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Exercise as a therapeutic intervention in chronic kidney disease: are we nearly there yet?

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Purpose of review
The opportunity to review the more recent evidence for prescribing exercise-based physical rehabilitation for people living with chronic kidney disease (CKD) is timely. There has been a recent global focus evaluating how physical activity interventions might improve health-related quality of life and outcomes for people living with chronic health conditions in a post-COVID era. There is finally a long overdue commitment from the kidney research and clinical community to deliver pragmatic interventions to help people living with CKD to be able to live well with their condition.

Recent findings
This article reviews recent research, and discusses the challenges and potential solutions, for providing exercise-based therapeutic options for people living with CKD; including predialysis self-management interventions, options for both prehabilitation and posttransplant rehabilitation, pragmatic considerations for delivery of exercise therapy for people receiving haemodialysis treatment and the role of virtual kidney-specific rehabilitation.

Summary
Whilst there remains a need for further research in this area of patient care, there is now a body of evidence and kidney-specific guidelines that firmly support a rollout of pragmatic and scalable exercise-based interventions for people living with CKD. We are indeed nearly there now.

Keywords
physical activity, quality of life, rehabilitation

INTRODUCTION

Holistic healthcare incorporates interventions and approaches to the physical, mental, emotional, social and spiritual needs of the patient. There are many examples of good quality holistic care that incorporate physical rehabilitation for people living with long-term health conditions: People living with chronic lung and cardiac conditions being offered cardiac [1] and pulmonary rehabilitation [2]; and people diagnosed with Cancer have access to well resourced holistic Cancer rehabilitation [3]. Why is it, then, that people living with Chronic Kidney Disease (CKD) do not receive comparable holistic care? The medical model alone is insufficient to restore or prevent further deterioration in physical and mental health, and increasingly it is clear that without a more holistic approach to care, we are potentially condemning people living with CKD to a poorer quality of life, prolonged hospital stays and associated increased treatment costs.

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KEY POINTS

- Self-management interventions with a focus on physical activity and exercise behaviours are gaining increasing attention and should be offered at an early stage in the CKD patient pathway.
- Prehabilitation and posttransplant rehabilitation should be considered as an essential part of the enhanced recovery after surgery pathway for people receiving a kidney transplant.
- A programme that includes cycling but makes use of other exercise-based interventions (including digital platforms) is needed to effectively translate the encouraging results from recent studies into clinical practice.
- Virtual rehabilitation offers a potentially effective opportunity to deliver exercise-based rehabilitation at scale without major cost implications or the need for an extensive trained workforce for delivery.
- The introduction of a holistic wellbeing assessment for people approaching dialysis or who are at listing for kidney transplantation may be a practical approach to guide intervention needs and inform commissioning of appropriate exercise-based ehabilitation options for people living with CKD.

The first study to evaluate exercise-based rehabilitation for people living with CKD was published over 35 years ago [4]. Since then, research groups from across the globe have designed and investigated different ways to engage people living with CKD with a more physically active lifestyle. Sadly, little of this research has resulted in tangible changes to the delivery of routine care. Several credible reasons for this have been postulated, including a lack of high-quality evidence, a lack of clear guidelines on how to prescribe exercise-based therapy for this population, a lack of skilled workforce, and a chronic lack of funding in the healthcare system. In this review, we report recent research and developments in the context of a post-COVID era, discuss the current opinions on challenges and solutions for the implementation of therapeutic exercise interventions for people living with CKD, and ask the question; are we nearly there yet?

Self-management and predialysis interventions

Alongside providing services to people living with CKD, there is a need to support these individuals to better self-manage their condition. For people living with CKD, self-management behaviours include medication adherence, health and symptom monitoring, lifestyle modifications, and psychosocial coping. For self-management to be effective, individuals need to have the appropriate knowledge, skills, and confidence (i.e., patient activation) and be able to identify, access, and use resources and support available (i.e., health literacy). Empowering people to take a more active role in their health can result in increased levels of patient activation, self-efficacy, self-determination, and readiness to change [5,6]. Whilst improving people's confidence, belief, and ability to change behaviour is fundamental to initiating behaviour change, a substantial level of knowledge, motivation, and active engagement from the individual is required to successfully adopt and sustain positive behaviour change [7]. Providing more holistic approaches to key modifiable lifestyle behaviours, like exercise and physical activity, and incorporating it within self-management can optimise person-centred care for people living with CKD.

Given that positive changes in patient activation can result in better self-management and facilitate behaviour change and engagement with health-promoting behaviours, including regular physical activity [8], it is not surprising that self-management interventions with a focus on physical activity and exercise behaviours have gained increasing attention. Whilst we await findings from self-management interventions promoting physical activity in CKD [9▪,10▪,11▪,12], similar interventions in other long-term conditions have demonstrated beneficial effects on physical activity behaviours [13,14]. However, in those with multimorbidity, reductions in physical activity levels have been observed [15]. This unexpected finding may be a result of the complexity of multimorbidity, as high disease and treatment burden can impact an individual's patient activation and self-management abilities. Consideration is required when developing interventions for those with more advanced CKD and more complex health needs who may find self-management difficult [16]. Whilst these individuals may require more support to effectively self-manage, individuals at the earlier stages should not be ignored – often they are the ones who lack the knowledge and awareness to self-manage, and potentially have the most to gain from engaging in self-management and health-promoting behaviours.

There is growing evidence for the utilisation of exercise-based therapeutic options in the role of prevention and delayed progression of CKD. Recently published research [17,18] pertaining to the potential benefits for people at this early stage in the CKD patient pathway does reinforce the need

to focus on commissioning exercise-based rehabilitation as part of any prevention package, as well as the keen desire for exercise-based rehabilitation for people approaching end-stage care.

Rehabilitation for people receiving haemodialysis treatment

Over the last 3 years there have been several landmark studies exploring the effects of exercise interventions (particularly intra-dialytic interventions) in people receiving haemodialysis treatment. There has been a notable change in both the size and quality of much of this research. The PrEscription of intraDialytic exercise to improve quAlity of Life in Patients Receiving Haemodialysis (PEDAL) study was a UK-based multicentre randomized controlled trial (RCT) that assessed the effects of a 6-month programme of intra-dialytic exercise (cycling and resistance training) compared to usual care on health-related quality of life [19▪]. The study randomized 379 patients and despite demonstrating a between-group improvement in the primary outcome (the Kidney Disease Quality of Life Short-Form Physical Component Summary), this did not quite reach statistical significance ($P = 0.055$), perhaps due to lack of power from greater than anticipated rates of drop-out, and the sensitivity of the primary outcome to affect change. The PEDAL study did not demonstrate an effect on measures of physical function, but a similar recent study did. The Dialysis Training Therapy (DiaTT) trial randomized 1211 patients to a 12-month programme of combined cycling and resistance training or usual care [20▪▪]. The intervention led to clear improvements in physical function (the sit-to-stand-60, the timed up and go, and the six-minute walk test) compared to standard care and they also demonstrated similar improvements in quality of life as reported in the PEDAL study. Both PEDAL and DiaTT included patients of similar characteristics and older, more frail patients were included in both studies. The increased length of the intervention in the DiaTT study compared to PEDAL (12-months compared to six-months) and the larger sample size are likely to account for the differences observed in outcomes.

Whilst the PEDAL and DiaTT studies evaluated the effects of a combined intra-dialytic cycling and resistance training programme, the Improving cardiovascular health in dialysis patients using a structured programme of exercise (CYCLE-HD) study was an RCT that assessed the effects of a six-month programme of purely intra-dialytic cycling on cardiovascular structure and function [21▪]. The UK-based study of 130 patients showed cycling exercise during dialysis led to clear improvements in prognostically important measures of cardiovascular structure and function, including reduced left ventricular mass, myocardial fibrosis, and aortic stiffness compared to standard care. Whilst the study itself could not define the mechanisms through which these improvements occurred, subsequent mechanistic studies have suggested these improvements are likely to be driven by mitigation of the myocardial stunning events that occur during haemodialysis that are known to drive pathological changes in the left ventricle [22]. McGuire and colleagues showed dialysis-induced regional wall motion abnormalities are mitigated by intra-dialytic cycling [23], and Josse and colleagues showed that measures of left ventricular myocardial strain are preserved throughout the dialysis session compared to standard care [24]. Both of these studies give a clear steer as to the mechanisms through which intra-dialytic exercise may abrogate the adverse cardiovascular effects of dialysis and ultrafiltration.

Where does this currently leave us with exercise for people receiving haemodialysis treatment? Well the studies discussed were all studies of intra-dialytic exercise. These programs have better adherence rates than inter-dialytic exercise programmes. None of the studies showed any signal for harm and increasingly there is high quality evidence that they support physical function, quality of life and cardiovascular health. Indeed, there may be benefits to health services with the CYCLE-HD study showing the programme is potentially cost-effective [25]. It seems that implementation of these programmes is justified by the evidence-base, but a variety of barriers remain. Work-force development, staff training and service development and running costs are just a few of the factors that need to be addressed to support effective implementation and translation to clinical practice. Similarly, cycling on dialysis has been the main exercise intervention, but on its own it is not an acceptable or accessible intervention for many people receiving haemodialysis treatment. A more holistic programme that includes cycling but makes use of other interventions (including digital platforms) is needed to effectively translate the potential shown in the above studies to clinical practice.

Prehabilitation

It is increasingly recognised that people living with CKD on the transplant waiting list should be in an optimal state of health, both physically and psychologically, to withstand the stress of transplant surgery, mitigate postoperative complications, and enhance recovery after transplantation. However, people living with CKD often report compromised physical and mental well being due to disease

progression, comorbidities, and adverse effects of dialysis. Prehabilitation refers to the process of optimizing the patient's overall fitness before a surgical procedure to promote recovery and overall outcomes [26]. Prehabilitation primarily revolves around implementing lifestyle changes and typically consists of physical activity/exercise training, dietary management, and psychosocial interventions [26]. In addition, cessation of adverse lifestyle behaviors such as substance abuse or medication nonadherence may be addressed. The multimodal nature of this approach is essential, as it addresses the complex interplay between the physical and psychosocial health concerns of people living with CKD, thereby promoting the effectiveness of the intervention [27].

So far, few studies have addressed prehabilitation in the context of kidney transplantation and have primarily focused on exercise training [28–31]. These initial studies indicated that (i) exercise-based prehabilitation is safe, (ii) kidney transplant candidates consider exercise-based prehabilitation appropriate, acceptable, satisfying, and effective to improve physical function, and (iii) exercise-based prehabilitation improves physical function, cardiorespiratory fitness, muscle strength, physical activity levels, fatigue, frailty, body composition, and postoperative length of stay [28–31]. Recently, a consensus meeting on prehabilitation for solid organ transplant candidates was held under the flag of the European Society of Organ Transplantation (ESOT) [32▪]. Recommendations from this meeting stated that given the limited body of literature evidence, high-quality studies on prehabilitation in solid organ transplant candidates are needed, in which both the effectiveness and implementation of pretransplant multimodal prehabilitation are addressed. In addition, it was recommended that a Core Outcome Set and preferred assessment methodology should be developed to enable adequate comparison of the study results and identify the optimal modality, timing, duration, and delivery characteristics of prehabilitation interventions [32▪]. At the moment, two RCT's on multimodal prehabilitation interventions in people living with CKD who are also waitlisted for transplantation are underway: the FRAIL-MAR-study (NCT04701398) [33] and the PreCareTx-study (NCT05489432) [34].

Posttransplant rehabilitation

Evidence regarding exercise after kidney transplantation has been building for the past 25 years. The latest systematic review and meta-analysis evaluating the effects of exercise interventions on kidney transplant recipients, suggest a positive effect on physical fitness (cardiorespiratory fitness, strength, and physical function), and some markers of dyslipidaemia with no detrimental effects or safety concerns [35▪]. However, body mass index, body weight and glycaemic control remain unaffected. It has been hypothesised that to target body weight, body mass index and body composition, thus a combined intervention including exercise, diet, and behaviour change techniques is required [36]. Despite a call for more rigorous research (powered samples with adequately dosed and reported exercise interventions) over 10 years ago [37], studies are still highly heterogenous in sample size, duration, intervention content, outcome measure choice, and methods.

Moreover, people living with kidney transplants have asked for interventions to support them to be physically active [38], and follow a healthy lifestyle, with clear guidance, education and support [39–41]. They have placed an emphasis on the importance of the healthcare provider to support and guide the journey towards being more physically active and feeling safe and confident in doing so [38,42]. There are few existing exemplar programmes and services [43–45] that support people postkidney transplantation with physical activity behaviour.

Given the current evidence, and the request for support from people living with transplantation, there is a need for increased access to physical activity support and interventions for people living with kidney transplantation as part of routine post-transplant care. The developing evidence utilising digital interventions to support transplant recipients may offer a potential strategy to address this in those who are confident in moving forward without in-person guidance [9▪,12,46]. Future research in this field should look to investigate the exercise interventions required for different sub-groups such as kidney transplant recipients living with frailty, acute versus more established transplant recipients, and people living with complex and multiple comorbidities. Transparent and detailed reporting of adequately dosed exercise interventions (identified as a barrier across all exercise research in solid organ transplantation) [47], and study designs will facilitate synthesis of evidence, replication and adoption to clinical practice.

Virtual rehabilitation

An area that has received a lot of attention in recent years is the use of digital interventions to promote healthy lifestyles, activity, exercise, and improved self-management. Whilst digital health interventions potentially have broad reach, it is also clear that patients from lower socio-economic and

educational backgrounds, minority ethnic groups, elderly patients and those who face digital poverty are less likely to be able to access and benefit from these types of resources [48]. Indeed, these are precisely the groups that stand to benefit the most. Digital resources that improve exercise and activity levels in patients with CKD will be successful *if* they are developed and implemented to be equitably accessible for all. Two promising (and complementary) interventions that have been developed and tested with these important factors in mind are the Kidney BEAM [9▪,10▪] and My Kidneys & Me platforms [11▪,12]. Kidney BEAM is a digital physical activity and emotional well being self-management platform designed to support and engender sustained changes in physical activity and well being for patients with kidney disease. My Kidneys & Me is an evidence-based and theory-based structure digital self-management structured programme developed for peoples with CKD designed to improve kidney specific health literacy and the ability to self-manage aspects of health. Both studies have been rigorously tested in multicentre RCTs, with favourable results reported at UK Kidney Week 2023 and published results are expected in 2023/2024. As with all other interventions though, positive trial findings do not necessarily translate to clinical practice and a considerable amount of work will be needed (and is ongoing) to support successful implementation into practice, with the requirement for sustained commissioning of both platforms required to realise what could be a truly transformative approach to exercise and lifestyle management for people living with CKD.

Commissioning physical rehabilitation for people living with chronic kidney disease

Over the last two years NHS England has conducted a multiagency project, the Renal Services Transformation Programme (RSTP), that aimed to transform the delivery of kidney specialised services and formulate a comprehensive commissioning toolkit for renal care services across England. This programme of work aimed to highlight inequalities in kidney care and initiate cross-cutting themed projects to evaluate the requirements and proposed interventions that could inform commissioning on the principles of a whole person, whole care pathway approach. One cross-cutting theme highlighted due to the huge inequalities in the provision of routine care was 'living well with kidney disease'. This was a unique opportunity for a team of expert clinicians to conduct a modified Delphi process to inform the psychosocial and physical rehabilitation care for people living with CKD [49▪].

This study revealed high consensus amongst senior members of the kidney multidisciplinary team (MDT) and other key stakeholders on the importance of psychosocial and physical rehabilitation management for people living with CKD, and a desire for ways to implement pragmatic programmes of this care. The use of digital resources was strongly recommended, in addition to any available face-to-face care, to provide physical rehabilitation for people living with CKD. This may prove to be the only pragmatic way to deliver this type of care at scale as there is a lack of appropriately trained healthcare professionals, and limited fiscal resources for implementation of face-to-face services. That said, given the far-reaching benefits of physical activity, exercise and lifestyle interventions, it is important that all healthcare professionals are educated to recognise the psychosocial and physical rehabilitation needs of their patients and to understand how to refer and access relevant services specifically for people living with CKD, whether these are local, regional or national.

The Delphi consensus process achieved high levels of agreement between expert MDT members around recommendations for a holistic well being assessment for all people living with CKD who are approaching dialysis, or who are at listing for kidney transplantation [49▪]. This included the use of validated measurement tools to assess the need for further intervention, an approach that has been successfully used to inform the need for Cancer rehabilitation [50] and was instrumental in the change in the way rehabilitation services were commissioned in Cancer care. This may well be the biggest opportunity we have to ensure that kidney-specific psychosocial health and physical rehabilitation management becomes an essential component of optimal care pathways for people living with CKD. There is no doubt that the measurement, and requirement for reporting, of data will highlight where the biggest variations in care exist to help direct resources.

CONCLUSION

Utilising exercise as a therapeutic option to help people living with CKD manage their condition, prevent further deterioration, and potentially improve outcomes that are important to people who are living with the condition is finally gaining the interest of researchers, clinicians and most importantly, the policy makers. This is undoubtedly a direct result of the recently published, and eagerly anticipated, studies that evaluate and suggest pragmatic solutions for the delivery of exercise-based interventions, which can be delivered at scale

within a post-COVID healthcare system. With promising solutions suggested for the delivery of exercise-based therapy at various important transition points in the patient pathway, and a clear trajectory for planned future research, one can feel the change in momentum with regards to the priority level for this area of patient care, and the authors would indeed agree that we are in fact nearly there.

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Conflicts of interest

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