kidney and dialysis

Review

Next Steps for Intradialytic Cycling Research

Alexis C. King [1] and Kenneth R. Wilund [1,2,*]

[1] Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA; acking2@illinois.edu
[2] Division of Nutritional Sciences, University of Illinois at Urbana-Champaign, Urbana, IL 61801, USA
* Correspondence: kwilund@illinois.edu

Abstract: Hemodialysis patients typically have extremely low physical activity levels, which contributes to poor physical function and quality of life (QOL). Numerous studies show that exercise, intradialytic cycling in particular, may improve physical and cardiovascular function and QOL. But there are also significant inconsistencies in the literature, and the benefits in many studies are modest. This may be due in part to methodological limitations in intradialytic cycling trials, including small sample sizes, short interventions, low volume, and intensity of exercise prescriptions, and/or low retention and protocol adherence rates. The goal of this review is twofold. First, we summarize the current literature on intradialytic cycling in HD patients, highlighting benefits and concerns noted in several recently published trials that were among the most robust and clinically relevant trials conducted to date. Second, we will consider strategies for moving forward with exercise and physical activity interventions in HD, including promoting intradialytic cycling as a core component of a more patient-centric and comprehensive strategy that helps progress patients towards standard physical activity guidelines. We urge researchers and exercise professionals to consider intradialytic cycling as a valuable component of a comprehensive patient-centered, lifestyle intervention, as opposed to a stand-alone exercise prescription.

Keywords: hemodialysis; physical activity; exercise

check for updates

Citation: King, A.C.; Wilund, K.R. Next Steps for Intradialytic Cycling Research. *Kidney Dial.* **2022**, *2*, 287–295. https://doi.org/10.3390/kidneydial2020027

Academic Editors: Roman-Ulrich Müller, Sharlene A. Greenwood, Ellen M. Castle and Vladimir Tesar

Received: 22 March 2022
Accepted: 10 May 2022
Published: 2 June 2022

1. Introduction

Individuals with end stage kidney disease (ESKD) receiving maintenance hemodialysis (HD) have very low physical activity levels and poor physical function, and this contributes to a poor quality of life (QOL) and premature mortality [1]. For several decades, clinicians and researchers globally have attempted to combat this problem by prescribing different types of exercise programs for HD patients, most typically in the form of intradialytic cycling, as part of the standard of care [2,3]. Though intradialytic resistance training, at-home walking programs, and other forms of exercise have also been prescribed [4], intradialytic cycling is often considered to be the most time efficient and popular form of exercise to implement for HD patients [5]. Intradialytic cycling has been shown to improve maximal oxygen consumption, blood pressure control, physical, cardiovascular, and cognitive function, dialysis efficiency, quality of life, and other important outcomes [6–9] but it is important to recognize that there are also several caveats in the intradialytic cycling literature. First, the benefits in many studies are modest or inconsistent, and many have significant limitations such as small sample sizes, short interventions, low volumes, and intensities of exercise, and/or low retention and protocol adherence rates that make the data difficult to interpret [10–14]. Moreover, there are many barriers to implementing intradialytic exercise programs [15,16], so implementation in HD clinics remains low worldwide [15,17]. As a result, sedentary behavior and poor physical function continue to be hallmarks of the disease. This suggests that standard approaches to exercise in HD, particularly intradialytic cycling, needs to be re-evaluated.

The goal of this review is twofold. First, we will summarize the current literature on exercise in HD patients, with a specific focus on benefits and concerns noted in several recently published intradialytic cycling trials that were among the largest and longest conducted to date. Second, we will consider strategies for moving forward with physical activity and exercise interventions in HD, including promoting approaches that include intradialytic cycling as a core component of a more patient-centric and comprehensive strategy that helps progress patients towards standard physical activity guidelines.

2. Recent Advances in Intradialytic Cycling Research

In recent years, several studies have been published that have addressed some of the limitations in previous intradialytic cycling trials. This includes several randomized control trials (RCTs) with more robust sample sizes (n = 70 to 335) and longer intervention durations (6 to 12 months) than most prior trials [10,18–22]. While there were clear methodological differences between these studies, each included an intradialytic cycling group that exercised 3 days/week at a moderate intensity supervised by research staff [10,18–22]. Unfortunately, none of these 4 trials were able to demonstrate statistically significant improvements in either physical function or quality of life in the intradialytic cycling group compared to controls. While there were trends for improvements in the intradialytic cycling groups in each of these studies, particularly for physical function, this data suggests that standard intradialytic cycling protocols may yield only modest benefits for many patients. This may be due in part to the low volume and intensity of exercise, as evidenced by calculated energy expenditures of <75 kcal for typical intradialytic cycling sessions [8]. Other reasons for these disappointing results include low adherence and compliance with the exercise protocols, as well as low retention/high dropout rates.

Despite these negative results, there are also some reasons for optimism regarding intradialytic cycling, particularly related to its positive effects on cardiovascular structure and function seen in a few recent studies [19,21,22]. For example, the primary finding in the CYCLE trial [19] was that 6 months of intradialytic cycling significantly reduced left ventricular mass, despite failing to improve physical function or quality of life (secondary outcomes) [19]. And in contrast to the studies by Koh et al. and Jeong et al. [10,18], the CYCLE trial also found significant reductions in arterial stiffness in their intradialytic cycling group. A primary difference in the CYCLE study was that magnetic resonance imaging (MRI) was used to measure changes in these cardiovascular parameters, as opposed to ultrasound and arterial tonometry, which has typically been used to measure changes in cardiovascular structure and function in most previous intradialytic cycling studies. Another novel cardiovascular benefit from intradialytic cycling seen in recent studies is a reduction in myocardial stunning, which is a frequent problem during hemodialysis [21,22]. It is caused in part by ultrafiltration-induced intradialytic hypotension, which causes ischemia and cardiac dysfunction [21,22]. Two recent pilot studies demonstrated that a single bout of intradialytic cycling significantly reduced intradialytic myocardial stunning, particularly toward the end of the treatment [21,22]. These preliminary findings have the potential to be highly clinically significant if replicated in robust intervention trials. It should also be noted that intradialytic cycling has been demonstrated to be very safe. While some guidelines have suggested special contraindications to exercise for dialysis patients, including electrolyte abnormalities, excessive interdialytic weight gain, lung congestion, peripheral edema and others [23], these concerns appear to be hypothetical, as there is very little evidence of adverse events from intradialytic exercise in published clinical trials. This suggests that intradialytic cycling is safe and should be promoted in all clinics where possible [24–27].

In summary, while there are many potential benefits of intradialytic cycling, several of the most robust interventions published to date have failed to significantly improve physical function, strength, physical activity levels, and QOL in HD patients [19,21,22]. This is likely contributing to the poor implementation of exercise programs in HD clinics. Another barrier to implementation is that most clinics are unable to employ exercise professionals to run a program, while clinic staff and nephrologists have limited training relative to exercise prescription [28]. Exercise and physical activity guidelines for HD patients are also unclear on specifics of frequency, intensity, type and timing or the focus on endurance, resistance, balance, and flexibility training in this population [29]. Perhaps because of these concerns, the US Kidney Disease Outcomes Quality Initiative (K/DOQI) removed its exercise recommendations in 2015 as part of their clinical practice guidelines for HD [30]. Without policy change or guidelines to support change, the implementation of exercise programs in HD clinics will remain low, and physical activity levels in HD patients will remain poor. It is important that we consider new approaches to implementing exercise in HD patients, given that the decades-long experience with using intradialytic cycling as the cornerstone of exercise programs has not provided more robust outcomes, as displayed in Table 1.

Table 1. Types of exercise interventions implemented in hemodialysis patients.

Exercise Mode	Selected Citations	Comment
Intradialytic Cycling	Goldberg, et al. (1986) [6] Painter, et al. (1986) [7] Moore, et al. (1998) [31] Kopple, et al. (2007) [14] Toussaint, et al. (2008) [32] Bohm, et al. (2014) [33] Jeong, et al. (2018) [34] McGuire, et al. (2019) [22] Penny, et al. (2019) [21] Graham-Brown, et al. (2019) [19] Greenwood, et al. (2021) [20]	Intradialytic cycling has been predominant form of exercise in HD patients worldwide since 1980′s. While many studies have demonstrated modest benefits in a variety of health-related outcomes, the benefits have often been modest or inconsistent.
Intradialytic Resistance Training	Cheema, et al. (2007) PEAK 1 & 2 [35] Kopple, et al. (2007) [14] Johansen, et al. (2009) [1] Chen, et al. (2010) [36] Kirkman, et al. (2014) [37]	Consistent improvements in strength; marginal/inconsistent benefits in physical function and body composition
Intradialytic Cycling + Resistance Training	Anding, et al. (2015) [38] Thompson, et al. (2016) [39]	Modest benefits, concerns with adherence/feasibility
Intradialytic Cycling + Nutrition Support	Prado, et al. (2007) [40] Hristea, et al. (2016) [41] Martin-Alemany, et al. (2016) [42] Jeong, et al. (2019) [18]	Exercise with concomitant nutrition support does not appear to have have additive benefits
Intradialytic Resistance Training + Nutrition Support	Dong, et al. (2011) [43] Molsted, et al. (2013) [44]	Modest additive benefits
Home Walking Programs	Koh, et al. (2010) [10] Manfredini, et al. (2017) [45] Baggatta, et al. (2018) [46]	Low intensity led to modest physical function improvements
Home Resistance Training	Headley, et al. (2002) [11]	Modest physical function benefits
Pedometers/Accelerometers	Gomes, et al. (2015) [47] Kittiskulnam, et al. (2019) [48]	Highlights the sedentary behaviors and PA levels within HD patients
Other (Activities of Daily Living, Laughter Yoga, Zumba, VR/Gaming)	Tawney, et al. (2000) * [49] Bennett, et al. (2012) [50] Bennet, et al. (2015) [51] Segura-Orti, et al. (2019) [52]	Small trials, modest benefits, likely difficult to implement

* This table provides examples of different types of interventions that have been implemented in HD population. Most show modest benefits, but there are limitations with each, and with few exceptions (Tawney, et al.) [49], almost none provide patients autonomy to choose their preferred type of activity.

3. The Future of Intradialytic Cycling

While intradialytic cycling has some obvious limitations, there is overwhelming evidence that it is safe, and it is still viewed as the most practical to administer and monitor compared to other types of exercise. As a result, it is likely to remain a significant component of future exercise programs for HD patients. So, the question remains: what can we do to address the primary concerns and limitations with intradialytic cycling, as well as improve implementation? Two needs are apparent: (1) more research is still needed to improve the evidence base regarding the efficacy of intradialytic exercise; and (2) the role of intradialytic cycling as a stand-alone intervention needs to be re-evaluated. Instead, intradialytic cycling should be considered a valuable *component* of a more comprehensive, patient-centered approach to increasing physical activity in HD patients. These issues are considered more thoroughly below.

In terms of research, more is needed to address gaps in the literature with intradialytic cycling. This includes a more thorough evaluation of its cardiovascular benefits, especially related to myocardial stunning. To date, the only studies to investigate this were two pilot studies demonstrating that a single bout of intradialytic cycling reduced myocardial stunning compared to a dialysis session without exercise [21,22]. Additional studies are needed to determine if sustained intradialytic cycling programs produce even greater reductions in myocardial stunning or other cardiovascular benefits. We must also improve our understanding of how the *timing* of intradialytic cycling (e.g., exercise during the 1st vs. 3rd or 4th hour of dialysis) affects its safety and efficacy. Only a few studies have examined this question, including two small pilot studies [31,34]. In the study by Moore, et al., exercise in the 3rd hour of dialysis caused intradialytic hypotension (IDH) but there were several important limitations in this study, including a small sample size ($n = 8$), and over half of the patients enrolled had high ultrafiltration rates which may have attributed to the hemodynamic instability during the third hour of cycling [31]. By contrast, Jeong, et al. showed that cycling during the 3rd hour of dialysis did not increase the risk of IDH or other intradialytic symptoms compared to cycling in the 1st hour [34]. This is an important finding that deserves further scrutiny, as exercise in the 3rd or 4th hour of dialysis is often contraindicated due to concerns with hemodynamic instability, cramping, and other symptoms [23]. Given how challenging it can be for patients to adhere to intradialytic cycling programs, this restriction may be serving as an unnecessary barrier to exercise for some patients.

There also needs to be more research examining the impact of intradialytic cycling on patient-related outcomes (PROs). To date, few studies have addressed this issue, but a recent review by Hargrove, et al. demonstrated intradialytic cycling improved PROs symptoms related to muscle cramping, fatigue, and restless leg syndrome [53]. One concern is that the assessment tools for measuring PROs are limited, so further development of these tools will be important [54].

There is also limited research evaluating the impact of intradialytic cycling on hard outcomes (e.g., hospitalization, mortality) and the cost-effectiveness of exercise programs, though a few recent studies have begun to examine these issues. For example, a secondary analysis of the CYCLE study showed there was a reduction in health care utilization costs in patients enrolled in an intradialytic cycling program compared to non-exercising controls, indicating the approach is potentially cost-effective [19]. However, more research is needed to demonstrate that intradialytic cycling, or any exercise program in general, can improve hard-outcomes and/or is cost-effective for dialysis patients.

4. Moving beyond the Bike

In our opinion, a second critical need is that researchers and clinicians need to stop relying on intradialytic cycling as a stand-alone exercise intervention. Intradialytic cycling programs have been around for more than 40 years. If they were going to work, we would have robust research evidence by now demonstrating feasibility and efficacy. Despite a few promising programs around the world [55] widespread implementation is lacking [8].

Instead, we believe intradialytic cycling should be considered a valuable component of a more comprehensive physical activity program for HD patients. Programs need to be developed that provide patients the autonomy to choose the types of activities they can engage in, instead of specific activities like intradialytic cycling being mandated. In addition, the volume and intensity of the activities should attempt to progress patients towards the standard physical activity guidelines, as appropriate for the individual. There are hypothetical advantages and limitations related to both intradialytic cycling as well as more personalized approaches to exercise prescription. We have described some of these in Table 2.

Table 2. Advantages and limitations of Intradialytic Exercise vs the proposed "Patient-Centered" approach to exercise.

Exercise Method	Advantages	Limitations
Standard Approach: Intradialytic Exercise	Captive Audience Efficient Less patient burden Higher compliance Exercise monitoring	Restricted movement/mobility Boredom/uninterested Less patient autonomy
Proposed Approach: Patient-Centered, personalized exercise prescription	Unlimited exercise types More patient autonomy Fewer exercise restrictions based on patient ability	Unsupervised exercise Exercise resources are limited by financial & environment access

For a physical activity program to succeed, the implementation must consider how patients view the barriers and benefits to exercise and include an individualized patient-centered comprehensive lifestyle approach to exercise prescription. The term "patient-centered" empowers patients to become active participants in their health care needs [56]. Patient-centered care has the potential to create an efficient way for clinicians to address specific challenges patients encounter [57]. Instead, current research approaches are typically "clinician-centered", which often assess clinical measures pertaining to physiological function [58]. While these measures are important, patients may disagree on their priority in relation to their needs. To implement a program that is patient-centered, clinicians and researchers must welcome patients to assert their humanity and individuality in their treatment plan [59]. A patient-centered exercise program incorporates the patient's voice in the design and implementation of programs. In addition, it is essential for studies to target patient reported outcomes measures pertaining to fatigue, pain and other symptoms associated with the disease and HD treatment. By providing more autonomy to HD patients to choose their preferred types of physical activity, it is more likely that we will reduce sedentary behavior increase in physical activity participation, and subsequently reduce symptoms of fatigue and other factors that improve patient's perceived wellness and quality of life.

Several recent reviews have advocated for a paradigm shift towards a comprehensive lifestyle intervention supported by members of the patient care team and family targeting the "patient-centered" approach [8,60,61]. This patient-centered exercise prescription consists of combining intradialytic exercise, light-intensity activities of daily living, and high-intensity exercise as an individualized approach to embody the lifestyle of the HD patient. Thus, the specific aim to increase physical activity is achieved and clinical outcomes are more likely to improve [55].

There is evidence from other clinical populations that comprehensive lifestyle interventions can be successful. These programs implement counseling, comprehensive behavior change, and goal setting techniques which allow individuals the autonomy to decide and prioritize their path to make a change in their wellness [62,63]. An example of this concept was IDES study which involved enrolling 300 individuals with type 2 diabetes and measured the change in physical activity volume and time spent participating in exercises using an accelerometer over 3 years. The participants were randomized to two groups: (1) a control/standard care group which received the American Diabetes Association recommended guidelines; and (2) a behavioral intervention that received 16 individual counseling sessions to help participants set and achieve goals pertaining to diet, exercise, and behavior modifications. The primary outcome was that the behavioral group experienced an increase in physical activity and a decrease in sedentary time compared to the control group. The study had a high retention rate in both groups (89%) and was a successful model for implementing a comprehensive lifestyle program rather than 'exercise' only. Unfortunately, multifactorial models including behavior modifications or social factors in tandem have not been widely implemented in HD patients.

For this approach to work, it is evident that clinics must employ exercise professionals who will motivate patients to prioritize exercise as part of their care. HD patients indicate that there is a lack of clinic staff expertise to oversee exercise in the clinic, and this is a significant barrier to implementing programs [64]. Furthermore, international organizations including the Global Renal Exercise (GREX) Network [17] and the UK Renal Association [24] have also suggested that exercise programs for all individuals with ESKD/CKD be designed by appropriately trained staff. Unfortunately, there is a lack of funding to achieve this in most dialysis centers around the world, and significant policy barriers need to be addressed for this to happen [65].

5. Conclusions

Intradialytic cycling has been the primary component of exercise programs for HD patients worldwide since the 1980′s. It is demonstrated to be safe, and recent research suggests it may provide unique benefits such as a reduction in specific intradialytic symptoms (e.g., cramping, intradialytic hypotension, and myocardial stunning). However, its effects on other important outcomes, including physical function and quality of life, are questionable. Because of this, research groups around the world have begun moving away from intradialytic cycling as a stand-alone intervention and including it instead as a component of a more comprehensive, patient-centered approach to increasing dialysis patients' physical activity levels. However, most of these comprehensive programs are in their initial phases, and more research will be needed to demonstrate the most feasible approaches and those that have the greatest promise for improving the health and quality of life of this critically ill patient population.

Author Contributions: A.C.K. developed the outline, conducted the literature review, and composed the first draft of the manuscript. K.R.W. helped developed the outline and provided revisions to the original draft. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Johansen, K.L. Anabolic and catabolic mechanisms in end-stage renal disease. *Adv. Chronic Kidney Dis.* **2009**, *16*, 501–510. [CrossRef] [PubMed]
2. Deschamps, T. Let's programme exercise during haemodialysis (intradialytic exercise) into the care plan for patients, regardless of age. *Br. J. Sports Med.* **2016**, *50*, 1357–1358. [CrossRef] [PubMed]
3. Cheema, B.S.B.; Smith, B.C.F.; Singh, M.A.F. A rationale for intradialytic exercise training as standard clinical practice in ESRD. *Am. J. Kidney Dis.* **2005**, *45*, 912–916. [CrossRef] [PubMed]
4. Fang, H.Y.; Burrows, B.T.; King, A.C.; Wilund, K.R. A Comparison of Intradialytic versus Out-of-Clinic Exercise Training Programs for Hemodialysis Patients. *Blood Purif.* **2020**, *49*, 151–157. [CrossRef] [PubMed]

5. Sheng, K.; Zhang, P.; Chen, L.; Cheng, J.; Wu, C.; Chen, J. Intradialytic exercise in hemodialysis patients: A systematic review and meta-analysis. *Am. J. Nephrol.* **2014**, *40*, 478–490. [CrossRef]
6. Goldberg, A.P.; Geltman, E.M.; Hagberg, J.M.; Gavin, J.R., 3rd; Delmez, J.A.; Carney, R.M.; Naumowicz, A.; Oldfield, M.H.; Harter, H.R. Therapeutic benefits of exercise training for hemodialysis patients. *Kidney Int. Suppl.* **1983**, *16*, S303–S309.
7. Painter, P.L.; Nelson-Worel, J.N.; Hill, M.M.; Thornbery, D.R.; Shelp, W.R.; Harrington, A.R.; Weinstein, A.B. Effects of Exercise Training during Hemodialysis. *Nephron* **1986**, *43*, 87–92. [CrossRef]
8. Wilund, K.R.; Viana, J.L.; Perez, L.M. A Critical Review of Exercise Training in Hemodialysis Patients: Personalized Activity Prescriptions Are Needed. *Exerc. Sport Sci. Rev.* **2020**, *48*, 28–39. [CrossRef]
9. Johansen, K.L.; Chertow, G.M.; Kutner, N.G.; Dalrymple, L.S.; Grimes, B.A.; Kaysen, G.A. Low level of self-reported physical activity in ambulatory patients new to dialysis. *Kidney Int.* **2010**, *78*, 1164–1170. [CrossRef]
10. Koh, K.P.; Fassett, R.G.; Sharman, J.E.; Coombes, J.S.; Williams, A.D. Effect of Intradialytic Versus Home-Based Aerobic Exercise Training on Physical Function and Vascular Parameters in Hemodialysis Patients: A Randomized Pilot Study. *Am. J. Kidney Dis.* **2010**, *55*, 88–99. [CrossRef]
11. Headley, S.; Germain, M.; Mailloux, P.; Mulhern, J.; Ashworth, B.; Burris, J.; Brewer, B.; Nindl, B.; Coughlin, M.A.; Welles, R.; et al. Resistance training improves strength and functional measures in patients with end-stage renal disease. *Am. J. Kidney Dis.* **2002**, *40*, 355–364. [CrossRef] [PubMed]
12. Mustata, S.; Chan, C.; Lai, V.; Miller, J.A. Impact of an exercise program on arterial stiffness and insulin resistance in hemodialysis patients. *J. Am. Soc. Nephrol.* **2004**, *15*, 2713–2718. [CrossRef] [PubMed]
13. Johansen, K.L.; Chertow, G.M.; Ng, A.V.; Mulligan, K.; Carey, S.; Schoenfeld, P.Y.; Kent-Braun, J.A. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int.* **2000**, *57*, 2564–2570. [CrossRef]
14. Kopple, J.D.; Wang, H.; Casaburi, R.; Fournier, M.; Lewis, M.I.; Taylor, W.; Storer, T.W. Exercise in maintenance hemodialysis patients induces transcriptional changes in genes favoring anabolic muscle. *J. Am. Soc. Nephrol.* **2007**, *18*, 2975–2986. [CrossRef] [PubMed]
15. Tentori, F.; Elder, S.J.; Thumma, J.; Pisoni, R.L.; Bommer, J.; Fissell, R.B.; Fukuhara, S.; Jadoul, M.; Keen, M.L.; Saran, R.; et al. Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): Correlates and associated outcomes. *Nephrol. Dial. Transplant.* **2010**, *25*, 3050–3062. [CrossRef] [PubMed]
16. Johansen, K.L.; Kaysen, G.A.; Dalrymple, L.S.; Grimes, B.A.; Glidden, D.V.; Anand, S.; Chertow, G.M. Association of physical activity with survival among ambulatory patients on dialysis: The comprehensive dialysis study. *Clin. J. Am. Soc. Nephrol.* **2013**, *8*, 248–253. [CrossRef]
17. Wilund, K.; Thompson, S.; Bennett, P.N. 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*, 467–470. [CrossRef]
18. Jeong, J.H.; Biruete, A.; Tomayko, E.J.; Wu, P.T.; Fitschen, P.; Chung, H.R.; Ali, M.; McAuley, E.; Fernhall, B.; Phillips, S.A.; et al. Results from the randomized controlled IHOPE trial suggest no effects of oral protein supplementation and exercise training on physical function in hemodialysis patients. *Kidney Int.* **2019**, *96*, 777–786. [CrossRef]
19. Graham-Brown, M.P.M.; March, D.S.; Young, R.; Highton, P.J.; Young, H.M.L.; Churchward, D.R.; Dungey, M.; Stensel, D.J.; Bishop, N.C.; Brunskill, N.J.; et al. A randomized controlled trial to investigate the effects of intra-dialytic cycling on left ventricular mass. *Kidney Int.* **2021**, *99*, 1478–1486. [CrossRef]
20. Greenwood, S.A.; Koufaki, P.; Macdonald, J.H.; Bhandari, S.; Burton, J.O.; Dasgupta, I.; Farrington, K.; Ford, I.; Kalra, P.A.; Kean, S.; et al. Randomized Trial—PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Hemodialysis. *Kidney Int. Rep.* **2021**, *6*, 2159–2170. [CrossRef]
21. Penny, J.D.; Salerno, F.R.; Brar, R.; Garcia, E.; Rossum, K.; McIntyre, C.W.; Bohm, C.J. Intradialytic exercise preconditioning: An exploratory study on the effect on myocardial stunning. *Nephrol. Dial. Transplant.* **2019**, *34*, 1917–1923. [CrossRef] [PubMed]
22. McGuire, S.; Horton, E.J.; Renshaw, D.; Chan, K.; Jimenez, A.; Maddock, H.; Krishnan, N.; McGregor, G. Cardiac stunning during haemodialysis: The therapeutic effect of intra-dialytic exercise. *Clin. Kidney J.* **2021**, *14*, 1335–1344. [CrossRef] [PubMed]
23. Smart, N.A.; Williams, A.D.; Levinger, I.; Selig, S.; Howden, E.; Coombes, J.S.; Fassett, R.G. Exercise & Sports Science Australia (ESSA) position statement on exercise and chronic kidney disease. *J. Sci. Med. Sport* **2013**, *16*, 406–411. [CrossRef] [PubMed]
24. Baker, L.A.; March, D.S.; Wilkinson, T.J.; Billany, R.E.; Bishop, N.C.; Castle, E.M.; Chilcot, J.; Davies, M.D.; Graham-Brown, M.P.; Greenwood, S.A. Clinical practice guideline exercise and lifestyle in chronic kidney disease. *BMC Nephrol.* **2022**, *23*, 75. [CrossRef] [PubMed]
25. Tzvetanov, I.; West-Thielke, P.; D'Amico, G.; Johnsen, M.; Ladik, A.; Hachaj, G.; Grazman, M.; Heller, R.U.; Fernhall, B.; Daviglus, M.L.; et al. A novel and personalized rehabilitation program for obese kidney transplant recipients. *Transplant. Proc.* **2014**, *46*, 3431–3437. [CrossRef]
26. Riess, K.J.; Haykowsky, M.; Lawrance, R.; Tomczak, C.R.; Welsh, R.; Lewanczuk, R.; Tymchak, W.; Haennel, R.G.; Gourishankar, S. Exercise training improves aerobic capacity, muscle strength, and quality of life in renal transplant recipients. *Appl. Physiol. Nutr. Metab.* **2014**, *39*, 566–571. [CrossRef]
27. Zelle, D.M.; Corpeleijn, E.; Klaassen, G.; Schutte, E.; Navis, G.; Bakker, S.J.L. Fear of Movement and Low Self-Efficacy Are Important Barriers in Physical Activity after Renal TransplantationLow Self-Efficacy Are Important Barriers in Physical Activity after Renal Transplantation. *PLoS ONE* **2016**, *11*, e0147609. [CrossRef]

28. Taryana, A.A.; Krishnasamy, R.; Bohm, C.; Palmer, S.C.; Wiebe, N.; Boudville, N.; MacRae, J.; Coombes, J.S.; Hawley, C.; Isbel, N.; et al. Physical activity for people with chronic kidney disease: An international survey of nephrologist practice patterns and research priorities. *BMJ Open* **2019**, *9*, e032322. [CrossRef]
29. Coates, P.T.; Devuyst, O.; Wong, G.; Okusa, M.; Oliver, J.; York, N.; Pattaro, C.; Peixoto, A.; Haven, W.; Perazella, M.; et al. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney. *Dis. Kidney Int.* **2020**, *98*, S1–S115.
30. Rocco, M.; Daugirdas, J.T.; Depner, T.A.; Inrig, J.; Mehrotra, R.; Rocco, M.V.; Suri, R.S.; Weiner, D.E.; Greer, N.; Ishani, A.; et al. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 Update. *Am. J. Kidney Dis.* **2015**, *66*, 884–930. [CrossRef]
31. Moore, G.E.; Painter, P.L.; Brinker, K.R.; Stray-Gundersen, J.; Mitchell, J.H. Cardiovascular response to submaximal stationary cycling during hemodialysis. *Am. J. Kidney Dis.* **1998**, *31*, 631–637. [CrossRef] [PubMed]
32. Toussaint, N.D.; Polkinghorne, K.R.; Kerr, P.G. Impact of intradialytic exercise on arterial compliance and B-type natriuretic peptide levels in hemodialysis patients. *Hemodial. Int.* **2008**, *12*, 254–263. [CrossRef] [PubMed]
33. Bohm, C. Effects of intradialytic cycling compared with pedometry on physical function in chronic outpatient hemodialysis: A prospective randomized trial. *Nephrol. Dial. Transplant.* **2014**, *29*, 1947–1955. [CrossRef] [PubMed]
34. Jeong, J.H.; Biruete, A.; Fernhall, B.; Wilund, K.R. Effects of acute intradialytic exercise on cardiovascular responses in hemodialysis patients. *Hemodial. Int.* **2018**, *22*, 524–533. [CrossRef]
35. Cheema, B.S.; Abas, H.; Smith, B.; O'Sullivan, A.; Chan, M.; Patwardhan, A.; Kelly, J.; Gillin, A.; Pang, G.; Lioyd, B.; et al. Progressive exercise for anabolism in kidney disease (PEAK): A randomized, controlled trial of resistance training during hemodialysis. *J. Am. Soc. Nephrol.* **2007**, *18*, 1594–1601. [CrossRef]
36. Chen, J.L.T.; Godfrey, S.; Ng, T.T.; Moorthi, R.; Liangos, O.; Ruthazer, R.; Jaber, B.L.; Levey, A.S.; Castaneda-Sceppa, C. Effect of intra-dialytic, low-intensity strength training on functional capacity in adult haemodialysis patients: A randomized pilot trial. *Nephrol. Dial. Transplant.* **2010**, *25*, 1936–1943. [CrossRef]
37. Kirkman, D.L.; Mullins, P.; Junglee, N.A.; Kumwenda, M.; Jibani, M.M.; Macdonald, J.H. Anabolic exercise in haemodialysis patients: A randomised controlled pilot study. *J. CachexiaSarcopenia Muscle* **2014**, *5*, 199–207. [CrossRef]
38. Anding, K.; Bär, T.; Trojniak-Hennig, J.; Kuchinke, S.; Krause, R.; Rost, J.M.; Halle, M. A structured exercise programme during haemodialysis for patients with chronic kidney disease: Clinical benefit and long-term adherence. *BMJ Open* **2015**, *5*, e008709. [CrossRef]
39. Thompson, S.; Tonelli, M.; Klarenbach, S.; Molzahn, A. A qualitative study to explore patient and staff perceptions of intradialytic exercise. *Clin. J. Am. Soc. Nephrol.* **2016**, *11*, 1024–1033. [CrossRef]
40. Prado de Negreiros Nogueira Maduro, I.; Elias, N.M.; Nonino Borges, C.B.; Padovan, G.J.; Cardeal da Costa, J.A.; Marchini, J.S. Total Nitrogen and Free Amino Acid Losses and Protein Calorie Malnutrition of Hemodialysis Patients: Do They Really Matter? *Nephron Clin. Pract.* **2007**, *105*, c9–c17. [CrossRef]
41. Hristea, D.; Deschamps, T.; Paris, A.; Lefrançois, G.; Collet, V.; Savoiu, C.; Ozenne, S.; Coupel, S.; Testa, A.; Magnard, J. Combining intra-dialytic exercise and nutritional supplementation in malnourished older haemodialysis patients: Towards better quality of life and autonomy. *Nephrology* **2016**, *21*, 785–790. [CrossRef] [PubMed]
42. Martin-Alemañy, G.; Valdez-Ortiz, R.; Olvera-Soto, G.; Gomez-Guerrero, I.; Aguire-Esquivel, G.; Cantu-Quintanilla, G.; Lopez-Alvarenga, J.C.; Miranda-Alatriste, P.; Espinosa-Cuevas, A. 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*, 1712–1720. [CrossRef] [PubMed]
43. Dong, J.; Sundell, M.B.; Pupim, L.B.; Wu, P.; Shintani, A.; Ikizler, T.A. The Effect of Resistance Exercise to Augment Long-term Benefits of Intradialytic Oral Nutritional Supplementation in Chronic Hemodialysis Patients. *J. Ren. Nutr.* **2011**, *21*, 149–159. [CrossRef] [PubMed]
44. Molsted, S.; Harrison, A.P.; Eidemak, I.; Andersen, J.L. The Effects of High-Load Strength Training With Protein- or Nonprotein-Containing Nutritional Supplementation in Patients Undergoing Dialysis. *J. Ren. Nutr.* **2013**, *23*, 132–140. [CrossRef]
45. Manfredini, F.; Mallamaci, F.; D'Arrigo, G.; Baggetta, R.; Bolignano, D.; Torino, C.; Lamberti, N.; Bertoli, S.; Ciurlino, D.; Rocca-Rey, L.; et al. Exercise in patients on dialysis: A multicenter, randomized clinical trial. *J. Am. Soc. Nephrol.* **2017**, *28*, 1259–1268. [CrossRef]
46. Baggetta, R.; D'Arrigo, G.; Torino, C.; Elhafeez, S.A.; Manfredini, F.; Mallamaci, F.; Zoccali, C.; Tripepi, G.; Bolignano, D.; Lamberti, N.; et al. Effect of a home based, low intensity, physical exercise program in older adults dialysis patients: A secondary analysis of the EXCITE trial. *BMC Geriatr.* **2018**, *18*, 248. [CrossRef]
47. Gomes, E.P.; Reboredo, M.M.; Carvalho, E.V.; Teixeira, D.R.; Carvalho, L.F.C.D.O.; Filho, G.F.F.; Oliveira, J.C.A.D.; Sanders-Pinheiro, H.; Chebli, J.M.F.; Paula, R.B.D.; et al. Physical Activity in Hemodialysis Patients Measured by Triaxial Accelerometer. *Biomed Res. Int.* **2015**, *2015*, 645645. [CrossRef]
48. Kirkman, D.L.; Ramick, M.G.; Muth, B.J.; Stock, J.M.; Pohlig, R.T.; Townsend, R.R.; Edwards, D.G. Effects of aerobic exercise on vascular function in nondialysis chronic kidney disease: A randomized controlled trial. *Am. J. Physiol. Physiol.* **2019**, *316*, F898–F905. [CrossRef]
49. Tawney, K.W.; Tawney, P.J.; Hladik, G.; Hogan, S.L.; Falk, R.J.; Weaver, C.; Moore, D.T.; Lee, M.Y. The life readiness program: A physical rehabilitation program for patients on hemodialysis. *Am. J. Kidney Dis.* **2000**, *36*, 581–591. [CrossRef]
50. Bennett, P.; Corradini, A.; Ockerby, C.; Cossich, T. Exercise during hemodialysis the intradialytic Zumba Gold. *Nephrol. News Issues* **2012**, *26*, 31–32.

51. Bennett, P.N.; Parsons, T.; Ben-Moshe, R.; Neal, M.; Weinberg, M.K.; Gilbert, K.; Ockerby, C.; Rawson, H.; Herbu, C.; Hutchinson, A.M. Intradialytic Laughter Yoga therapy for haemodialysis patients: A pre-post intervention feasibility study. *BMC Complementary Altern. Med.* **2015**, *15*, 1–7. [CrossRef] [PubMed]
52. Segura-Ortí, E.; García-Testal, A. Intradialytic virtual reality exercise: Increasing physical activity through technology. *Semin. Dial.* **2019**, *32*, 331–335. [CrossRef] [PubMed]
53. Hargrove, N.; El Tobgy, N.; Zhou, O.; Pinder, M.; Plant, B.; Askin, N.; Bieber, L.; Collister, D.; Whitlock, R.; Tangri, N.; et al. Effect of aerobic exercise on dialysis-related symptoms in individuals undergoing maintenance hemodialysis a systematic review and meta-analysis of clinical trials. *Clin. J. Am. Soc. Nephrol.* **2021**, *16*, 560–574. [CrossRef] [PubMed]
54. Aiyegbusi, O.L.; Kyte, D.; Cockwell, P.; Marshall, T.; Gheorghe, A.; Keeley, T.; Slade, A.; Calvert, M. Measurement properties of patient-reported outcome measures (PROMs) used in adult patients with chronic kidney disease: A systematic review. *PLoS ONE* **2017**, *12*, e0179733. [CrossRef] [PubMed]
55. Viana, J.L.; Martins, P.; Parker, K.; Madero, M.; Pérez Grovas, H.; Anding, K.; Degenhardt, S.; Gabrys, I.; Raugust, S.; West, C.; et al. Sustained exercise programs for hemodialysis patients: The characteristics of successful approaches in Portugal, Canada, Mexico, and Germany. *Semin. Dial.* **2019**, *32*, 320–330. [CrossRef] [PubMed]
56. Reynolds, A. Patient-centered Care. *Radiol. Technol.* **2009**, *81*, 133–147.
57. McLaren, S.; Jhamb, M.; Unruh, M. Using Patient-Reported Measures to Improve Outcomes in Kidney Disease. *Blood Purif.* **2021**, *50*, 649–654. [CrossRef]
58. Turnbull, A.E.; Rabiee, A.; Davis, W.E.; Nasser, M.F.; Venna, V.R.; Lolitha, R.; Hopkins, R.O.; Bienvenu, O.J.; Robinson, K.A.; Needham, D.M. Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications. *Crit. Care Med.* **2016**, *44*, 1267–1277. [CrossRef]
59. Berwick, D.M. What 'patient-centered' should mean: Confessions of an extremist. *Health Aff. (Proj. Hope)* **2009**, *28*, w555–w565. [CrossRef]
60. Aucella, F.; Battaglia, Y.; Bellizzi, V.; Bolignano, D.; Capitanini, A.; Cupisti, A. Physical exercise programs in CKD: Lights, shades and perspectives [corrected]. *J. Nephrol.* **2015**, *28*, 143–150. [CrossRef]
61. Regolisti, G.; Sabatino, A.; Fiaccadori, E. Exercise in patients on chronic hemodialysis: Current evidence, knowledge gaps, and future perspectives. *Curr. Opin. Clin. Nutr. Metab. Care* **2020**, *23*, 181–189. [CrossRef] [PubMed]
62. Knowler, W.C.; Barrett-Connor, E.; Fowler, S.E.; Hamman, R.F.; Lachin, J.M.; Walker, E.A.; Nathan, D.M. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* **2002**, *346*, 393–403. [CrossRef] [PubMed]
63. Balducci, S.; D'Errico, V.; Haxhi, J.; Sacchetti, M.; Orlando, G.; Cardelli, P.; Vitale, M.; Bollanti, L.; Conti, F.; Zanuso, S.; et al. Effect of a Behavioral Intervention Strategy on Sustained Change in Physical Activity and Sedentary Behavior in Patients With Type 2 Diabetes: The IDES_2 Randomized Clinical Trial. *JAMA* **2019**, *321*, 880–890. [CrossRef]
64. Castillo, G.; Presseau, J.; Wilson, M.; Cook, C.; Field, B.; Garg, A.X.; McIntyre, C.; Molnar, A.O.; Hogeterp, B.; Thornley, M.; et al. Addressing feasibility challenges to delivering intradialytic exercise interventions: A theory-informed qualitative study. *Nephrol. Dial. Transplant.* **2022**, *37*, 558–574. [CrossRef] [PubMed]
65. Bennett, P.N.; Kohzuki, M.; Bohm, C.; Roshanravan, B.; Bakker, S.J.L.; Viana, J.L.; MacRae, J.M.; Wilkinson, T.J.; Wilund, K.R.; Van Craenenbroeck, A.H.; et al. Global Policy Barriers and Enablers to Exercise and Physical Activity in Kidney Care. *J. Ren. Nutr.* **2021**. [CrossRef]