial. Methods Protoc [Internet]. 2020 Dec 6;3(4):83. Available from: https://www.mdpi.com/2409-9279/3/4/83
121. Manera KE, Johnson DW, Craig JC, Shen JI, Gutman T, Cho Y, et al. Establishing a Core Outcome Set for Peritoneal Dialysis: Report of the SONG-PD (Standardized Outcomes in Nephrology–Peritoneal Dialysis) Consensus Workshop. Am J Kidney Dis [Internet]. 2020 Mar;75(3):404–12. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638619311163

CHAPTER 9

9. PHYSICAL EMPOWERMENT OF PEOPLE IN DIALYSIS

The hereby reported methods for the study performed, were published by Manfredini F et al. in the journal *Methods Protoc*. 2020;3(4):83. doi:10.3390/mps3040083

9.1 Aim of the project

The first goal of the PhD project is to prove the effectiveness of an exercise intervention, focusing on the inclusion of the Exercise Facilitator figure within the HD center to improve the physical, psychological, and social well-being of patients. Recognizing the role of the EF among the operational figures within the HD center would be crucial because it would fill a gap in the service that is currently offered to patients.

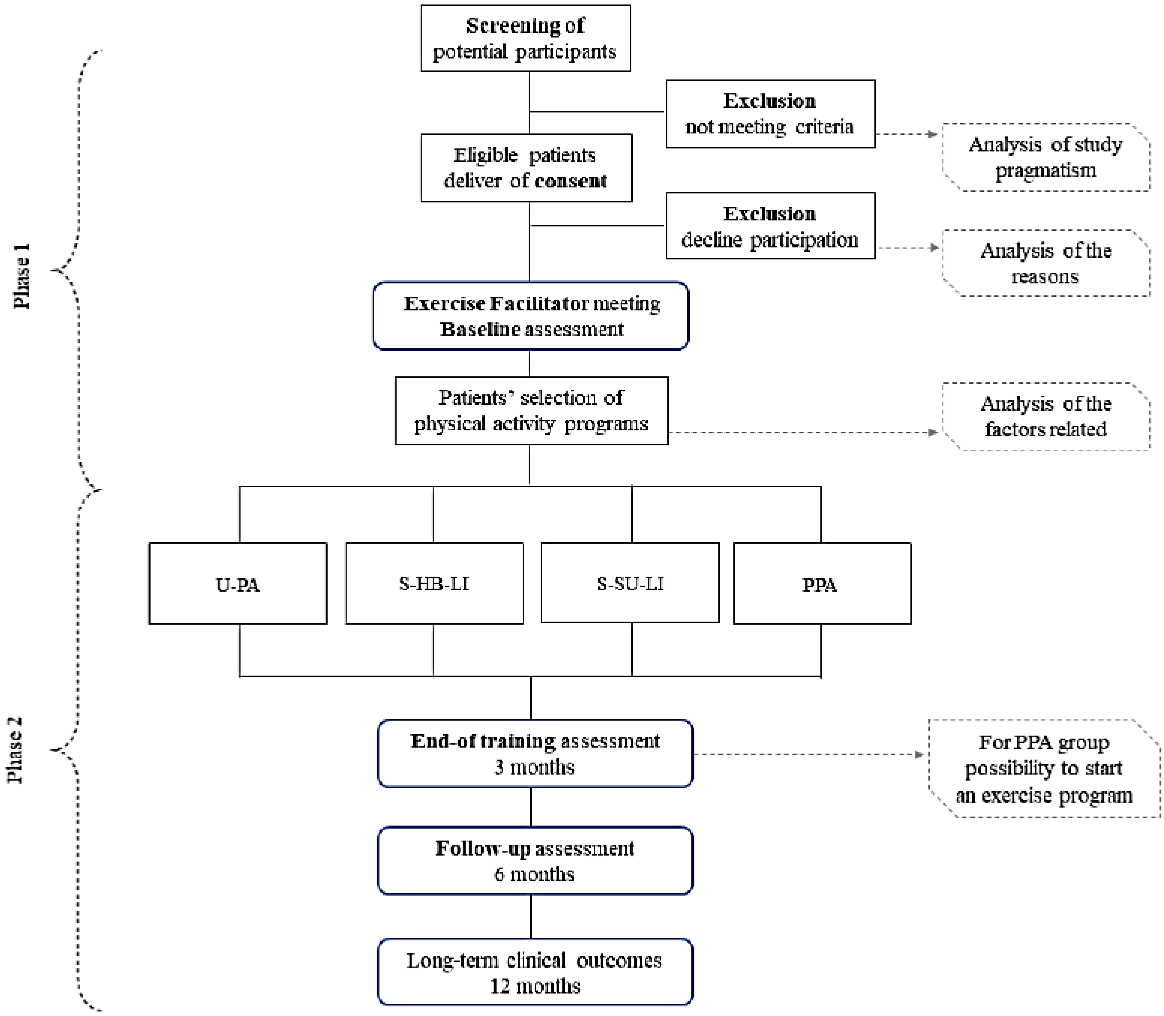
The possibility for patients to engage with an expert daily who can recommend and guide them in carrying out validated exercise patterns is a first possibility, enabling them to overcome many barriers to exercise reported by patients. In addition, the request for an exercise specialist to be available in the HD center was a specific request from Excite trial participants, 90% of whom felt that the presence of an EF would be helpful to them. Thus, this project consists of bottom-up implementation of a request from stakeholders.

9.2 Methods

Study design

The study is a pragmatic feasibility nonrandomized implementation trial with a qualitative analysis. The trial has been registered at: Clinicaltrials.gov NCT04282616 [Registered:24/02/2020]. The study included two different phases and was completed in three years.

Figure 1. Study design



U-PA-I: unstructured physical activity increase; S-HB-LI: structured home-based low-intensity; S-SU-LI: structured supervised low-intensity; PPA: physical performance assessment.

Study settings

Originally, the study took place at two centers of the Operative Unit of Nephrology and Dialysis located at two different sites: at the University Hospital of Cona, Ferrara, and at Città della Salute, Ferrara. During my time abroad, it was possible to add two HD centers in Cordoba, Spain: University Hospital Reina Sofia, Cordoba, and Perpetuo Socorro, Cordoba. All scheduled interventions and outcome measure assessments were performed in a purposely selected space inside each dialysis center.

Participants

The study aimed to recruit ESKD patients undergoing PD or HD treatment.

- ***Inclusion criteria***: male and female patients aged ≥18 years; able to walk for at least 6 m; performing dialysis for at least 3 months in stable conditions; Mini-Mental Status Examination score ≥18/30 sufficient or patients to give informed consent.
- ***Exclusion criteria***: uncorrected anemia (hemoglobin concentration <9 g/dL); acute infectious disease (C-reactive protein >10 mg/L), severe cardio-respiratory conditions (e.g., unstable angina; severe heart failure identified by New York Heart Association class III-IV), musculoskeletal or neurological conditions (e.g., major lower extremity amputation) that inhibit exercise. As this is an implementation feasibility trial, e exclusion criteria were kept to a minimum.

During the first meeting with potential participants, study staff verified the patients' interest in participating in the study; in case of a positive response, a screening visit was performed to verify compliance with the inclusion criteria. Patients who met the eligibility criteria received a letter explaining the study and the consent form and were encouraged to ask any questions. Within seven days, patients were asked to return a signed copy of the consent form; if patients had not yet decided, they were given adequate time to reflect on their participation. Following SPIRIT statements [1], the total number of screened subjects found to be ineligible (and reasons for ineligibility) or unwilling to participate in the study (along with reasons and key clinical characteristics, if provided) was monitored. Pre-participation screening with exercise testing was not included because of the low intensity of the proposed exercise program, as it was designed for special populations [2]. For those who volunteered to participate, sessions to measure outcomes at baseline were scheduled within two weeks of joining. During this time, patients were provided with a wrist-worn fitness tracker to wear for 6 days, including at night and during rest periods. The number of daily steps, hours of sleep or rest, and heart rate were recorded.

Procedures

Phase 1

At this stage, the EF was embedded in the HD center. This was an experienced physical therapist and/or a qualified exercise specialist available in the HD centers for several hours per day to counsel patients and answer questions about physical activity. The EFs had been adequately trained by members of the Rehabilitation Medicine Unit of Ferrara University Hospital on the management of frail patients, having experience with severely disabled patients with various conditions before the study began.

Stakeholder Involvement: The EF, in collaboration with team members, prepared information materials for the project. Team members then held meetings with unit staff and patient group coordinators to introduce the EF, explain the goals of the project, and answer concerns and questions.

After assessing outcomes at baseline, the EF proposed one of the four interventions to patients with the help of a specifically designed brochure. Qualitative outcomes were employed in the first phase (Table 1). The rate of patients providing consent compared to the number of eligible patients, as well as the rate of patients choosing each of the proposed training options, were calculated to determine patients' willingness to practice and their preferences for training. The impact of patient characteristics and other variables on program choice was also analyzed.

Table 1. Outcome measures flow diagram

	Study Period				
	Enrollment	Allocation	Post-Allocation		Close-Out
Time Point	−15 Days (Maximum)	0 Baseline	3-Month End of Training	6-Month Follow Up	12-Month
Eligibility screening	X				
Informed consent	X				
Allocation		X			
Interventions					
U-PA-I		◆————	————◆		
S-HB-LI		◆————	————◆		
S-SU-LI		◆————	————◆		
PPA		X	X		
Outcomes					
Phase 1					
% Patients responders/eligible		X			
Physical and emotional status		X			
Exercise program choices		X			
Factors related to choices		X			
Phase 2					
Safety (adverse events, interruptions)			X		
Adherence (% sessions completed)			X		
6MWT (primary outcome)		X	X	X	
Gait speed, lower limbs strength, quality of life, depression, estimated capacity, fear of falling (secondary)		X	X	X	
Biochemical/laboratory markers		X	X	X	
Hospitalizations and mortality				X	X

U-PA-I: unstructured physical activity increase; S-HB-LI: structured home-based low-intensity; S-SU-LI: structured supervised low-intensity; PPA: physical performance assessment; 6MWT: 6-minute walk test.

Phase 2

The EF asked each enrolled patient to choose an intervention and then enter one of the following arms.

Unstructured physical activity (U-PA)

Based on the previously measured baseline physical activity level, the EF advised patients to start or increase their spontaneous activity, giving them guidance on total exercise time, mode, intensity, and frequency, as suggested by the guidelines [3-4]. A logbook and wearable physical activity monitor were provided to each patient to encourage adherence and objectively measure exercise activities. The instruments were returned at follow-ups.

Structured home-based low-intensity exercise (S-HB-LI)

Based on each patient's basal physical activity level, a semipersonalized walking program was provided. This program, derived from previous experience with ESKD patients [5], has also been successfully tested in other frail populations, such as stroke or multiple sclerosis survivors [6-7]. The exercise program was performed at home at a prescribed speed and involved a 10-minute daily session of intermittent walking (1 or 2 minutes of work and 1 minute of seated rest). The speed, which is converted to walking cadence, is increased weekly and is monitored at home with the help of a metronome (Table 2). Patients received a daily diary containing detailed exercise prescriptions and free lines to provide feedback on exercise performance and any related symptoms.

Structured supervised low-intensity exercise (S-SU-LI)

Patients met the EF in a specific location (room or corridor) within the HD unit for the exercise program, in groups of up to four subjects. Exercise sessions were scheduled at a frequency of 2 to 3 times per week and were performed immediately before or after HD treatment or according to patient preference, considering the post-dialytic fatigue that affects this population [8].

Each session included low-intensity walking exercises (similar to S-HB-LI) and resistance exercises with elastic bands and ankle and wrist weights. Each session started and ended with a warm-up and cool-down period with stretching. The total duration of the session was about 30 minutes. Training intensity was set according to the patient's baseline capacity and was increased weekly (Table 2). The rate of perceived exertion was always detected.

Physical performance assessment only (PPA)

Patients who chose this option did not participate in any exercise program, only the outcome measures session. It was always possible to switch to another treatment, proposed periodically by the EF.

Table 2. The different interventions proposed to the patients by the exercise facilitator

Program	U-PA-I Unstructured Physical Activity Increase			S-HB-LI Structured Home-Based Low Intensity			S-SU-LI Structured Supervised Low Intensity			PPA Performance Assessment
Setting *Frequency*	Home Daily			Home Daily			Dialysis Center 2- or 3-Time a Week			-
Baseline 6MWD (m)	<200	201–400	>400	<200	201–400	>400	< 200	201–400	>400	-
Program features	Walking (mins) Intensity: moderate [27,28]			Walking: rest (min) × reps Speed (steps/min)			Walking * + strength leg extension/leg curl/shoulder abduction (reps × series − load)			
Week 1	5	10	15	1:1 × 6 − 60	1:1 × 8 − 60	1:1 × 8 − 72	3 × 2 − 0.5 kg	3 × 3 − 1 kg	3 × 3 − 1.5 kg	
2	5	10	15	1:1 × 6 − 63	1:1 × 8 − 63	1:1 × 8 − 76	3 × 2 − 0.5 kg	3 × 3 − 1 kg	3 × 3 − 1.5 kg	
3	10	15	20	1:1 × 8 − 63	1:1 × 8 − 66	1:1 × 8 − 80	4 × 2 − 1 kg	4 × 3 − 1 kg	4 × 3 − 1.5 kg	
4	10	15	20	1:1 × 8 − 66	1:1 × 8 − 69	1:1 × 8 − 84	4 × 2 − 1 kg	4 × 3 − 1 kg	4 × 3 − 1.5 kg	
5	15	15	20	1:1 × 8 − 66	1:1 × 8 − 72	1:1 × 8 − 88	3 × 3 − 1 kg	4 × 3 − 1.5 kg	4 × 3 − 2 kg	
6	15	20	20	1:1 × 8 − 69	1:1 × 8 − 72	1:1 × 8 − 92	3 × 3 − 1 kg	4 × 3 − 1.5 kg	4 × 3 − 2 kg	-
7	15	20	25	1:1 × 8 − 69	1:1 × 8 − 76	2:1 × 4 − 72	4 × 3 − 1 kg	4 × 4 − 1.5 kg	4 × 4 − 2 kg	
8	20	20	25	1:1 × 8 − 72	1:1 × 8 − 76	2:1 × 4 − 76	4 × 3 − 1 kg	4 × 4 − 1.5 kg	4 × 4 − 2 kg	
9	20	20	25	1:1 × 8 − 72	1:1 × 8 − 80	2:1 × 4 − 80	4 × 3 − 1.5 kg	4 × 4 − 2 kg	4 × 4 − 2.5 kg	
10	20	25	25	1:1 × 8 − 76	1:1 × 8 − 80	2:1 × 4 − 84	4 × 3 − 1.5 kg	4 × 4 − 2 kg	4 × 4 − 2.5 kg	
11	20	25	30	1:1 × 8 − 76	1:1 × 8 − 84	2:1 × 4 − 88	4 × 4 − 1.5 kg	5 × 4 − 2 kg	5 × 4 − 3 kg	
12	25	25	30	1:1 × 8 − 80	1:1 × 8 − 84	2:1 × 4 − 92	4 × 4 − 1.5 kg	5 × 4 − 2 kg	5 × 4 − 3 kg	
Monitoring	Daily log and physical activity monitor			Daily log			Exercise facilitator			Daily log

* Walking program as S-HB-LI group; Abbreviations: 6MWD: 6-min walking distance; reps: repetitions; min: minute.

Discontinuing the intervention

Patients who chose one of the three training options were interviewed weekly by the EF to monitor their adherence to the program. In addition, when possible, daily records were reviewed. In general, all intercurrent pathologies inherent to patients in training were noted. Since this was a nonrandomized study in which patients chose the option they preferred, it was always possible to switch between training modes. However, team members tried to motivate patients to complete their chosen 3-month program.

Harms

Well-established and safe exercise programs [4-7], in combination with strict management of potential harms according to local hospital policy, were used in the study to minimize all potential risks. In case of any unfavorable effects of the training or a concomitant or intercurrent illness, team members thoroughly evaluated patients to determine their suitability to continue the program. Any potential harm was treated according to the local university hospital's policy, including insurance coverage.

Concomitant care and recommendations

During the training period, patients maintained their usual lifestyle. Concomitant treatments (e.g., physical therapy sessions) were allowed, but the appropriate analysis was performed when analyzing outcomes. Finally, patients were asked to wear the same shoes and orthotics during all test and training sessions. At the end of the 3-month training period, patients were suggested to maintain a sufficient level of physical activity. To determine the amount of exercise performed during the follow-up period, patients were asked to complete a daily log or wear a fitness tracker.

Phase 2 outcomes

First, the feasibility and safety of the exercise program were assessed in terms of adverse events, falls, and intercurrent problems. In addition, each patient's adherence to the selected exercise option was determined by analyzing the number of sessions completed, the total minutes of exercise, and the percentage of patients who achieved the amount of physical activity specified by the guidelines. Qualitative outcomes were collected before the start of the training program, at the end (three months), and at a six-month follow-up.

The primary outcome was exercise capacity, measured by the 6-minute walking test (6MWT). Subjects were instructed to walk with their usual walking device as far as possible in 6 minutes. The tests were performed in a 22-meter corridor. Patients had the opportunity to slow down and rest if

Necessary. Total distance walked, pain-free walking distance, and perceived exertion at the end of the test (Borg scale 1-10) were recorded [9].

The secondary outcomes included are as follows:

- Gait speed was assessed through the 10-m walking test.
- Lower limb strength was evaluated with the 5-time sit-to-stand test.
- Health-related QoL was measured by the Italian version of the Short Form Health Survey (SF-36).
- Fear of falling was assessed through the Short Falls Efficacy Scale.
- The estimated functional capacity was measured by the Duke Activity Status Index.
- Depression was evaluated by the Beck Depression Inventory-II and the Demoralization Scale.
- Heart rate, oxygen saturation, and blood pressure
- Laboratory outcomes: Serum creatinine levels, estimated glomerular filtration rate, Kt/v, glycemia, total cholesterol, and a full blood count will also be determined.
- Long-term outcomes: Other clinical outcomes, such as mortality and all-cause hospitalization, will be recorded at 3, 6, 12, and 24 months from the end of the exercise program.

Blinding

The outcome assessors were blinded to the group assignment and no unblinding was allowed for these researchers. Participants who had to discontinue their chosen program before the scheduled 3 months for any reason were required to conduct the outcome measurement session if possible.

Sample size

To the best of our knowledge, this is the first study of its kind to explore patients' program preferences and compare the outcomes of these programs. Therefore, it was impossible to calculate power by assuming a better effect of one program over another; moreover, the investigators did not assign interventions and did not know a priori how many patients would select each training option.

Otherwise, we had set out to recruit a sufficient number of participants to meet the objectives of implementing the study. The Nephrology Unit of the University Hospital of Ferrara manages about 140 dialysis patients. The entry of new patients into the dialysis service was checked every 3 months. An attempt was made to offer the programs to all eligible patients assuming a 50% acceptance rate, which could be progressively increased by word of mouth among patients.

According to a power calculation based on a theoretical response rate of 50% and considering a margin of error of 5% and a confidence level of 90%, a total of 88 patients were estimated to be needed for data collection to make the first qualitative phase of the study representative of the population.

To optimize recruitment, all members of the hospital's Nephrology Unit were informed about the study during team meetings. Information about the study procedures was also provided to the CKD and ESKD support groups, who could share information about the study through their newsletters and websites.

Finally, the EF was available daily in the HD room to encourage patient participation. Informational material literature was also made available in the departments of the Nephrology Unit.

Data protection

All outcome data were recorded on different spreadsheets by two researchers, and the accuracy of the data was checked by the research coordinators. Participants' data were stored in a password-protected personal computer kept in a suitably selected closed room. The privacy of participants and their medical records is guaranteed by processing data according to the latest European Union General Data Protection Regulation (2016/679).

Statistical analysis

In the first qualitative phase, descriptive statistics, chi-square tests, and mixed analysis models were used. Regression analyses were conducted to determine whether different variables (e.g., distance from the HD center and presence of a caregiver) could interfere with patients' decisions. In addition, the level of physical activity and physiological and psychological variables assessed at baseline were considered independent variables in the regression models.

In the second phase, standard analysis methods for clinical trials were used. First, the characteristics of each group were compared with demographic data and primary and secondary outcome measures. The distribution of the data was also checked through the Shapiro-Wilk test. A two-way repeated-measures analysis of variance was used to compare differences in primary and secondary outcomes. Within-group comparisons were performed by Student's t-test or Wilcoxon test, as appropriate. If a significantly different distribution was identified among the group's baseline characteristics, a secondary analysis was performed employing multivariate modeling to adjust for these factors (e.g., linear mixed models for repeated measures analysis). In addition, Kaplan-Meier analysis and Cox regression were used to model incidence rates for long-term clinical outcomes (rate of hospitalization and death). Finally, a post hoc power analysis was performed to determine the clinical impact of the results.

All analyses were conducted using the intention-to-treat method. Missing values, while making every effort to reduce their incidence, were treated with the multiple imputation procedure. In addition, a per-protocol analysis was performed to assess the stability of the study conclusions. Appropriately gender-oriented analyses were performed for most of the results. A p value of 0.05 was considered statistically significant.

Statistical analyses were performed with SPSS 21.0 (IBM, Armonk, NY, USA) and MedCalc statistical software (version 19.4.0 and later, MedCalc Software bvba, Ostend, Belgium).

Ethics

The trial was approved by the Area-Vasta Emilia-Romagna Centro Ethics Committee with approval number 48/2019. Written informed consent was obtained from all participants.

Patient and Public Involvement

This starting hypothesis of the study was developed without patient involvement but was based on previous suggestions and experiences. After the first drafting of the trial, the representatives of patients' groups were invited to several meetings with the researchers. In these consultations, the trial design was exposed to patients, who gave their opinions and finally expressed appreciation for the study. The final registered version of the trial reflects the collaboration between the researchers and the patients' associations.

Study limitations

This study has several limitations in that it is a nonrandomized study. In addition, there is no typical treatment training option during dialysis, despite evidence from the literature. However, the goal was to test training solutions that require minimal space and equipment that are implementable in most HD centers around the world and that do not overly engage the staff and routine of an HD center. In addition, the study design is likely to introduce a selection bias in the enrolled population, as fitter patients might opt for walking or mixed exercise programs, while less fit patients might choose the unstructured increase in physical activity. To overcome the lack of randomization, appropriate analysis methods were used. These factors may limit the generalizability of the findings and the possibly small sample size that will occur in case of limited participation of patients.

References

1. Chan, A.-W.; Tetzla, J.M.; Altman, D.G.; Laupacis, A.; Gøtzsche, P.C.; Krleža-Jeri´c, K.; Hróbjartsson, A.; Mann, H.; Dickersin, K.; Berlin, J.A.; et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. Ann. Intern. Med. 2013, 158, 200–207.
2. Johansen, K.L.; Painter, P. Exercise in Individuals With CKD. Am. J. Kidney Dis. 2012, 59, 126–134.
3. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription, 10th ed.;Wolters Kluwer: Philadelphia, PA, USA, 2018.
4. Malagoni, A.M.; Catizone, L.; Mandini, S.; Soffritti, S.; Manfredini, R.; Boari, B.; Russo, G.; Basaglia, N.; Zamboni, P.; Manfredini, F. Acute and long-term effects of an exercise program for dialysis patients prescribed in hospital and performed at home. J. Nephrol. 2008, 21, 871–878.
5. Lamberti, N.; Straudi, S.; Malagoni, A.M.; Argirò, M.; Felisatti, M.; Nardini, E.; Zambon, C.; Basaglia, N.; Manfredini, F. Effects of low-intensity endurance and resistance training on mobility in chronic stroke survivors. A pilot, randomized, controlled study. Eur. J. Phys. Rehabil. Med. 2016, 53, 228–239.
6. Malagoni, A.M.; Vagnoni, E.; Felisatti, M.; Mandini, S.; Heidari, M.; Mascoli, F.; Basaglia, N.; Manfredini, R.; Zamboni, P.; Manfredini, F. Evaluation of patient compliance, quality of life impact and cost-effectiveness of a "test in-train out" exercise-based rehabilitation program for patients with intermittent claudication. Circ. J. 2011, 75, 2128–2134.
7. Lamberti, N.; Straudi, S.; Donadi, M.; Tanaka, H.; Basaglia, N.; Manfredini, F. Effectiveness of blood flow-restricted slow walking on mobility in severe multiple sclerosis: A pilot randomized trial. Scand. J. Med. Sci. Sports 2020.
8. Cromm, K.; Fischer, K.I. Striking New Path(way)s—How a Conceptual Model of Patient Outcomes Can Help Us Advance Outcomes That Matter to Patients. Nephrol. Dial. Transplant. 2020.
9. Borg, G. Perceived exertion as an indicator of somatic stress. Scand. J. Rehabil. Med. 1970, 2, 92–98.

CHAPTER 10

10. PHASE 1

10.1 Contact with patients

During Phase 1, the EF was embedded within the HD centre, where it made contact with nephrologists and nurses. Despite the daily presence of EF in the HD centre, it was impossible to contact all patients for logistical reasons.

Due to the cooperation of the staff, the EF was able to access information about the various patients, with special reference to their medical history. The cooperation of doctors and nurses was crucial at this stage to accelerate the screening of patients. In particular, the information transfer allowed the EF to exclude patients who did not fit the inclusion criteria.

Afterward, the EF contacted patients individually during an HD session. It was decided to take advantage of the duration of therapy so as not to require any more time from the patient beyond that needed for HD. The same procedure was used for PD patients, who were scheduled for a nephrologist visit on the day at which the EF contacted the patients.

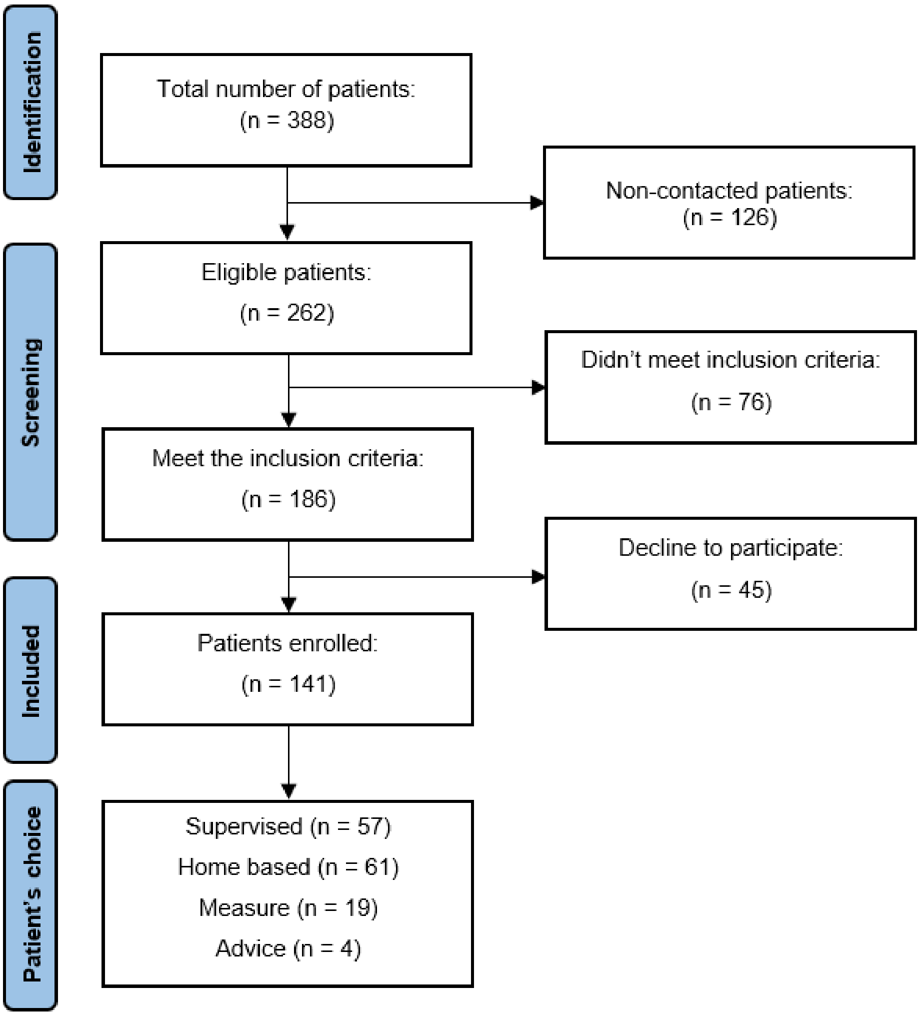
During the interview, the EF asked each patient what his/her physical activity habits were, what functional capacity he/she felt or had, and whether he/she felt satisfied or would prefer to improve his/her autonomy. At this stage, the EF tried not to influence the patients' responses and was available for dialog to understand the individual patient's condition, reassuring them, and giving them information regarding the effectiveness of exercise for the HD patient.

After the initial approach, the EF offered the patient to join the project, explained the potential benefits, and briefly presented the structure of the four planned training programs. The patient was then given a brochure containing information about the project and a sheet to fill out the preferred exercise option. The EF approximately two weeks after the interview (or sooner in case of patient request) returned to collect the response. In the case of adherence, the first evaluation was scheduled. For PD patients, the second interview was conducted by telephone.

10.2 Patients enrolment

There were 388 patients on HD treatment at the centres where the study was conducted. Of these, 126 (32.4%) could not be contacted. Figure 1 shows the patient recruitment process.

Figure 1. Flow chart of patients enrollment



10.3 Patients excluded

Of the 262 patients contacted, 76 (29%) did not fit the inclusion criteria. The reasons were inability to ambulate (n=40, 53%), inability to communicate with the EF in English, Italian, or Spanish (n=18, 24%), cachexia (n=13, 17%), lower limb amputations (n=4, 5%), or inability to provide consent (n=1, 1%). The mean age of the excluded patients was 73.3 years (SD 15.42) and the subjects were 40 males and 36 females, and these patients were on average older than the men were (76.2 years vs. 70.6). The mean dialysis age was 4.2 years (SD 3.74).

Figure 2. Patients who didn't meet the inclusion criteria

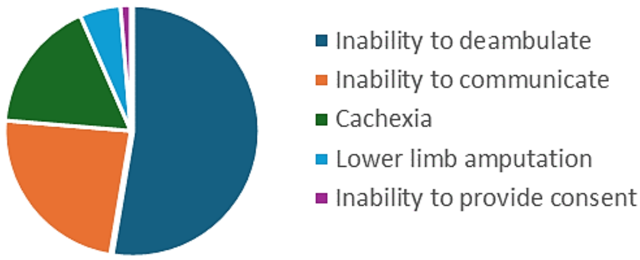


Table 1. Characteristics of patients who didn't meet the inclusion criteria

Total patients	N = 76	
	Total males	N = 40 (53%)
	Total females	N = 36 (47%)
Mean age (SD)	73.3 years (15.42)	
	Mean age males	70.6 years
	Mean age females	76.2 years
	Patients in the age range 30-39	4 (5%)
	Patients in the age range 40-49	3 (4%)
	Patients in the age range 50-59	8 (11%)
	Patients in the age range 60-69	10 (13%)
	Patients in the age range 70-79	20 (26%)
	Patients in the age range 80-89	24 (32%)
	Patients in the age range 90+	8 (11%)
Years of dialysis (SD)	4.2 years (3.74)	

10.4 Refusals to participate

Of the 186 patients who met the inclusion criteria, 45 (24%) declined to participate in the program. The reasons reported were low interest in physical activity (n=30, 67%), satisfaction with one's current level of autonomy (n=10, 22%), lack of time (n=3, 7%), difficulty following the program (n=1, 2%), and being involved in a rehabilitation program (n=1, 2%).

There were more male (n=33) than female (n=12) participants, and the mean age was 70.7 years (SD 14.91), with no significant gender differences. The mean dialysis age was 4.4 years (SD 3.28).

Distance to the HD centre was also calculated to assess when this affected the decision to participate in the program; patients who did not adhere distanced an average of 19 kilometres (SD=14.95) from the place of care

Figure 3. Patients who declined to participate in the study

Table 2. Characteristics of patients who declined to participate in the study

Total patients	N = 45	
	Total males	N = 33 (73%)
	Total females	N = 12 (27%)
Mean age (SD)	70.7 year (14.91)	
	Mean age males	70.6 years
	Mean age females	71 years
	Patients in the age range 30-39	1 (2%)
	Patients in the age range 40-49	5 (11%)
	Patients in the age range 50-59	5 (11%)
	Patients in the age range 60-69	7 (16%)
	Patients in the age range 70-79	11 (24%)
	Patients in the age range 80-89	12 (27%)
	Patients in the age range 90+	4 (9%)
Years of dialysis (SD)	4.4 years (3.28)	
Distance from dialysis center (SD)	19 km (14.95)	

10.5 Participants

The remaining 141 people agreed to participate in one of the proposed exercise options. This is a satisfactory result because it far exceeds the number of patients identified as representative. Considering the patients contacted, the adherence rate was 53.8%. If we restrict the sample to individuals who meet the inclusion criteria, this percentage increases to 75.8%. This means that three out of four people the EF contacted followed his recommendations. Additionally, in this group, male subjects (n=99) outnumbered female subjects (n=41), and they were also older on average (68.3 vs 65 years).

The mean age of the sample was 67.3 years (SD 12.93), so the people who participated were younger on average than those who refused, while the mean dialytic age of participants (4.7 years, SD=2.97) was greater (4.4, SD=3.28).

The distance to the HD centre, which was 18.9 kilometres (SD=14.93), was also calculated for the participants.

Figure 4. Programs chosen by patients

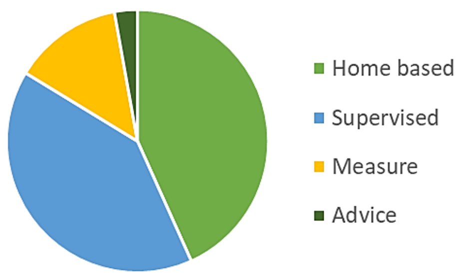


Table 3. Characteristics of patients who agreed to participate in the study

Total patients	N = 141	
	Total males	N = 99 (70%)
	Total females	N = 42 (30%)
Mean age (SD)	67.3 year (12.93)	
	Mean age males	68.3 years
	Mean age females	65 years
	Patients in the age range 30-39	1 (1%)
	Patients in the age range 40-49	14 (10%)
	Patients in the age range 50-59	24 (17%)
	Patients in the age range 60-69	37 (26%)
	Patients in the age range 70-79	34 (24%)

	Patients in the age range 80-89	30 (21%)
	Patients in the age range 90+	1 (1%)
Years of dialysis (SD)	4.7 years (2.97)	
Distance from dialysis center (SD)	18.9 km (14.93)	

The analysis of the differences between the three groups showed that the subjects who joined the study were younger, on average, than the denials and noneligible individuals. However, this population is still elderly (67,3 years).

An interesting finding, however, is given by HD age, where the reverse trend can be seen (although in this case, the difference between the groups is less pronounced); indeed, it is the group of participants who are receiving HD treatment for the longest time. This is an important finding because it means that EF intervention can help even long-term HD individuals abandon sedentary behaviour without excluding them from improving their condition.

No difference was found for distance from the HD centre, so it can be assumed that distance from the HD centre was not relevant to the decision to join, as confirmed by the fact that no patient refused this reason.

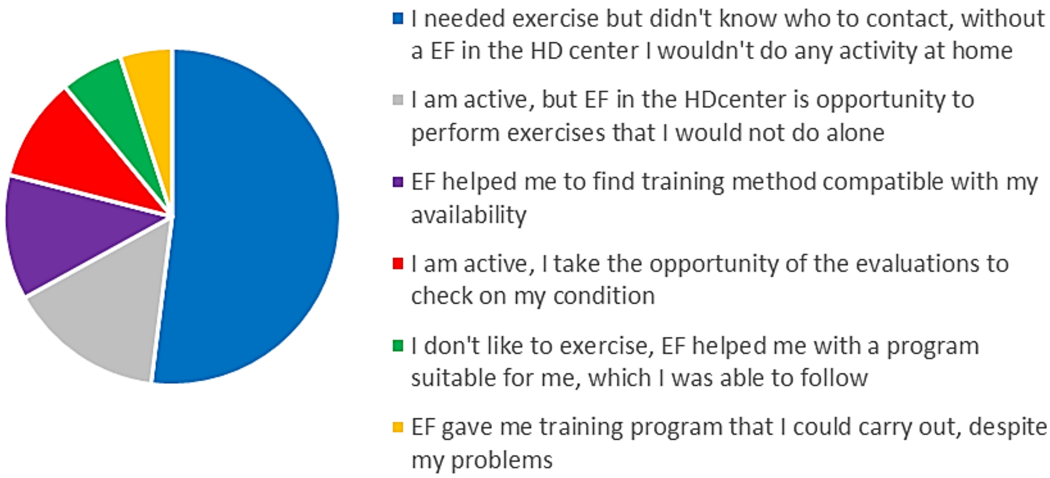
Table 4. Comparison between ineligible patients, refusals, and participants

	N° of patients	***Mean age (SD)***	***Years of dialysis (SD)***	***Distance from dialysis center (SD)***
Noneligible	76	73.3 (15.42)	4.2 (3.74)	17.9 (11.61)
Refusals	45	70.7 (14.91)	4.4 (3.28)	19 (14.95)
Noneligible + Refusals	121	72.3 (15.22)	4.2 (3.57)	19.5 (13.45)
Participants	141	67.3 (12.93)	4.7 (2.97)	18.9 (14.93)

Since the main purpose of EF inclusion was to increase patients' participation in exercise programs, those who joined the project were asked about their main motivation. Most respondents (n=52%) answered that the presence of the EF allowed them to exercise, as they would have liked to do previously, but that they were unable to do so because of the barriers already described. The 15% said that they were already active, but the EF provided them with exercises they would not have done on their own. Others (n=12%) had difficulty finding time to train, and the EF met their needs by providing programs they could carry out in the time available. More others (n=10%) described themselves as active and satisfied with their habits; however, they were happy to undergo assessments so that they could know and monitor their fitness level. A smaller percentage (n=6%) responded that although they do not like to exercise, the EF provided them with a non-invasive program that they could sustain effectively, and finally, that they appreciated despite limitations to exercise (n=5%). The prescribed program was suitable for their abilities.

The data collected during the interviews are compiled in Figure 5.

Figure 5. Reasons for subjects to join the program.



10.6 Baseline analysis

The sample of patients who participated in the study had a gender disparity; 70% were male (n=99), and 30% were female (n=42). The mean age of the sample was 67.3 years (SD=12.93), with men (68.3 years, SD=12.9) being more prevalent than women (65 years, SD=13.27), while the HD age of the whole sample was 4.7 years (SD=2.97).

Information was also collected on the means of public or private transportation used by patients to reach the healing centre to assess whether this aspect influenced the choice of the training program. Unfortunately, for 38% (n=54) of the subjects, these data could not be obtained. A majority of the 87 participants were moving independently (39%, n=55) compared to those using public services (23%, n=32).

Risk factor data and several laboratory parameters were also collected. The characteristics of the 141 participants are summarized in Table 5.

Table 5. Characteristics of participants

N° of patients	N = 141	
	N° males (%)	N = 99 (70%)
	N° females (%)	N = 42 (30%)
Mean age (SD)	67.3 years (12.93)	
	Mean age males (SD)	68.3 (12.9)
	Mean age females (SD)	65 (13.27)
Years of dialysis (SD)	4.7 (2.97)	
Transportation to dialysis center (%)	Public = 32 (23%) Private = 55 (39%) Unknown = 54 (38%)	
Country of living (%)	Italy = 93 (66%) Spain = 48 (34%)	
Risk factors (%)		
	Smoking	44.1%
	Hypertension	88.2%
	Dyslipidemia	17.2%
	Diabetes	28%
	Myocardial infarction	29%
	Congestive heart failure	36.6%
	Peripheral vascular disease	34.4%
	Stroke	7.5%
	Dementia	1.1%
	Chronic obstructive pulmonary disease	20.4%
	Connective tissue disease	5.4%
	Peptic ulcer disease	12.9%
	Liver disease	10.8%
	Hemiplegia	0%
	Chronic kidney disease	100%
	Solid tumor	32.3%
	Leukemia	2.2%
	Lymphoma	5.4%
	HIV	0%
Charlson Comorbidity Index (SD)	7.4 (2.76)	
Blood parameters (SD)		
	Cholesterol	165.5 (55.03)
	Triglycerides	156.2 (93.28)
	High-density lipoprotein	49.6 (18.89)
	Hemoglobin	11.1 (1.48)
	Red blood cells	3.7 (0.68)
	Calcium	9 (0.66)
	Phosphorus	5.9 (1.67)

	Blood glucose	115.9 (51.91)
	Urea	153.1 (40.63)
	Creatinine	8.44 (2.97)
	Glomerular Filtration Rate	6.7 (3.07)
	C-reactive protein	1.7 (2.06)

Participants in different types of programs were analysed. The most common training programs were supervised (n=57, 40%) and home-based (n=61, 43%) options; 19 (13%) patients chose to perform periodic assessments, and only four people (4%) asked for advice for unstructured activity.

Analysis of the characteristics of each group revealed that subjects in the supervised program were the oldest (72.6 years, SD=10.6) and most comorbid (Charlson Comorbidity Index, CCI, score=8.2, SD=2.66). Compared with these, subjects in the HB group were younger (64.5 years, SD=13.56) and less frail (CCI=6.9, SD=2.69), but they lived more distant from the HD centre (21.06 kilometres, SD=15.16, compared with 17.3 kilometres, SD=14, of the supervised group). In turn, those who opted for assessments only were younger (61.1 years, SD=12.11) and had fewer comorbidities (CCI=5, SD=1.5). The same trend was observed in the distance analysis from the HD centre. The subjects in the supervised group lived closer (17.3 km, SD=14) than did those in the home-based group (21.1 km, SD=15.16) and the evaluation group (23 km, SD=15.03).

In the analysis of laboratory parameters, no significant differences were found between the groups, except for creatinine. In this case, the values recorded in the Measure group were greater than those in the other groups.

Patient characteristics according to program choice are described in Table 6.

Table 6. Characteristics of patients according to the program chosen

	Supervised	***Home based***	***Measure***	***Advice***	***ANOVA p***
N° of patients	N = 57	N = 61	N = 19	N = 4	
N° of males (%)	N = 38 (67%)	N = 45 (74%)	N = 16 (84%)	N = 2 (50%)	0.66
N° of females (%)	N = 19 (33%)	N = 16 (26%)	N = 3 (16%)	N = 2 (50%)	
Mean age (SD)	72.6 (10.6)	64.5 (13.56)	61.1 (12.11)	56.3 (9.54)	
Years of dialysis (HD)	5.6 (3.05)	4 (2.42)	3 (2.78)	2.3 (2.3)	
Distance from dialysis center (SD)	17.3 (14)	21.1 (15.16)	23 (15.03)	14.8 (11.84)	
Public (%)	N = 21 (37%)	N = 10 (16%)	N = 1 (5%)	N = 0	0.186
Private (%)	N = 27 (47%)	N = 17 (28%)	N = 8 (42%)	N = 3 (75%)	

Unknown (%)	N = 9 (16%)	N = 34 (56%)	N = 10 (53%)	N = 1 (21%)	
Charlson Comorbidity Index (SD)	8.2 (2.66) [c]	6.9 (2.69)	5 (1.5) [a]	4.3 (1.53)	0.002
Blood parameters (SD)					
Cholesterol	172.3 (61.99)	155.4 (41.56)	186.7 (79.47)	145	0.436
Triglycerides	151.6 (63.05)	157.6 (79.12)	183 (152.29)	65	0.889
High-density lipoprotein	45.4 (12.38)	41.6 (8.82)	64.5 (30.4)	51	0.935
Hemoglobin	11.25 (1.56)	10.94 (1.43)	11.83 (1.15)	9.6 (0.91)	0.657
Red blood cells	3.66 (0.63)	3.76 (0.82)	3.87 (0.43)	3 (0.05)	0.696
Calcium	9.1 (0.65)	8.9 (0.74)	9 (0.49)	9.4 (0.38)	0.476
Phosphorus	5.7 (1.5)	6.2 (1.84)	6 (1.94)	5.2 (1)	0.564
Blood glucose	126.6 (64.79)	108.7 (36.68)	112 (47.67)	87.7 (3.79)	0.322
Urea	149.2 (38.52)	151 (39.54)	177.3 (50.2)	145.3 (43.36)	0.210
Creatinine	7.7 (2.36) [c]	8.19 (2.76) [c]	11.02 (3.42) [a b]	6.3 (1.43)	0.008
Glomerular Filtration Rate	7.7 (3.67)	6.8 (2.75)	4.7 (2.42)	8.5 (0.71)	0.193
C-reactive protein	2.2 (2.74)	1.38 (1.72)	1.81 (2.1)	0.55	0.809

[a] different from Supervised; [b] different from Home based; [c] different from Measure

Figure 6. Differences in the Charlson Comorbidity Index score between groups

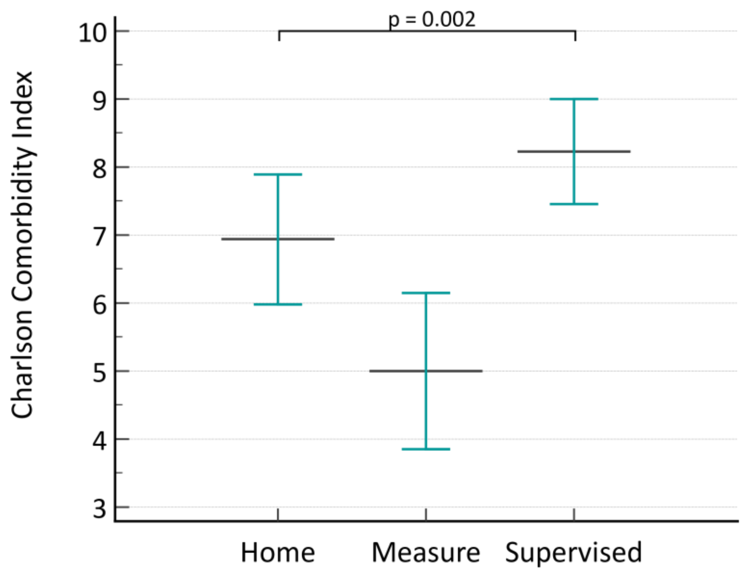
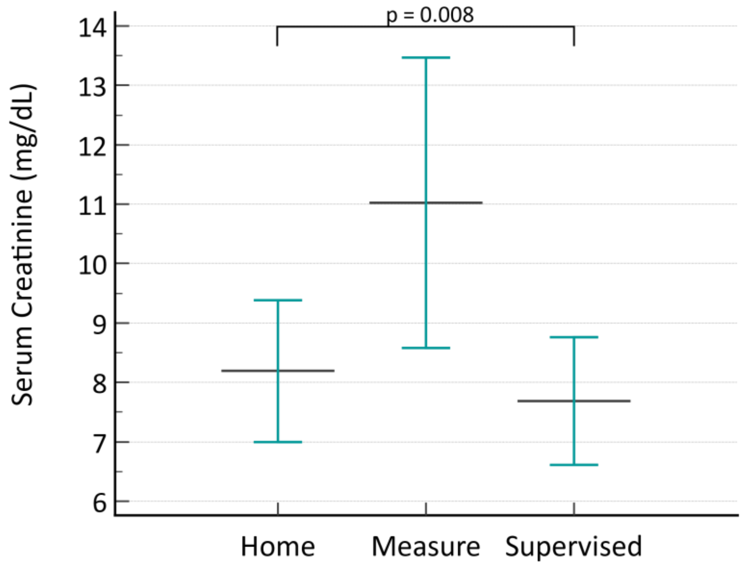


Figure 7. Differences in the serum creatinine level between the groups



The different functional abilities of the patients at baseline were analysed to determine whether these abilities influenced their choices. The three tests administered measured speed (10MWT), walking autonomy (6MWT), and lower limb strength (5TSTS). The results obtained were as expected given the differences in mean age and comorbidities between the groups.

Regarding the three most chosen options, the lowest ability group was supervised, which recorded the slowest walking speed (2.84 km/h), the shortest walking distance (6MWD=243.5 m) with the need to stop after 107.1 m, the shortest range at the occurrence of symptoms (PFWD=183 m) with the highest perceived exertion (5.6 on the Borg scale), and the lowest lower limb strength (18.4 s to complete the 5TSTS). The home-based exercise group was somewhat faster (2.92 km/h) and had greater walking ability (6MWD=311.9 m, PFWD=266.5 m, and first stop after 124.2 m), less effort (Borg=4.2), and greater leg strength (5TSTS=15.2 s). Compared with those in the other two groups, the speed (4.15 km/h), walking range (6MWD=377.6 m), and strength (5TSTS=12 s) of the subjects who only underwent the measurements were more even.

The results of the assessments at baseline for the different groups are presented in Table 7.

Table 7. Functional test outcomes at baseline according to the program chosen

	Supervised	***Home based***	***Measure***	***Advice***	***ANOVA p***
10MWT (SD)	7.6 (4.24)	7.4 (8.05)	4.2 (1.59)	10.5 (8.29)	0.138
6MWD (SD)	243.5 (112.46) [b c]	311.9 (124.88) [a]	377.6 (105.97) [a]	235 (122.36)	< 0.001
PFWD (SD)	183 (126.85) [b c]	266.5 (163.64) [a c]	407.1 (94.41) [a b]	138.8 (114.34)	< 0.001
1° stop distance (SD)	107.1 (60.8)	124.2 (85.24)	NA	170.7 (164.61)	0.548
N° of stops	0.8 (0.98) [c]	0.4 (0.93)	0 [a]	0.8 (0.5)	0.004
Borg scale	5.6 (2.43) [b c]	4.2 (2.01) [a c]	2.4 (1.5) [a b]	4 (1.83)	< 0.001
5TSTS (SD)	18.4 (12.82) [c]	15.2 (6.78)	12 (2.86) [a]	16.42	0.036

[a] different from Supervised; [b] different from Home based; [c] different from Measure

10MWT: 10-meter walk test; *6MWD*: 6-minute walking distance; *PFWD*: pain-free walking distance; *5TSTS*: 5-time sit-to-stand test

Figure 8. Differences in the 6MWD between groups

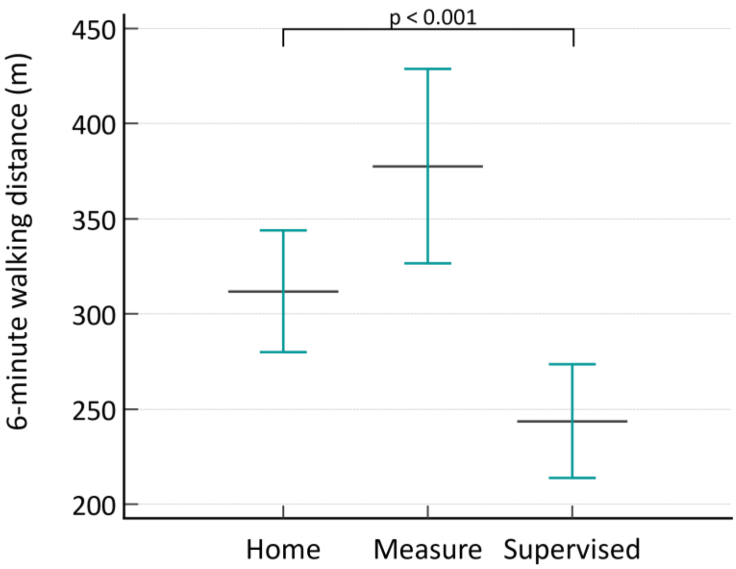
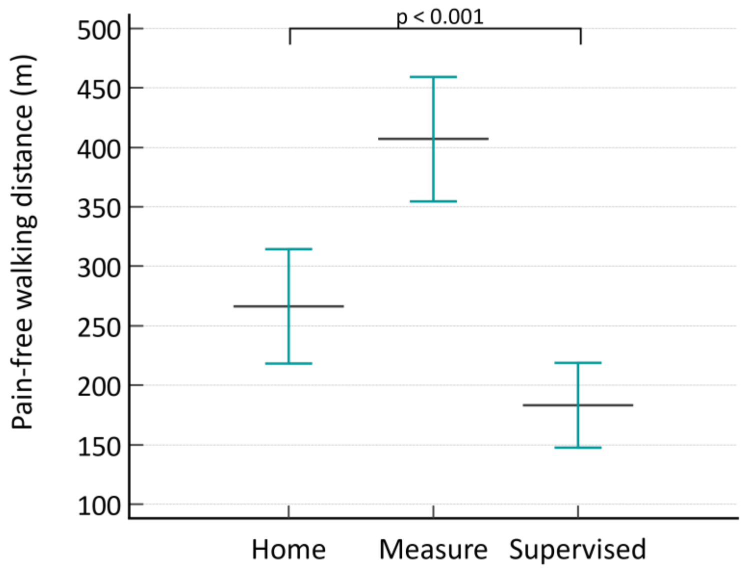


Figure 9. Differences in PFWD between groups



Further analysis was performed based on the results of the questionnaires administered. Data extrapolated from the validated questionnaires administered (SF-36, Duke Activity Status Index, Falls Efficacy Scale, and Beck Depression Inventory) further confirmed the findings of the functional assessments. Once again, the group with the lowest values at baseline was the patients who chose the supervised and measurement program. Specifically, significantly reduced levels of physical functioning and limitations due to emotional problems were recorded. In particular, the domains most closely related to physical well-being (e.g., Physical Functioning and Bodily Pain of the SF-36, DASI, and FES) had values that were very close to those of the healthy population. The same trend, where the supervised group again had lower scores than the others, was found for fear of falling and activity level. On the other hand, the analysis of the BDI did not reveal significant differences between the groups.

The results of the questionnaires at baseline for the different groups are presented in Table 8.

Table 8. Results of questionnaires at baseline according to the program chosen

	Supervised	*Home based*	*Measure*	*Advice*	*ANOVA p*
SF-36					
PF (SD)	59.4 (27.43) [b c]	73.6 (21.13) [a]	84.2 (13.52) [a]	50 (41.43)	< 0.001
RP (SD)	53.9 (36.53)	63.7 (34.17)	55.8 (50.16)	37.5 (43.3)	0.305
RE (SD)	63.4 (35.44) [c]	84.3 (29.67)	69.2 (41.87) [a]	50 (57.74)	0.003
VT (SD)	57 (19.21)	56.8 (19.54)	68.1 (19.74)	35 (33.17)	0.155
EWB (SD)	68.8 (20.1)	72 (17.8)	78.8 (22.23)	60 (23.78)	0.162
SF (SD)	64.8 (28.02)	74.7 (26.35)	75 (30.19)	46.9 (48.28)	0.090
BP (SD)	67.7 (31.45)	73.7 (24.39)	82.5 (24.77)	61.9 (33.75)	0.146
GH (SD)	42.6 (21.53)	45.7 (18.4)	50.8 (26.91)	26.3 (9.46)	0.376
HC (SD)	54.1 (27.96)	55.1 (21.95)	71.2 (36.58)	37.5 (43.3)	0.121
FES (SD)	10.9 (4.95) [c]	9.3 (3.35)	7.5 (0.78) [a]	10.8 (3.77)	0.013
DASI (SD)	23.5 (13.87) [b c]	33 (16.16) [a]	44.3 (20.78) [a]	17.7 (13.99)	< 0.001
BDI (SD)	10.9 (2.29)	9.9 (5.29)	8.5 (5.32)	13.7 (3.06)	0.253

[a] different from Supervised; [b] different from Home based; [c] different from Measure

PCS: Physical component score; *MCS*: Mental component score; *PF*: Physical functioning; *RP*: Role function – physical; *RE*: Role function – emotional; *VT*: Energy; *EWB*: Emotional well-being; *SF*: Social functioning; *BP*: Pain; *GH*: General health; *HC*: Health change; *FES*: Falls efficacy scale; *DASI*: Duke activity status index; *BDI*: Beck Depression Inventory

Figure 10. Differences in Physical Functioning on the SF-36 Questionnaire between groups

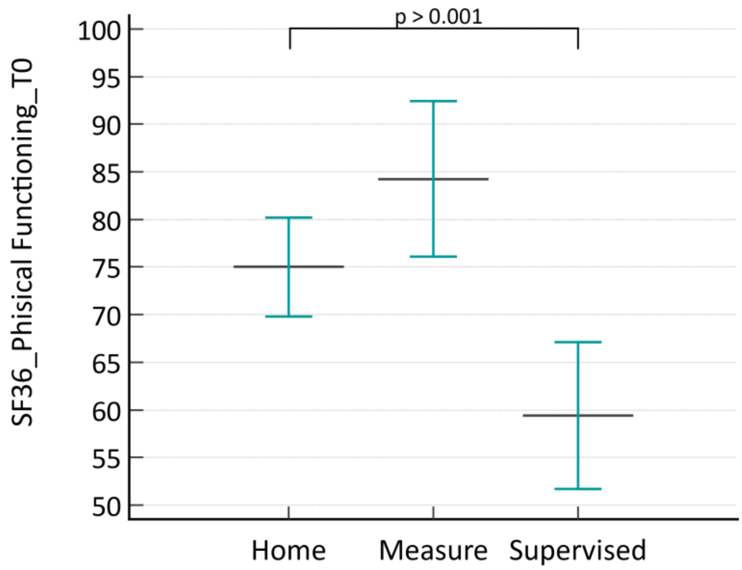


Figure 11. Differences in Emotional Limitation on the SF-36 Questionnaire between groups

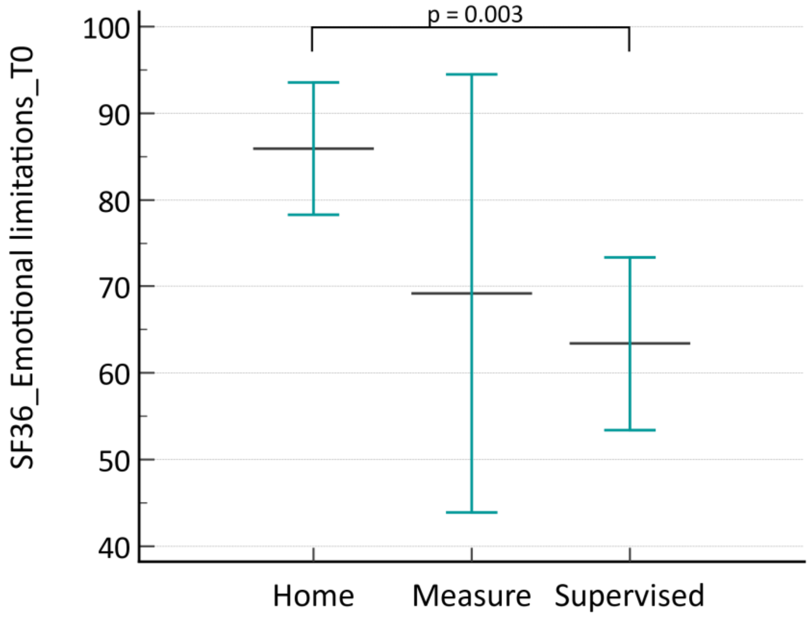


Figure 12. Falls Efficacy Scale Score differences between groups

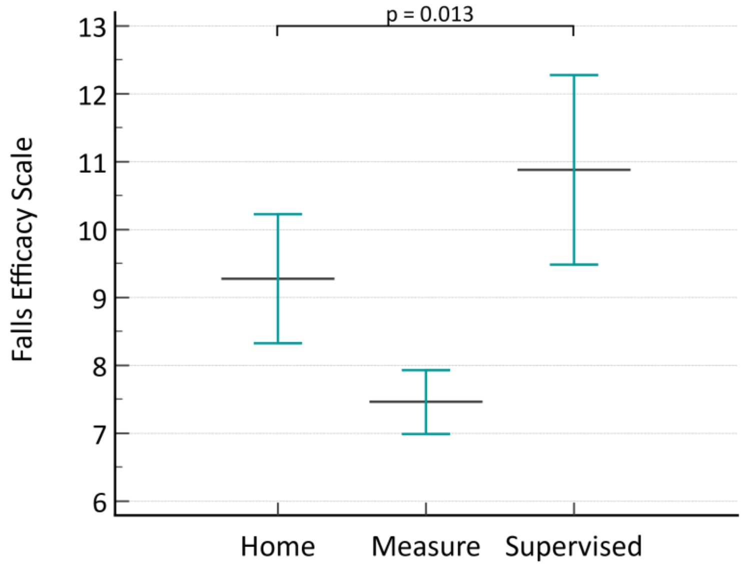
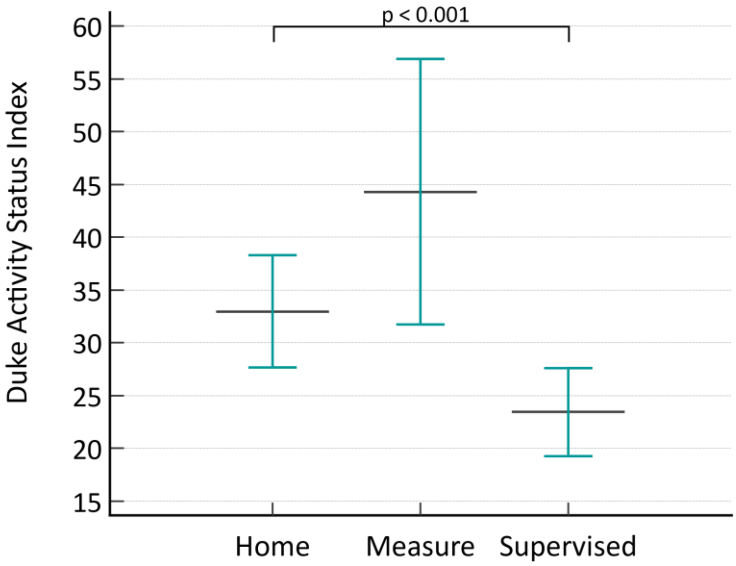


Figure 13. Differences in the Duke Activity Status Index between groups



10.7 Discussion

The study was effective in terms of patient recruitment. Respect to the 188 subjects who were expected to adhere, there were 141 participants. This finding places the trial among the highest-participation trials among exercise-based studies in HD populations. The only studies that involved more people were the previously mentioned Excite (n=296) [1], PEDAL (n=379) [2], and DiaTT (n=1211) [3] studies.

Unfortunately, the modality of approach was not comprehensive enough for the EF to propose the program to all patients being treated at the various HD centres. This resulted in a significant number of people (n=126, 32% of the total) being unable to choose whether to participate. Given that more than 50% of the patients contacted agreed to adhere, it can be assumed that approximately 50 potential participants were lost.

For patients who did not fit the inclusion criteria (n=76), the first cause of exclusion was the inability to ambulate (n=40, 53%). The cause may be that the two structured exercise modalities, as well as the chosen assessment tests, involved walking. In the future, to design even more inclusive programs, it might be effective to also include the option of exercising differently, possibly proposing an intradialytic training option, despite the problems this mode implies.

A total of 45 people declined the opportunity to participate in the program, and 24% of the total number of patients contacted met the inclusion criteria. The most reported reason (n=67%) was low interest in exercise. This is a relevant factor because the benefits of exercise are well understood by the treatment staff, and the fact that a significant number of patients are unaware of this is a factor that needs to be addressed. It would certainly be necessary for individuals in HD to be repeatedly encouraged to embrace an active lifestyle, but it would be even more effective for this approach to physical activity to be made in the earlier stages of the disease before the start of replacement treatment. Even in this context, the support of experienced exercise experts who can guide how to exercise is crucial for the well-being of patients, especially in preparation for the initiation of HD [4].

With the EF intervention, more than 50% of the total number of patients treated had adhered to an exercise program. Analysing the motivations that led patients to join, it appears that almost the entire sample of participants were aware of the benefits of physical activity and that they needed help to perform more of it. This finding follows what is reported in the literature [5]: patients know that physical activity is important to them, but they lack the knowledge or time, tools, etc., to exercise effectively. The EF's activity can be affirmed to have been effective, as it went to address a known necessity in appropriate ways. The EF's specific expertise was crucial because it allowed him to tailor the program to the needs of the specific individual patient, meeting the needs of sedentary people who needed total guidance, as well as already active individuals who were able to improve their habits thanks to his advice.

Analysis of participant characteristics according to the type of program chosen showed a rather clear trend. Older, comorbid, and lower-performing patients preferred the supervised exercise mode; younger and fit patients chose to take measurements only, without requesting further guidance; and "intermediate" subjects, in terms of age, comorbidities, and functional capacity, opted for home-based structured exercise. In summary, a worse condition was associated with the demand for supervision during exercise, while improving fitness corresponded with a decreasing willingness to be "constrained" in structured programs. Once again, to incentivize adherence, it was crucial for the patient to choose the program according to his or her preferences.

The same correlation between functional capacity and the chosen program was recognized in the analysis of the QoL questionnaires. The chosen tools assessed different aspects (quality of life, fear of falling, activity level, and depression), but again, the results of the various tests followed the same trend. Lower levels of mental health, as was the case for physical health, were associated with a preference to perform physical activity under the supervision of the EF, medium levels with the request for the structured program to be performed at home, and the highest levels with the willingness to perform only the assessments.

These data extrapolated from the assessments made at baseline are significant. Since this is the first trial in which HD patients themselves choose which type of exercise intervention to undergo, assisting such a clear and consistent stratification in all aspects analysed is certainly relevant. Differences between different patients are known in the present study, both in terms of age (range 38-95 years), walking ability (range 44-594 m), and all other factors examined. Given the possibility of choosing which treatment to undergo, such a clear spontaneous split highlights how crucial it is for patients to be allowed to take advantage of the EF's expertise. To propose effective exercise programs to improve the well-being of people in HD, there should therefore be the presence of this figure, who, by explaining to patients the pros and cons of each intervention and answering their questions, can help them overcome their doubts and embrace a more active lifestyle.

References

1. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2017 Apr;28(4):1259–68.
2. Greenwood SA, Koufaki P, Macdonald JH, Bhandari S, Burton JO, Dasgupta I, et al. Randomized Trial—PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Hemodialysis. Kidney Int Reports [Internet]. 2021;6(8):2159–70. Available from: https://doi.org/10.1016/j.ekir.2021.05.034
3. Anding-Rost K, von Gersdorff G, von Korn P, Ihorst G, Josef A, Kaufmann M, et al. Exercise during Hemodialysis in Patients with Chronic Kidney Failure. NEJM Evid. 2023;2(9).
4. Clyne N, Anding-Rost K. Exercise training in chronic kidney disease-effects, expectations and adherence. Clin Kidney J. 2021 Apr;14(Suppl 2):ii3–14.
5. Ghafourifard M, Mehrizade B, Hassankhani H, Heidari M. Hemodialysis patients perceived exercise benefits and barriers: the association with health-related quality of life. BMC Nephrol. 2021;22(1):1–9.

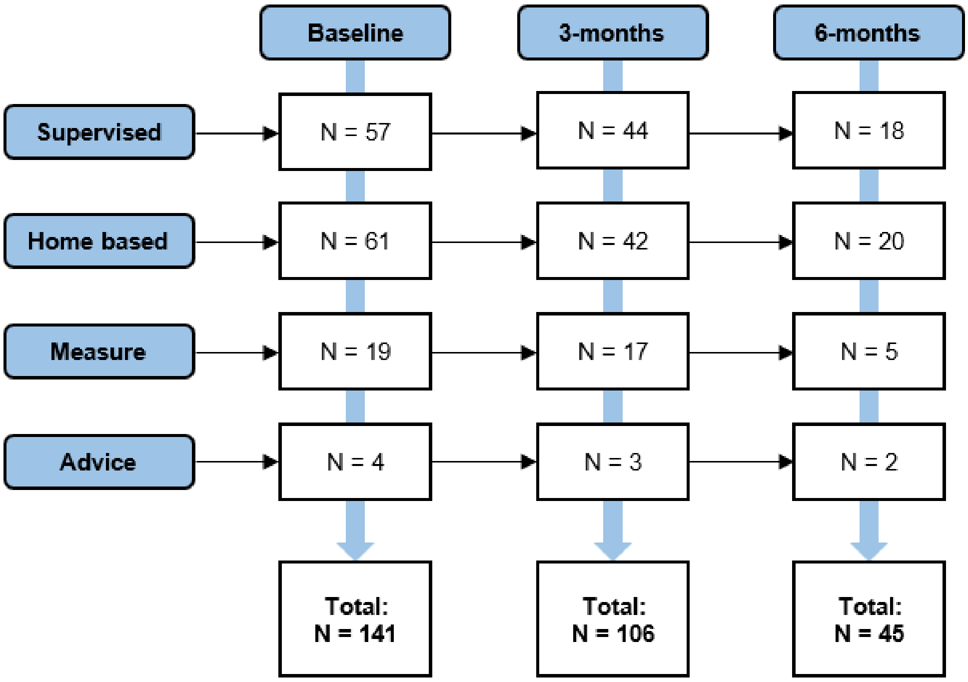
CHAPTER 11

11. PHASE 2

11.1 Planned assessments

In addition to advising patients on their program choices, the EF was also responsible for arranging the scheduled evaluations. There were three planned assessments: one at baseline, one at the end three months into the exercise program, and one after another three months.
In the case of patients in the Supervised program, the second evaluation was scheduled for the treatment day following the last day of training. For patients in the other three groups, as well as for the evaluation at six months, the EF contacted them during an HD session to schedule the testing date. Given the differences reported by patients on different days of the week, particularly between long and short skips from previous dialysis, the three measurements were taken on the same day of the week. A total of 292/423 (69%) scheduled evaluations were carried out.
Of the 141 patients who were measured at baseline, 106 (75%) repeated the assessment after the three-month exercise, and 45 after six months (42% of those who completed the program, and 32% of the total). Patients who could not make the assessment promptly after three months (n=3) due to transient reasons (e.g. hospitalization) were still assessed at six months. Figure 1 shows the patients in each group who performed the planned assessments.

Figure 1. Patients in each group who completed each scheduled assessment



11.2 Program interruption

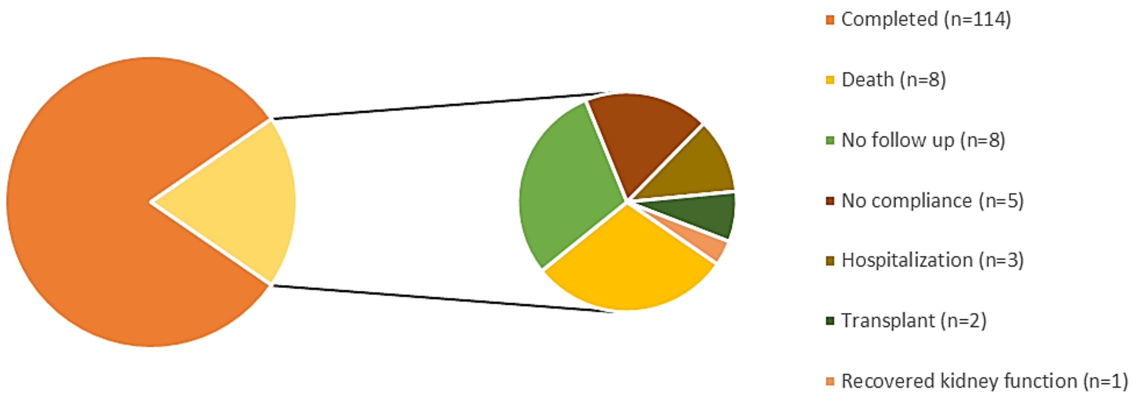
Of the 141 participants measured at baseline, 114 (80.1%) carried out at least two of the three planned evaluations, allowing the measurement of program effects.

For the 27 (19.9%) patients who did not complete the program, the cause of discontinuation was noted. The leading causes were death (n=8, 29.6%) and loss to follow-up (n=8, 29.6%), followed by the decision to discontinue the program (n=5, 18.5%), hospitalization (n=3, 11.1%), transplantation (n=2, 7.4%), and recovery of renal function (n=1, 3.8%). A dropout rate of 19.9% can be considered a positive figure when compared with large-number studies, in which it has always exceeded this value (Excite 23%, PEDAL 22%, DiaTT 25%).

Most subjects who did not take the second assessment were from the Home based group (n=14). However, for nine patients the discontinuation was due to the EF's inability to schedule the other evaluations, while one subject received renal transplantation. Therefore, the withdrawal of these individuals from the program can be attributed more to logistical limitations than adverse events. The second group with the highest number of dropouts was the Supervised (n=11, 40.7%). In this case, only three patients were lost to other causes (logistics, renal function recovery, transplantation) while the others went to hospitalization (n=2) or death (n=8). This is an expected finding, as it was the group with lower functional capacity and worse QoL, which is known to be associated with unfavourable outcomes. The

other two people, belonging one to the assessments group and the other to the advice group, were both lost to organizational reasons.
The reasons for program interruption are described in Figure 2.

Figure 2. Patients who did not complete the program and the reasons why



Analysis of the data gathered at baseline on this group does not reveal significant differences from the other patients. These patients had the same age and comorbidity level as the others and lived closer on average than the rest of the participants. In terms of functional capacity, they were on average between the subjects in the Supervised and Home Based groups, so they were not more fragile than the others.

Table 1. Baseline characteristics of patients who discontinued the program

Total patients	N = 27	
	Total males	N = 21 (78%)
	Total females	N = 6 (22%)
Mean age (SD)	67.2 year (10.88)	
Distance from dialysis center (SD)	13.3 Km (12.74)	
Charlson Comorbidity Index (SD)	7.6 (2.12)	
10MWD (SD)	7.35 (6)	
6MWT (SD)	286.9 (146.29)	
5TSTS (SD)	14.27 (3.74)	
FES (SD)	10.3 (4.6)	
DASI (SD)	26.2 (18.5)	

10MWT: 10 meter walk test; *6MWD*: 6-minute walking distance; *PFWD*: Pain-free walking distance; *5TSTS*: 5-time sit-to-stand test; *PCS*: Physical component score; *MCS*: Mental component score; *PF*:

Physical functioning; *RP*: Role function – physical; *RE*: Role function – emotional; *VT*: Energy; *EWB*: Emotional well-being; *SF*: Social functioning; *BP*: Pain; *GH*: General health; *HC*: Health change; *FES*: Falls efficacy scale; *DASI*: Duke activity status index

11.3 Program completed: functional outcomes

The assessment after the three months allowed the evaluation of the effects of the two structured exercise programs, and the possible changes in the Measure group, who maintained their habits, or in those who had asked for the unstructured advice.

No falls or adverse events were recorder during the entire training sessions.
The supervised group had an adherence rate of 95% of the scheduled sessions; the home-based group completed the 85% of the prescribed sessions.

Supervised group
In the supervised group all outcomes exhibited a significant improvement (Table 2). Walking speed improved by more than 18% (+0.53km/h), walking range improved (6MWD: +30.3m and PFWD: +49.8m) with less perceived exertion (Borg scale: -1), and lower limb strength also increased (5TSTS: -1s).

Home based group
The Home based group improved speed in the 10MWT (+0.64Km/h) and all values in the 6MWT, especially 6MWD (+20.1m), PFWD (+58.4m), and distance to first stop (+30.6m), while no changes were recorded in lower limb strength (Table 2).

Measure group
Regarding the Measure group, which can be considered a sort of control group, no changes in performance were recorded in the 10MWT and 5TSTS. The changes recorded in the 6MWT were mainly attributable to the loss at T3 of the worst-performing subject at baseline (Table 2).
The Advice group, the lower-numbered one, on the other hand, showed significant deterioration in all the parameters measured.

Between group comparison

Considering the baseline imbalances between group, an analysis of covariance was conducted applying Age, Dialysis vintage, Charlson Index, baseline values of 6MWT, 10M, 5STS and domains of SF-36 as covariates.

A significant between group comparison was observed for the primary outcome for HB and Supervised versus Measure group (Bonferroni's corrected p value < 0.001) and for the 10m test ($p=0.001$).

No significant differences were observed for all the outcomes between the two exercise groups (Hb vs supervised) (Table 2).

Table 2. Differences in functional parameters between groups

	Supervised (n = 44)			Home based (n = 42)			Measure (n = 17)			ANCOVA p
	T0	*T3*	*Δ*	*T0*	*T3*	*Δ*	*T0*	*T3*	*Δ*	
10MWT (s)	7.7 (6.4 – 9)	6.8 (6 – 7.7)	-0.9* (-1.6 - -0.2)	7.2 (4.7 – 9.7)	5.8 (4.6 – 7)	-1.5*† (-3 – 0)	4.2 (3.2 – 5.2)	4.2 (3.2 – 5.2)	0 (-0.3 – 0.3)	0.001
6MWD (m)	243 (212 – 274)	272 (242 – 301)	29** † (19 – 38)	309 (277 – 341)	347 (316 – 378)	38** † (26-50)	392 (340 – 443)	401 (347 – 454)	9 (-4 – 22)	<0.001
5TSTS (s)	19.4 (14.8 – 23.4)	16.8 (13.5 – 20.6)	- 2.5* (-4.6 – 0.1)	15.3 (13.2 – 17.5)	13.6 (11.5 – 15.7)	-1.8** (-2.4 - -1.1)	11.9 (10.4 – 13.5)	11.2 (9.7 – 12.5)	-0.8 (-2.3 – 0.6)	0.43
FES	11 (9.5 – 12.6)	10.5 (9 – 12)	-0.5 (-1.2 – 0.5)	9.3 (8.3 – 10.3)	9.5 (8.4 – 10.6)	0.2 (-0.4 – 0.7)	7.5 (7 – 8)	7.1 (6.9 – 7.3)	-0.5 (-0.9 – 0)	0.12
DASI	22.9 (18.2 – 27.7)	20.3 (16.9 – 23.7)	-2.6 (-6.3 – 1.1)	32.7 (26.9 – 38.4)	34 (28.1 – 39.7)	1.3 (-1.6 – 4.1)	47.3 (34 – 65.2)	41.1 (32.1 – 50.2)	-6.2 (-17.7 – 5.4)	0.22

* P<0.05

** p<0.01

† different from Measure group

Figure 3. Difference in perceived exertion on Borg scale between groups

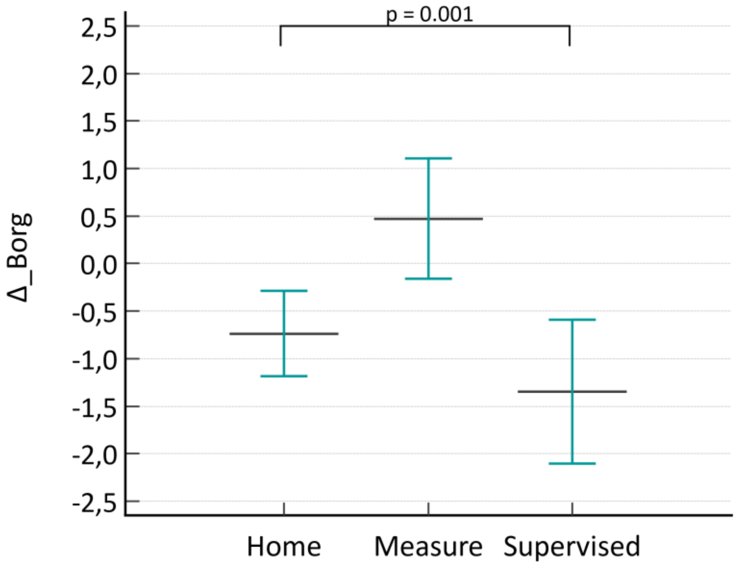


Figure 4. Difference of the variations in the 10MWT between groups

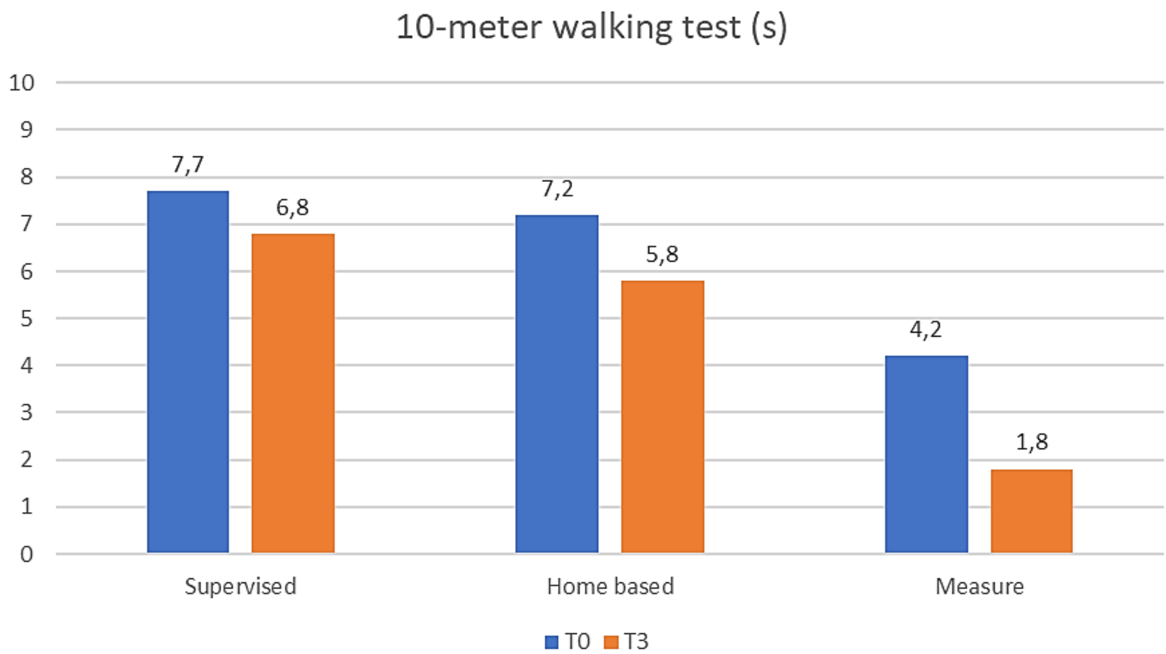


Figure 5. Difference of the variations in the 6MWD between groups

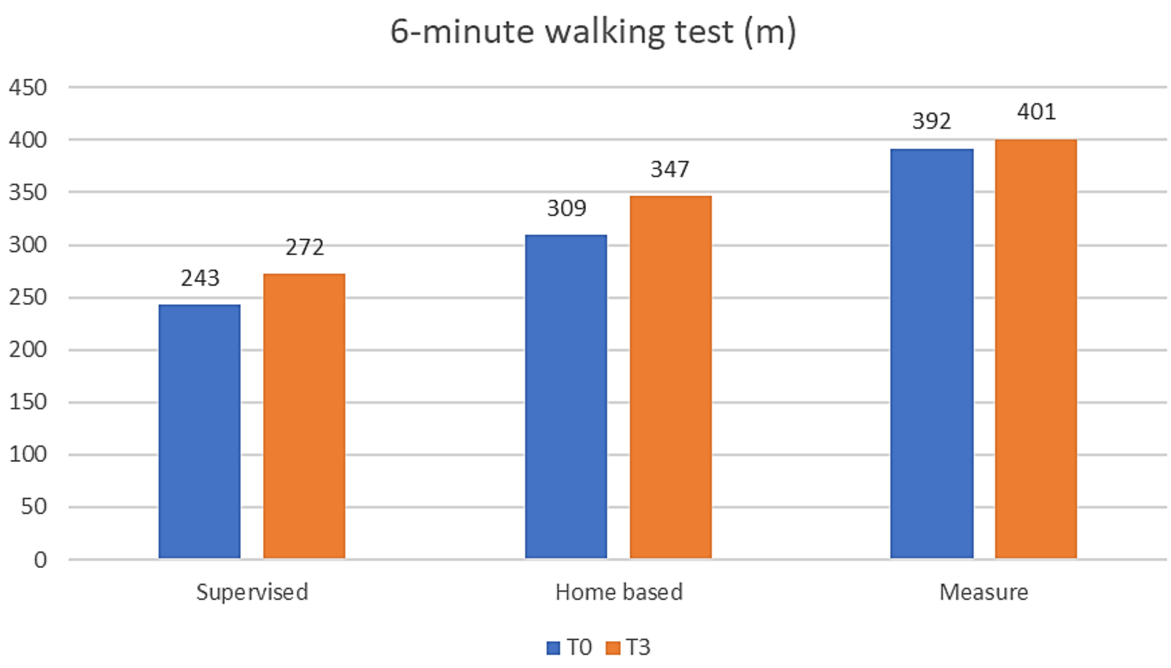


Figure 6. Difference of the variations in the 5TSTS between groups

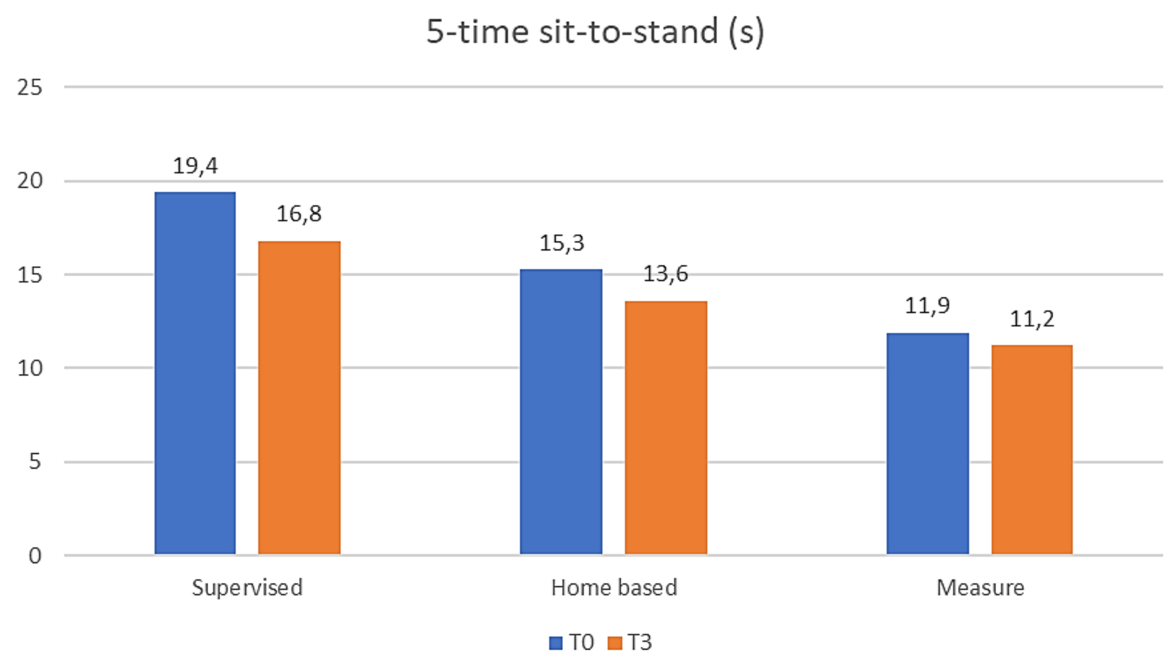


Figure 7. Difference of the variations in the Falls Efficacy Scale score between groups

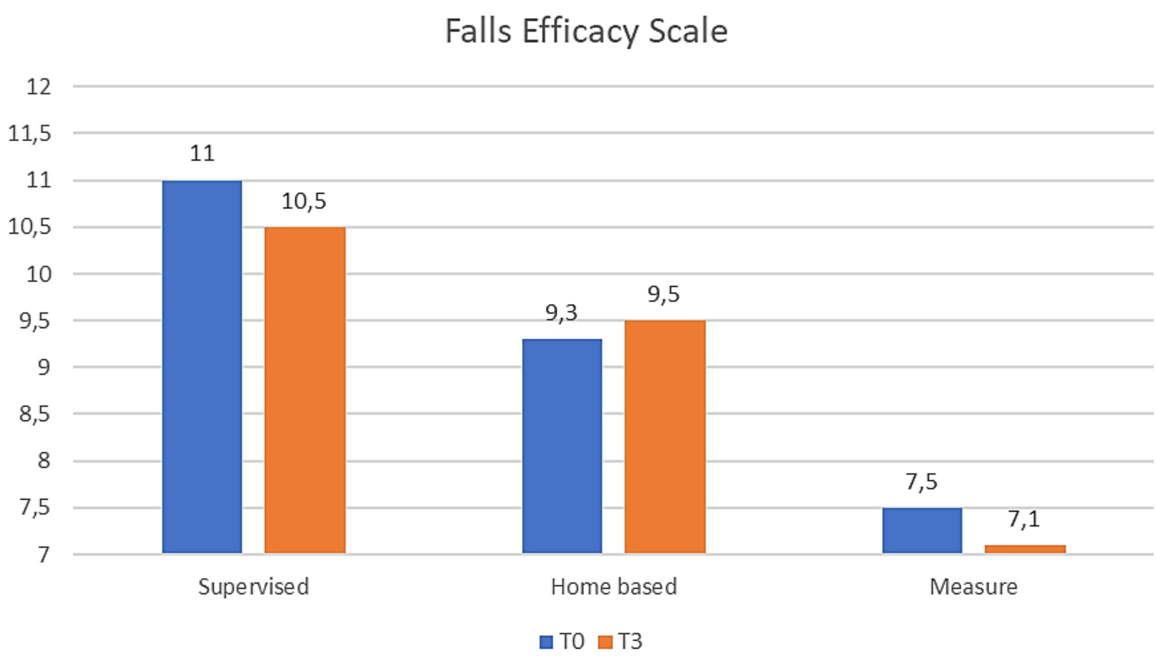
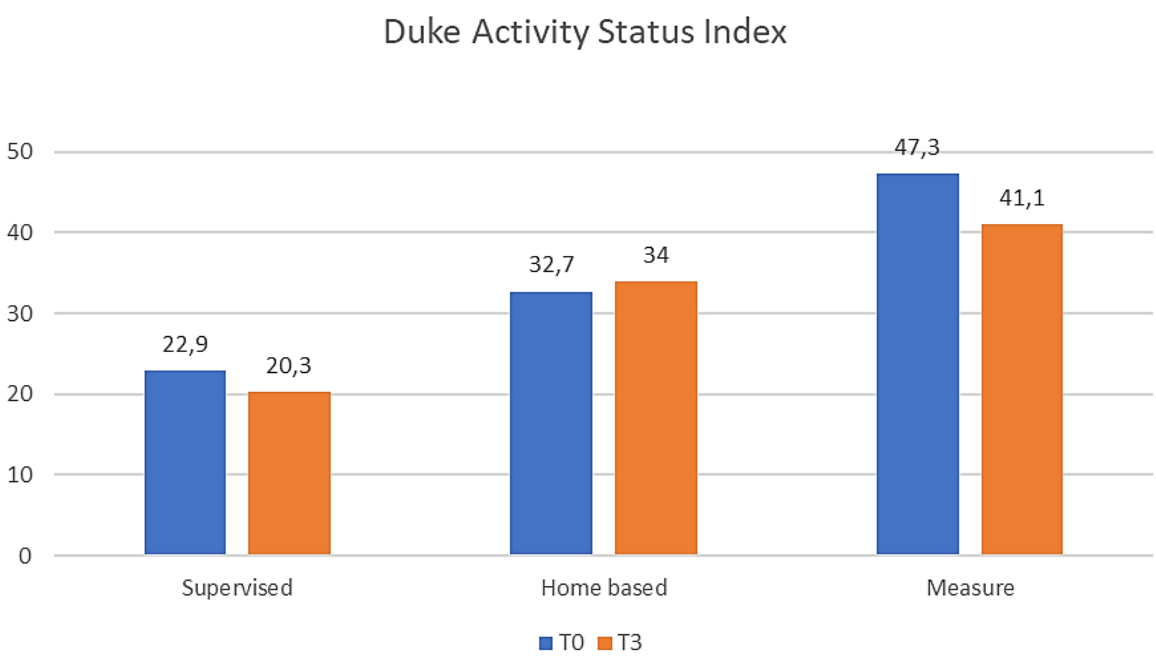


Figure 8. Difference of the variations in the Duke Activity Status Index score between groups



11.4 Program completed: psychological outcomes

The three-month evaluation allowed the effects of the two structured exercise programs, as well as any changes in the measure group, to be assessed on quality of life and depression levels.

Supervised group

In the supervised group all the SF-36 domains exhibited a significant improvement (Table Y), particularly in Physical Function (+7%), Emotional Role (+6%) and Physical Role (+5%).

The supervised group was the only one to show a significant improvement in the BDI score (-1 point).

Home based group

The Home based group also had significant improvements in all domains of the SF-36. The best data were recorded in physical functioning (+4%), physical role (+9%), energy vitality (+17%), social functioning (+4%), bodily pain (+7%), and general health (+6%).

The BDI score was unchanged.

Measure group

The Measure group did not show a significant improvement on the questionnaires administered, in contrast to the two intervention groups.

Between group comparison

Considering the baseline imbalances between group, the appropriate analysis of covariance was conducted.

A significant between group comparison was observed only for the vitality domain of the SF-36 questionnaire ($p = 0.021$), while no other significant differences were observed.

Table 3. Differences in functional parameters between groups

	Supervised (n = 44)			Home based (n = 42)			Measure (n = 17)			ANCOVA p
	T0	*T3*	*Δ*	*T0*	*T3*	*Δ*	*T0*	*T3*	*Δ*	
PF	58 (50 – 67)	65** (57 – 72)	6 (2 – 11)	74 (69 – 79)	78* (73 – 83)	4 (0 – 8)	86 (79 – 93)	89 (83 – 95)	3 (-2 – 9)	0.32
RE	54 (48 – 60)	60* (54 – 66)	6 (0 – 12)	86 (77 – 94)	86 (77 – 94)	0 (-4 – 4)	73 (46 – 99)	82 (59 – 100)	9 (-17 – 35)	0.52
RP	66 (55 – 77)	71 (60 – 80)	5 (-5 – 15)	56 (51 – 61)	65* (61 – 69)	9 (3 – 14)	70 (56 – 84)	68 (53 – 83)	-2 (-10 – 7)	0.043
VT	56 (47 – 67)	58 (47 – 69)	2 (-10 – 15)	64 (54 – 74)	81** (72 – 91)	18 † (9 – 26)	57 (23 – 90)	59 (27 – 91)	2 (-7 – 11)	0.021
EWB	68 (61 – 74)	69 (62 – 75)	1 (-4 – 5)	73 (68 – 77)	75 (71 – 79)	3 (-1 – 6)	78 (62 – 93)	78 (59 – 97)	0 (-6 – 6)	0.57
SF	64 (55 – 72)	67 (60 – 75)	3 (-4 – 11)	74 (67 – 81)	78 (73 – 83)	4 (-1 - 8)	75 (59 – 95)	80 (60 – 100)	5 (-1 – 12)	0.40
BP	68 (58 – 78)	67 (56 – 76)	-1 (-11 – 7)	73 (66 – 79)	80* (75 – 86)	7 (2 – 13)	87 (74 – 100)	83 (64 – 100)	-4 (-22 – 13)	0.07
GH	40 (34 – 46)	43 (36 – 49)	3 (-4 – 10)	46 (41 – 52)	52* (46 – 58)	6 (1 – 11)	51 (32 – 70)	52 (31 – 72)	1 (-5 – 7)	0.12
BDI	11 (9 – 12)	10** (8 – 11)	-1 (-2 - -1)	9 (7 – 11)	9 (7 – 11)	-1 (-2 – 1)	9 (6 – 11)	9 (5 – 11)	0 (-2 – 2)	0.23

* P<0.05

** p<0.01

† different from Measure group

Figure 9. Difference of the variations in the *Physical functioning* domain of the SF-36

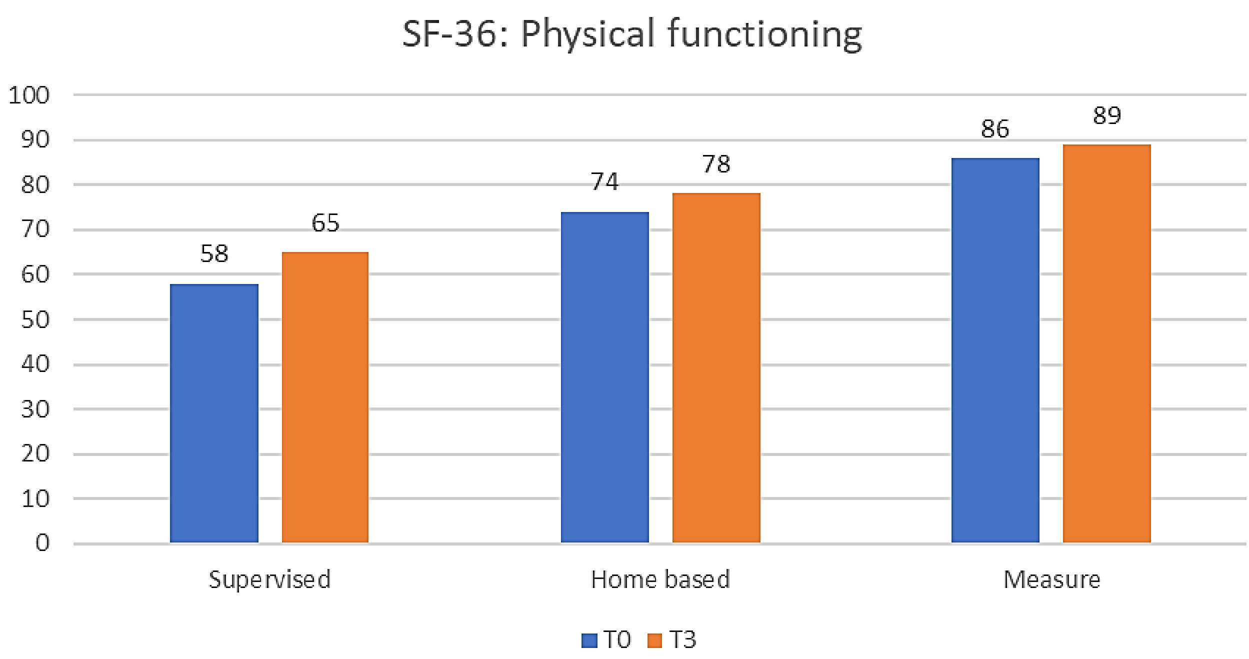


Figure 10. Difference of the variations in the *Role emotional* domain of the SF-36

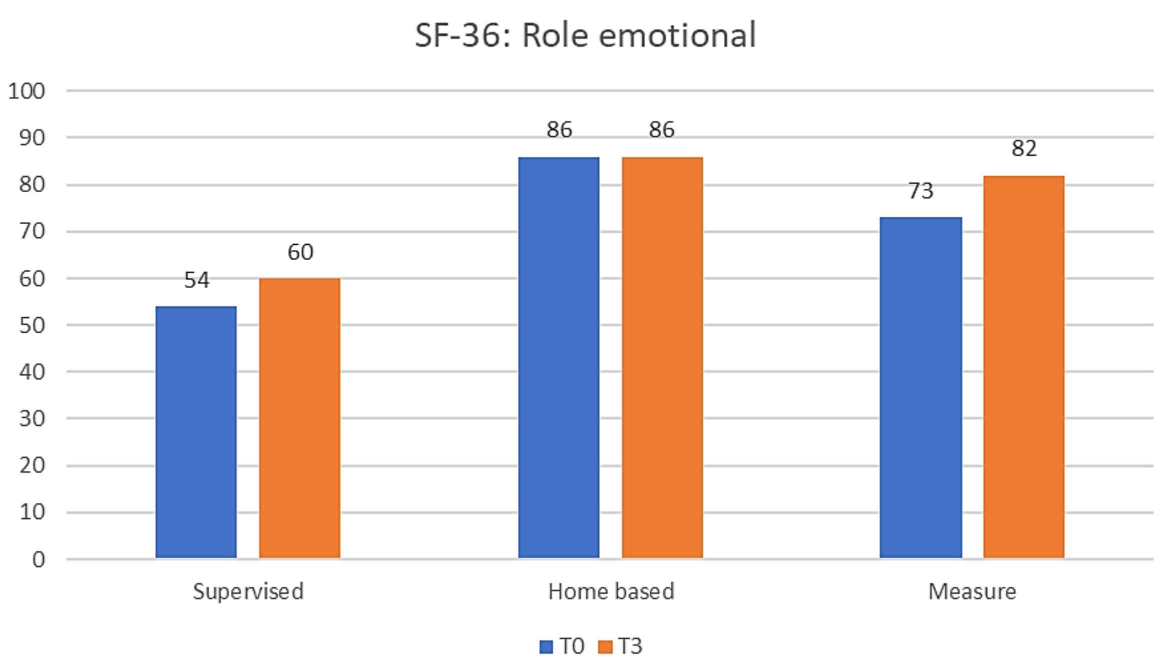


Figure 11. Difference of the variations in the *Role physical* domain of the SF-36

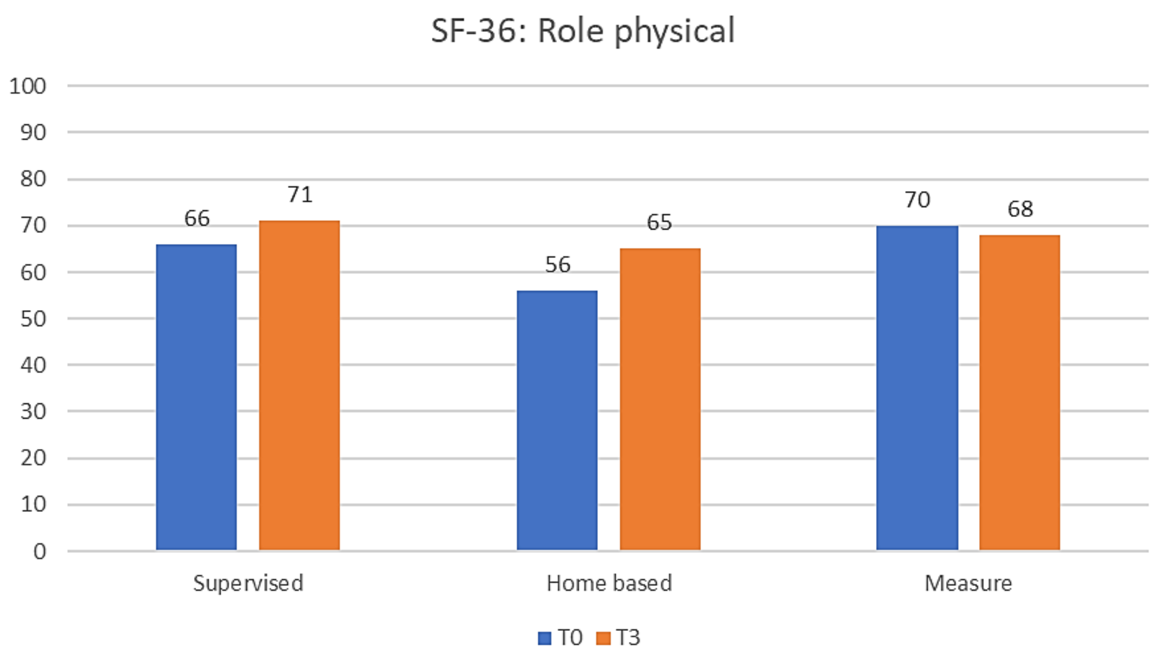


Figure 11. Difference of the variations in the *Energy, vitality* domain of the SF-36

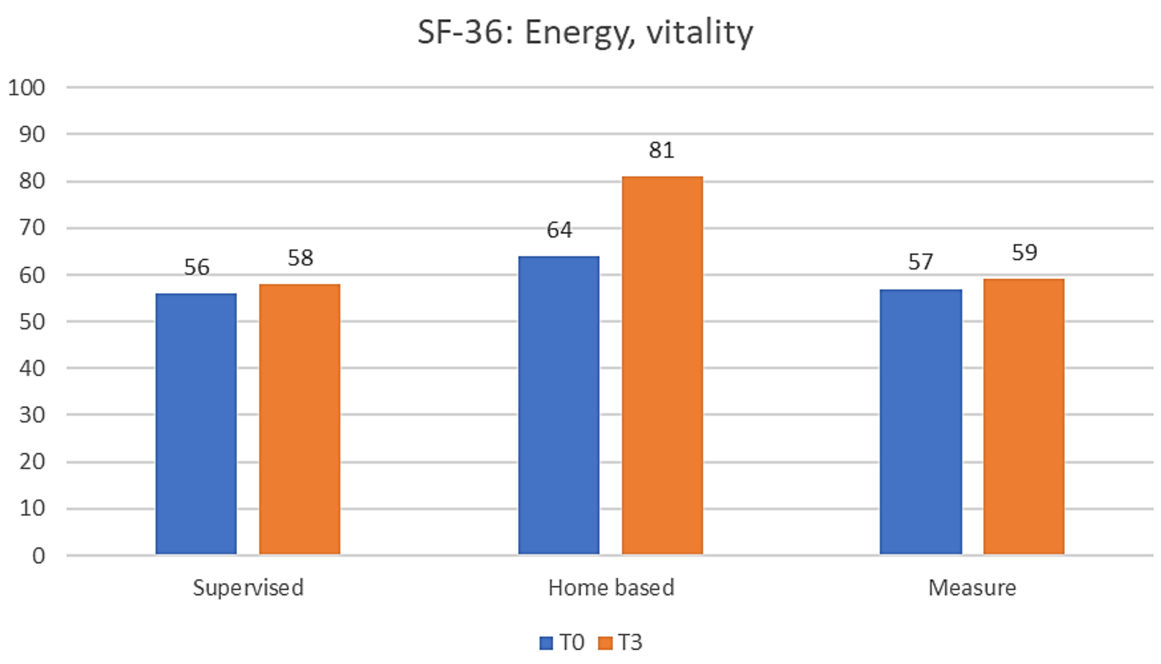


Figure 12. Difference of the variations in the *Emotional well-being* domain of the SF-36

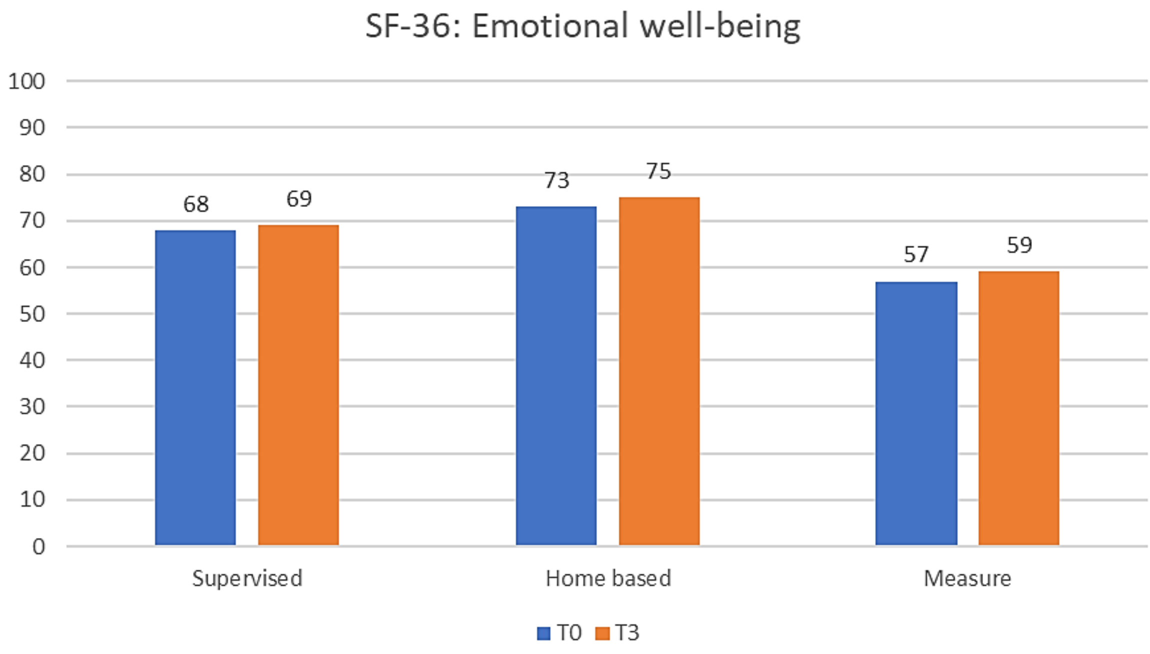


Figure 13. Difference of the variations in the *Social functioning* domain of the SF-36

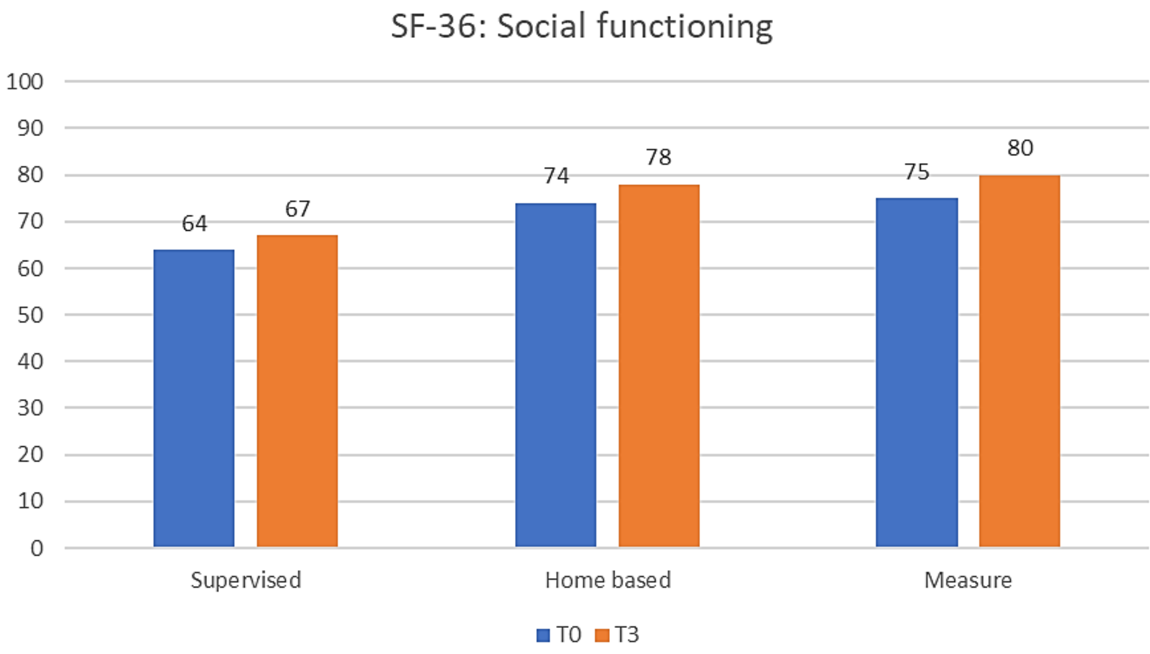


Figure 14. Difference of the variations in the *Bodily pain* domain of the SF-36

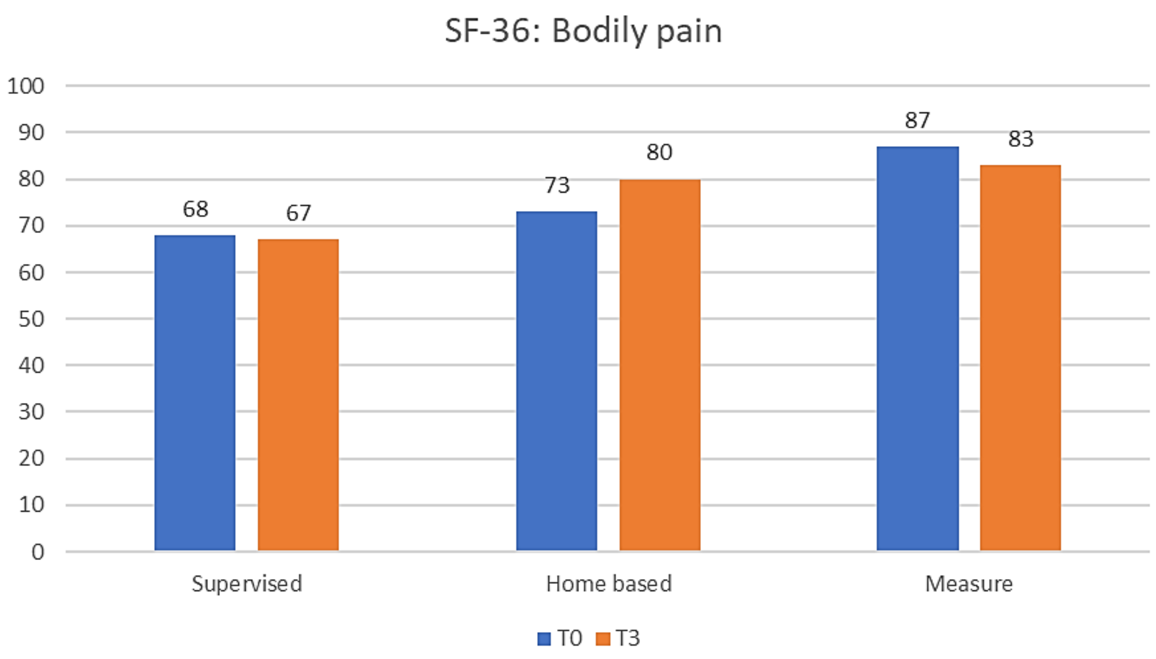


Figure 15. Difference of the variations in the *General health* domain of the SF-36

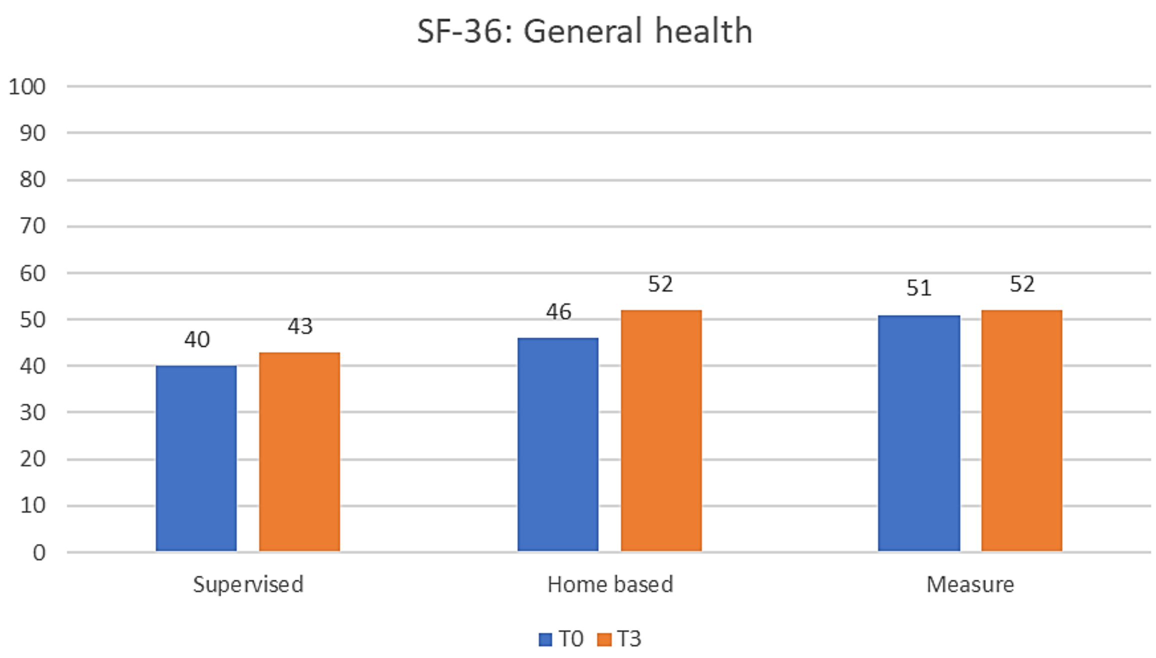
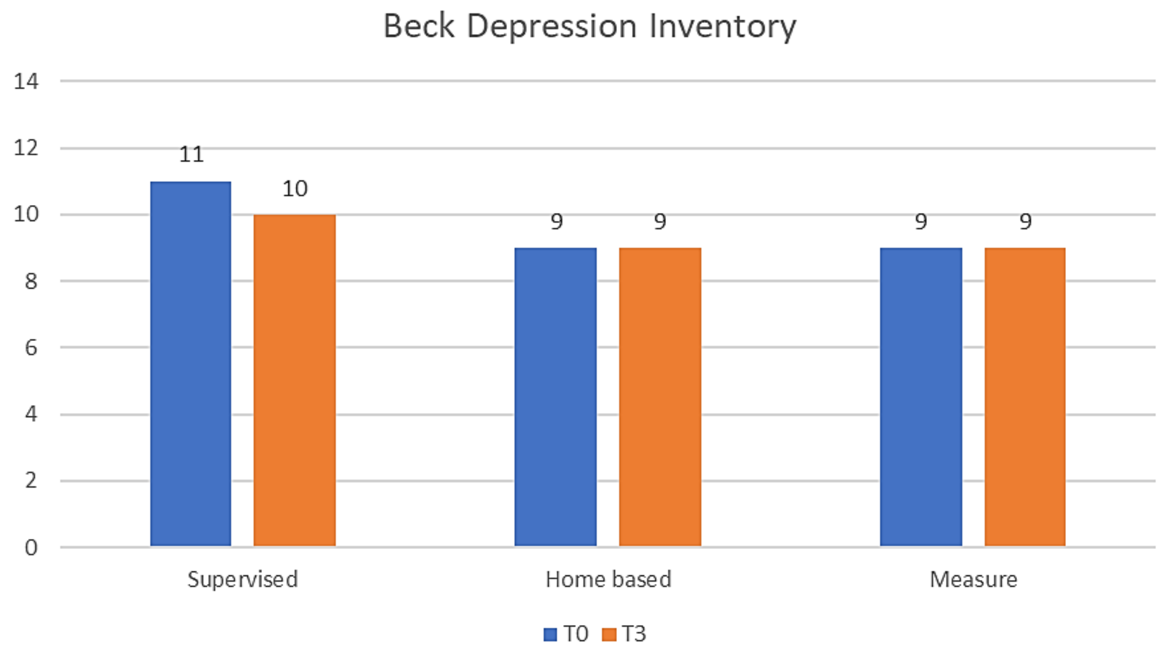


Figure 16. Difference of the variations in the Beck Depression Index score between groups



11.5 Discussion

Incorporating EF into the dialysis centre proved to be an effective intervention, increasing the number of physically active patients, and safe, as no related adverse events were reported during the exercise period. The training proposals proved to be appropriate for the target population, as more than 80% of the participants attended the two scheduled assessments. The dropout rate of 19.9% (due in part to EF's inability to recontact some patients for logistical reasons) is a satisfactory result when compared to other studies in the literature. Patients lost in the other three large-number studies were 23% for Excite [1], 34% for PEDAL [2], and 28% in DiaTT [3], respectively. Therefore, EF's constant presence at the HD centre was effective in keeping patients in the program.

The group-by-group analysis of functional outcomes allowed the effectiveness of the two structured exercise programs to be evaluated compared with those who underwent the assessments alone, which can be considered a control group. In the analysis, it is important to bear in mind that the assignment of subjects to the different programs was not the result of randomization, so that the three groups had significant differences at baseline. Although this may be considered a limitation of the study, it is actually its strength, as allowing patients to choose which program to participate in resulted in a large number of people being recruited.

The supervised program proved effective for the population that chose it (on average, older and frailer), as demonstrated by high adherence (95% of scheduled sessions completed) and improvement in all physical outcomes. Again, this is a higher result than the previously mentioned studies. While Excite [1] still had high adherence (83%), the PEDAL [2] study had only 18% adherence to exercise prescription.

Although there were improvements in all of the skills measured, it is worth noting that the "natural" trend in this type of subject would be a slow decline. Therefore, it can be concluded that an exercise program conducted under the supervision of an EF in the dialysis centre was successful in reversing the decline.

Similar effects were seen in the home-based population, which was generally younger and fitter than the supervised population, but still improved on all measures. Since they were more autonomous subjects, the presence of the EF was particularly useful in providing them with precise guidance on how to train, using training patterns that had been previously tested on dialysis patients. The results in terms of walking autonomy are similar to those reported in the Excite [1] study (6MWD: +38m, compared to +39m of Excite), the exercise model of which was proposed for this group of patients.

In contrast, subjects in the Measure group did not show significant improvement. This was despite being the highest performers at baseline. However, it is possible that the presence of the facilitator during the assessments was an incentive to maintain or increase their level of physical activity. The other studies that did not include the advice of an exercise expert showed a worsening of the outcomes measured in the control group.

The data from the QoL questionnaires showed similar results to the functional tests. The groups that received the structured exercise programs (supervised and home-based) showed improvements in the domains inherent in the physical component of the SF-36, as frequently reported in literature [1,4-6]. No significant differences were observed between the two active groups, calling for a non-superiority of one treatment respect to the other. Interestingly, the SF-36 questionnaire domains related to the mental component, had slight still not significant, favourable variations or showed stable trends. The measure group maintained similar levels between baseline and the second assessment and did not show any significant changes.

Interesting data were observed when analysing the BDI-II scores. This questionnaire was previously validated in dialysis people and it was associated with mortality and morbidity [7]. Considering the reported cutoff score > 17 for the diagnosis of depression in dialysis patients [8], just over 15% of our populations exceeded this value. In our study, a significant reduction in BDI score was observed in Supervised group only. This may be related to the psychological support function of the EF who, in his daily relationship with the patients, was able to help them through the difficult days by adapting the exercise program to their actual abilities, listening to their problems, and using his expertise to give them guidance on how to cope with the daily difficulties inherent in their physical disabilities. In addition, the possibility to perform exercise training in small groups of people, may have favored the social relationships and consequently improved the perceived levels of QoL and depression, as reported in literature. Other few studies reported variations of BDI in the dialysis population after exercise training. A study by Rezaei et al. [9] showed a mean reduction of BDI score of 12 points in a depressed population with ESKD. A recent meta-analysis [10] showed that depressive symptoms in studies using the BDI demonstrated a greater reduction in BDI score with exercise as compared with control (mean difference −7.57; 95% confidence interval, −8.25 to −6.89) in just three studies with an unclear risk of bias. However, in all the analysed studies, the BDI level of dialysis patients was significantly higher than that observed in our study, favouring the positive variations observed.

Finally, the positive variations observed in quality of life and depression indexes at the end of the 3-month program are notable, with a 33% of patients that reached the minimally clinical important difference set at a 17.5% reduction of the baseline score [11]. The intention-to-treat analysis of all the outcomes will confirm the results here reported empowering their statistical power.

References

1. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in Patients on Dialysis: A Multicenter, Randomized Clinical Trial. J Am Soc Nephrol. 2017 Apr;28(4):1259–68.
2. Greenwood SA, Koufaki P, Macdonald JH, Bhandari S, Burton JO, Dasgupta I, et al. Randomized Trial—PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Hemodialysis. Kidney Int Reports [Internet]. 2021;6(8):2159–70. Available from: https://doi.org/10.1016/j.ekir.2021.05.034
3. Anding-Rost K, von Gersdorff G, von Korn P, Ihorst G, Josef A, Kaufmann M, et al. Exercise during Hemodialysis in Patients with Chronic Kidney Failure. NEJM Evid. 2023;2(9).
4. Painter P, Carlson L, Carey S, Paul SM, Myll J. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis [Internet]. 2000 Mar;35(3):482–92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0272638600702022
5. Greenwood SA, Koufaki P, Macdonald JH, Bulley C, Bhandari S, Burton JO, et al. Exercise programme to improve quality of life for patients with end-stage kidney disease receiving haemodialysis: the PEDAL RCT. Health Technol Assess (Rockv) [Internet]. 2021 Jun;25(40):1–52. Available from: https://www.journalslibrary.nihr.ac.uk/hta/hta25400
6. Ghafourifard M, Mehrizade B, Hassankhani H, Heidari M. Hemodialysis patients perceived exercise benefits and barriers: the association with health-related quality of life. BMC Nephrol. 2021;22(1):1–9.
7. Schouten RW, Harmse VJ, Dekker FW, van Ballegooijen W, Siegert CEH, Honig A. Dimensions of Depressive Symptoms and Their Association With Mortality, Hospitalization, and Quality of Life in Dialysis Patients: A Cohort Study. Psychosom Med [Internet]. 2019 Sep;81(7):649–58. Available from: https://journals.lww.com/10.1097/PSY.0000000000000723
8. Preljevic VT, Østhus TBH, Sandvik L, Opjordsmoen S, Nordhus IH, Os I, et al. Screening for anxiety and depression in dialysis patients: Comparison of the Hospital Anxiety and Depression Scale and the Beck Depression Inventory. J Psychosom Res [Internet]. 2012 Aug;73(2):139–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022399912001237

9. Rezaei J, Abdi A, Rezaei M, Heydarnezhadian J, Jalali R. Effect of Regular Exercise Program on Depression in Hemodialysis Patients. Int Sch Res Not [Internet]. 2015 Jan 6;2015:1–6. Available from: https://www.hindawi.com/journals/isrn/2015/182030/
10. Hargrove N, El Tobgy N, Zhou O, Pinder M, Plant B, Askin N, et al. Effect of Aerobic Exercise on Dialysis-Related Symptoms in Individuals Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol [Internet]. 2021 Apr;16(4):560–74. Available from: https://journals.lww.com/10.2215/CJN.15080920
11. Button KS, Kounali D, Thomas L, Wiles NJ, Peters TJ, Welton NJ, et al. Minimal clinically important difference on the Beck Depression Inventory - II according to the patient's perspective. Psychol Med [Internet]. 2015 Nov 13;45(15):3269–79. Available from: https://www.cambridge.org/core/product/identifier/S0033291715001270/type/journal_article

CHAPTER 12

12. BIOPHILIC INTERVENTION IN THE DIALYSIS CENTRE

Complementary interventions to exercise were considered to improve patient well-being, especially during the stay in the health care setting. Because the facilitator's activity took place mainly in the dialysis centre of Cona Hospital in Ferrara, which is the unit where most patients were recruited, we focused on how to improve the intervention there.

12.1 Modification of the indoor environment of the dialysis centre

In assessing how to improve possibly, it was immediately visible, as confirmed by the patients themselves and all HD staff members, that the centre’s indoor environment was uncomfortable and unpleasant. The structure of the dialysis unit provides the first space (a corridor) through which patients enter the unit, which is separate from the room in which the therapy is performed. In the corridor, many patients spend much time before and after dialysis, and this is the same place where the exercises were performed under the supervision of the EF. Since this place is used constantly and patients have stated that it gives them a feeling of discomfort, how to make it more pleasant was investigated.

Figure 1. Corridor of the dialysis centre at Cona Hospital, Ferrara

Figure 2. Corridor of the dialysis centre at Cona Hospital, Ferrara

Because of the limitations imposed by the hospital's internal regulations, several intervention options were evaluated to determine the best option for optimizing the relationship between effectiveness and feasibility. A review by Jamshidi [1] investigated the impact of environmental factors in the hospital setting on patients' perceptions. The authors affirm that the environmental factors that affect patient outcomes are (1) form, (2) unit layout, (3) floor material, (4) room features, (5) medical equipment visibility, (6) nature, (7) lighting, and (8) music. Given the limited possibilities for intervention and the intention to impose non-invasive modifications, nature was identified as the factor with which to intervene. This decision was also based on previous knowledge about the benefits of natural elements to healthcare settings.

The positive effects of the natural environment on people's physical and mental health are recognized [2], and several studies have demonstrated that natural elements are a motivation for people to engage in physical activity [3-5]. It is also recognized that exercise performed in a green environment provides additional benefits [6]. Certainly, it would not be possible to install real plants in the corridor of the dialysis unit because they would not meet the hygienic standards required by a sterile environment. However, Beukeboom et al. [7]

showed that in the hospital setting, viewing artificial natural elements has effects comparable to those of real nature.

Three proposals were developed for the design of the dialysis unit. These were very low-cost ones that would have limited effects, the best possible one that aimed to create the most natural environment without considering any limitations, and an intermediate proposal that sought a balance between effectiveness and feasibility. The three options are described in Table 1.

Table 1. Three proposed changes to the dialysis centre at Cona Hospital, Ferrara

Proposal	Interventions		Benefits	Disadvantages
Low cost	Artificial plants Colorized path on the floor Green panels	  	Cheap interventions. Easy-to-find materials. Sterile, sanitizable material. Does not require complex installations. Minimal maintenance needed.	Poor “nature” effect. Visual-only stimuli. Poor impact on mood. Nonsubstantial changes in environment.
Intermediate	Artificial plants Colorized path on the floor Nature-themed panels on the wall Screen-playing nature-themed videos Fixed training machines Relaxing sounds	     	Affordable costs. Easy-to-find materials. Sterile, sanitizable materials. Do not require extensive modifications. Effects proven in previous trials. Visual, auditory, and tactile stimuli. Opportunity to exercise in the natural environment. Minimal maintenance is needed.	Artificial nature, not real. No possibility of direct interaction with natural elements. No olfactory stimulus was provided.
Best possible	Real plants Greenhouse managed by patients Green installations (nature in the box) Nature-themed exercise machines Natural scents Relaxing sounds	     	Real natural elements. Direct interaction with nature. Opportunity to exercise in a natural environment Exercise exploiting natural materials. Visual, auditory, tactile, olfactory stimuli. Possible to engage patients in nature-based activities. Effects proven in previous trials.	High costs. Nonsterile materials, impossible to sanitize. Maintenance of green areas is expensive and requires dedicated staff. Requires structural modification.

Once structured, the three proposals were submitted to the unit Head, who could choose the best one in terms of feasibility and effectiveness and make suggestions for improving the project. Of the three projects, the most successful was the *intermediate* one because of the potential benefits achievable at a low cost. For several reasons, the Head asked that some planned elements (the artificial plants, the colorized path on the floor, and the training machines) not be included in the final project design.

The *low-cost* proposal was rejected because the effect achieved was considered insufficient to meet the demand. In contrast, the *best possible* proposal aroused great interest because the effect achieved would certainly be impactful. However, hygienic regulations prohibited the inclusion of some planned elements (real plants), while other installations were judged unfeasible despite their evident potential (greenhouse managed by patients).

Therefore, the installation of panels depicting natural motifs and the placement of artificial "green walls" that could also provide patients with a tactile stimulus could be effective ways to recreate a more pleasant environment.

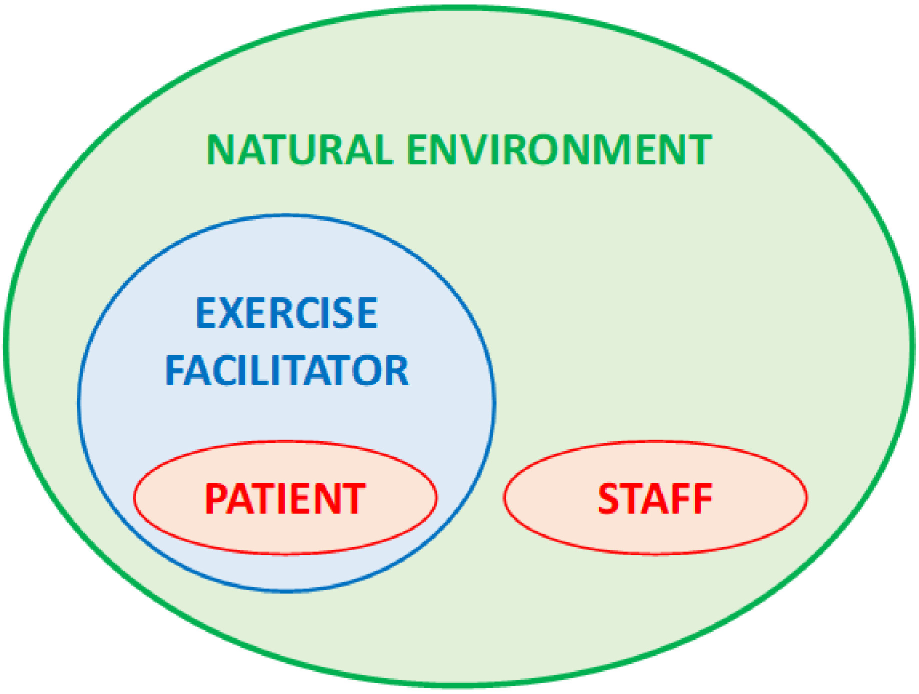
Figure 3. Proposed redesign of the dialysis centre corridor

In addition to visual and tactile stimuli, appropriate sound stimuli could further enhance positive feelings. Studies have shown that listening to natural sounds in the hospital environment can reduce anxiety and pain perceived by patients [8,9]. To add this component, a screen was planned to be placed in the waiting area within one of the green panels, on which videos of natural environments are projected, and the sounds are broadcast into the corridor.

Figure 4. Proposed redesign of the dialysis centre corridor

In the modified environment, upon entering the dialysis unit, the patient would immediately be welcomed into a place with elements reminiscent of nature. He/she might decide to wait for the therapy to begin by sitting in the waiting area, relaxing in a comfortable environment, and being surrounded by the sounds of nature, with the opportunity to watch images and videos. The green corridor would accompany patients to the locker room, from which they would then access the therapy and equally guide them to the centre's exit. This would keep them in contact with a pleasant environment both before and after dialysis to reduce its negative impact on mood. This would ensure benefits for all patients entering the centre and the caregivers waiting for them at the end of dialysis. For people who choose to exercise together with EF in the dialysis unit, the benefits will be even greater because of the already described exercise-environment synergy that provides greater effects than that of the two separate components.
In addition to patients, dialysis centre staff could also benefit from the proposed redesign. Both nephrologists and nurses experience greater levels of stress than colleagues working in other departments [10,11]. This is due to the frequent loss of patients typical of dialysis units, the complexity of treatments, and the need to interact with constantly evolving technologies. In the specific case of Cona Hospital, staff complained that the dialysis environment itself contributes to the perceived level of discomfort. An aseptic, impersonal environment lacking decorative elements does not help the staff's mood while conducting activities. Because previous studies have shown that interactions with natural environments reduce stress levels [12], we believe that staff members could also enjoy the benefits of renewing the setting.

Figure 5. Graphic conceptualization of the proposed intervention



12.2 Modification of the hospital's outdoor environment

In addition to the modification of the indoor environment, the design of some interventions in the space outside the hospital, near the exit from the dialysis unit, is also in the beginning phase.

Figure 6. Space outside the dialysis centre at Cona Hospital, Ferrara.

Figure 7. Space outside the dialysis centre at Cona Hospital, Ferrara.

The concept is to create an outdoor corner where patients and staff members can take a seat, which is organized by exploiting elements similar to those that will enrich the interior of the centre itself. This would create continuity between the two spaces (indoor and outdoor) that would welcome the patient even before he/she enters the hospital, guide him/her to the care room, and then accompany him/her again on the return drive.

12.2.1 Vertical gardens

Installing a "vertical garden" on one of the hospital's walls was one of the options considered. A vertical garden (or green wall) is a technique developed by the French botanist Patrick Blanc, which he has used to beautify buildings worldwide [13]. The system can be implemented in both internal and external environments. The system consists of three layers: a PVC layer, a felt layer, and a metal mesh. It is a self-supporting system that can be suspended in air without the need for a foundation. The advantages of a vertical garden are numerous: it enhances air quality, decreases energy consumption, acts as a natural sound barrier, and is aesthetically pleasing.

Figure 8. One of the living walls of the Quai Branly Museum

Figure 9. Caixaforum Madrid vertical garden

Although this intervention has potential, it cannot be implemented due to current conditions. Therefore, an alternative solution had to be sought.

12.2.2 Proposed modification of the external environment

To fulfil the Head's requests, we attempted to create a proposal that requires only minor interventions. The project included drawing a line along the outside wall to guide people to a reserved corner. This would allow the use of a currently disused area where it would be possible to relax while maintaining privacy.

Figure 10. Redesign project of the space outside the dialysis centre at Cona Hospital, Ferrara.

This corner was reorganized by inserting plants to decorate the area and installing panels along the exterior walls that again recalled natural elements. Comfortable benches would be placed here, on which patients could sit while waiting to begin therapy or at the end before returning to their homes.

Figure 9. Redesign project of the space outside the dialysis centre at Cona Hospital, Ferrara.

12.3 Discussion

To develop a multidisciplinary intervention aimed at improving the well-being of patients who frequently visit dialysis unit, it was decided, after analysing various possibilities, to explore the application of biophilic interventions. This choice was motivated by the search for an approach that would complement the intervention based on the involvement of the exercise facilitator in the centre itself to improve the functional capacity of the patients. This reason, supported by the fact that the indoor environment had been described by patients and staff as "depressing" and "giving off bad vibes", led to an attempt to develop a redesign of the dialysis unit that would be both effective and feasible, as requested by the Head.
The effects of natural elements in the hospital environment on the well-being of patients and staff are well documented in the literature and have been applied in various forms with similar results. To meet the director's needs and not know exactly how far he could go in altering the dialysis centre environment, we structured three different intervention options. Starting with a low-cost proposal, passing through an intermediate one, and arriving at the best possible position, the dialysis unit corridor where the EF supervised patient exercise was assumed to be remodelled. The goal was to create a more pleasant environment that would evoke positive feelings in patients waiting for treatment and staff walking through it. In addition, the natural environment constitutes a booster that can enhance the beneficial effects of exercise on physical and mental health.

Of the three proposals, the intermediate option was chosen. The project, which is currently under consideration by the hospital's appropriate offices, includes the installation of panels with natural patterns along the corridor walls, a green wall, and a screen that will project videos and natural sounds. With these modifications, the patient would receive visual, auditory, and potentially tactile stimuli that could significantly improve the quality of time spent in the dialysis centre.
Since the entrance to the dialysis unit is very close to the hospital entrance, the possibility of intervening in the external environment was also investigated. The concept was to create an outdoor space that welcomes patients even before they enter the dialysis unit and is reminiscent of the natural elements inside. Creating continuity between the outside and the inside would be a kind of "accompaniment" for patients, who would be guided by a pleasant and uniform environment on their way to the place of care and on their return to the vehicle that would take them home.
Several possibilities for the exterior design were also explored. The one that was deemed most feasible was the redevelopment of a space adjacent to the currently unused hospital entrance, creating a secluded corner where patients could relax, beautified with the installation of natural elements. This project will be presented to the head later. Once the interior design is completed.

12.4 Limitations and perspectives

The hospital environment has several limitations in regard to incorporating natural elements. In particular, dialysis units have more stringent regulations than other departments because vascular access for patients requires particularly rigorous hygiene standards. This is the reason why the therapy room could not be part of the intervention.
In the search for the best possible interventions, the option of installing green walls with real plants inside the corridor was considered but was rejected by management due to the aforementioned hygiene regulations. However, a review of the literature has provided reassuring evidence that viewing real and reproduced nature has similar psychophysical effects on people [7]. Therefore, to structure an effective (and not just aesthetic) intervention, it was felt that the placement of nonreal elements would still have the desired effect.
The redesign project was later extended to the exterior. At present, no structural intervention is conceivable that would significantly alter the appearance of the hospital. Therefore, it was decided to propose a small, low-cost intervention for the recovery of a currently unused area

that could still be useful for patients. In the future, it is conceivable that a more significant intervention could be undertaken that would significantly reshape the exterior of the structure. The installation of a vertical garden, using the technique developed by the botanist Patrick Blanc [13], would be a significant intervention that would improve the appearance of the building. These installations have been successfully implemented in various hospital facilities around the world (Hospital Quirón Sagrado Corazón in Sevilla, Khoo Teck Puat Hospital in Singapore, etc.). As elevated concentrations of microorganisms in the air, on the plant wall, and in the water increase the risk of infection within the structures [14], the installation of an outdoor vertical garden could prove to be an effective intervention with a lower risk.

References

1. Jamshidi S, Parker JS, Hashemi S. The effects of environmental factors on the patient outcomes in hospital environments: A review of literature. Front Archit Res [Internet]. 2020;9(2):249–63. Available from: https://doi.org/10.1016/j.foar.2019.10.001
2. Jimenez MP, Deville N V., Elliott EG, Schiff JE, Wilt GE, Hart JE, et al. Associations between nature exposure and health: A review of the evidence. Int J Environ Res Public Health. 2021;18(9).
3. Repke MA, Berry MS, Conway LG, Metcalf A, Hensen RM, Phelan C. How does nature exposure make people healthier?: Evidence for the role of impulsivity and expanded space perception. PLoS One. 2018;13(8):1–20.
4. Keskinen KE, Rantakokko M, Suomi K, Rantanen T, Portegijs E. Nature as a facilitator for physical activity: Defining relationships between the objective and perceived environment and physical activity among community-dwelling older people. Heal Place [Internet]. 2018;49(January):111–9. Available from: https://doi.org/10.1016/j.healthplace.2017.12.003
5. McGinn AP, Evenson KR, Herring AH, Huston SL. The relationship between leisure, walking, and transportation activity with the natural environment. Heal Place. 2007;13(3):588–602.
6. Piva G, Caruso L, Gómez AC, Calzolari M, Visintin EP, Davoli P, et al. Effects of forest walking on physical and mental health in elderly populations: a systematic review. Rev Environ Health. 2022;1–16.
7. Beukeboom CJ, Langeveld D, Tanja-Dijkstra K. Stress-reducing effects of real and artificial nature in a hospital waiting room. J Altern Complement Med. 2012;18(4):329–33.
8. Amiri MJ, Sadeghi T, Negahban Bonabi T. The effect of natural sounds on the anxiety of patients undergoing coronary artery bypass graft surgery. Perioper Med. 2017;6(1):1–6.
9. Saadatmand V, Rejeh N, Heravi-Karimooi M, Tadrisi SD, Vaismoradi M, Jordan S. Effects of Natural Sounds on Pain: A Randomized Controlled Trial with Patients Receiving Mechanical Ventilation Support. Pain Manag Nurs [Internet]. 2015;16(4):483–92. Available from: http://dx.doi.org/10.1016/j.pmn.2014.09.006
10. Pawłowicz E, Nowicki M. Burnout syndrome among nephrologists- A burning issue-results of the countrywide survey by the Polish Society of Nephrology. BMC Nephrol. 2020;21(1):1–9.

11. Kersten M, Vincent-höper S, Nienhaus A. Stress of Dialysis Nurses — Analyzing the Bu ff ering Role of Influence at Work and Feedback. :10–3.

12. Daniels S, Clemente DBP, Desart S, Saenen N, Sleurs H, Nawrot TS, et al. Introducing nature at the work floor: A nature-based intervention to reduce stress and improve cognitive performance. Int J Hyg Environ Health [Internet]. 2022;240(November 2021):113884. Available from: https://doi.org/10.1016/j.ijheh.2021.113884

13. Blanc P. Le mur végétal: de la nature à la ville. Michel Lafon; 2008.

14. Surial B, Vázquez M, Steiger W, Rolli E, Brand S, Mühlethaler K, et al. Assessing the infection risk of a vertical garden in a hospital setting. Infect Control Hosp Epidemiol. 2022;43(2):273–5.

13. PRACTICAL APPLICATIONS AND FUTURE RESEARCH DIRECTIONS

This PhD project investigated which forms of exercise are preferred by people with HD, and the different levels of effectiveness of these types of exercise on functional capacity and quality of life. The study design (pragmatic, non-randomised) allowed for the identification of patient preferences and encouraged participation in the study. However, the opportunity to choose meant that participants were 'stratified' according to their different characteristics, particularly age and functional capacity. In order to establish the effectiveness of the exercise programmes tested in this project, it would be helpful if randomised trials could be conducted to test the differences between exercise and control groups with homogeneous characteristics.

At the same time, the 'natural' redesign of the dialysis unit represents a novelty that should be further explored and possibly implemented. Once the practical implementation of the project will be completed, it will be important to measure the effects of the new environment on the mental health of patients and dialysis staff. If its efficacy would be confirmed, it would represent another non-pharmacological intervention in the management of this type of patient.

14. CONCLUSION

This PhD project evaluated the effectiveness of implementing a multidisciplinary intervention model to improve the psychological and physical well-being of people in the dialysis centre. Research should focus on this population, which requires specific interventions that meet the needs of patients, which often vary from individual to individual. For this reason, a pragmatic, non-randomized study based on physical exercise was designed, in which the patients themselves chose the exercise program best suited to them, after listening to the advice of the exercise facilitator. This aspect was crucial to the success of the study, as it encouraged patient participation and maintained a high level of adherence to the prescribed programs.

The multidisciplinary approach was based on the figure of the EF, who served not only as an exercise prescriber and trainer but also as a key figure in helping patients overcome the barriers to exercise commonly described in these patients. His involvement has been essential in introducing patients to forms of exercise appropriate to their abilities, and in helping those with whom he was in constant contact to overcome daily difficulties that limit their ability to exercise. This was confirmed by the results of the physical tests and psychosocial questionnaires administered to the participants, which showed improvement in the patients who had chosen the structured programs, while those who had only taken the control assessments showed a stable condition.

In parallel with the implementation of the exercise trial, the dialysis centre environment itself was identified as a potential area for improvement in the search for complementary interventions that could enhance its impact. The influence of the environment on people's mood is well documented in the literature, and because of the nature of the care, patients spend much more time in the dialysis unit than other people. After evaluating several alternatives, it was determined that modifying the indoor environment of the dialysis centre by incorporating natural elements would be effective in improving the patient and staff experience. A project was then carried out, the feasibility of which is being evaluated by management. Once accomplished, the next step could be to expand the redesign to the hospital's outdoor environment.

Facilitator activities in a "green" dialysis unit could be even more effective in improving the mood and quality of life in the dialysis centre for patients and medical and nursing staff.