Prehabilitation in end stage kidney disease

Introduction

Clinical frailty and sarcopaenia are significant consequences of end stage kidney disease (ESKD), affecting up to 75% of dialysis patients (Bao *et al,* 2012). Their development is a multifactorial and complex sequence of events, largely driven by disease and dialysis-related inflammation and catabolism and uraemia (Kim *et al,* 2013), and significantly impacts several outcomes, including reduced quality of life (Mansur *et al,* 2014), increased rate of disease progression (Roshanravan *et al*, 2012), increased hospitalisation (Kang *et al,* 2017) and significantly increased mortality risk (McAdams-DeMarco et al, 2013). Many studies that aim to mitigate against frailty, sarcopaenia and related complications of ESKD comprise single interventions, however, the role of multi-component interventions in preventing functional and nutritional decline, maintaining quality of life, and improving survival in patients with ESKD is an emerging area of interest. This paper outlines the potential role for these multi-component interventions and the role of 'prehabilitation' in ESKD.

Complications of end stage kidney disease

Significant physical and psychosocial complications of ESKD include protein energy wasting (PEW), fatigue, reduced physical functioning, frailty, anxiety and depression (Carrerro *et al,* 2013; Hiraki *et al,* 2013; Kurella Tamura *et al,* 2016; Segura-Orti *et al,* 2017; Nixon *et al,* 2017). Their development is complex and multi-factorial, driven largely by inflammation, catabolism, and uraemia (Kim et al, 2013), often leading to adverse clinical outcomes, increased hospitalisation and mortality, decline in cognitive function, and reduced health-related quality of life (HRQoL) (Lacson *et al,* 2011; Tonelli *et al,* 2015). There is a marked decline in functional ability and increased cumulative mortality that begins around the initiation of dialysis and accelerates during the first 12 months of dialysis (Kurella-Tamura *et al,* 2009). This is particularly apparent for older dialysis patients (Fischer *et al,* 2016), where dialysis, sarcopaenia and PEW influence frailty and lead to a decline in functional ability (Fouque *et al*, 2011; Carrerro *et al,* 2013; Cupisti *et al,* 2013), leading to increased hospitalisation (McAdams-DeMarco *et al,* 2013). Consequently, mortality rates within the first year of dialysis are high, with 3.6% of patients not surviving to 90 days after dialysis initiation, and 9.6% mortality during the following 12 months (UK Renal Registry, 2021).

Kidney transplantation has significant benefits over dialysis, yet severe frailty reduces the chance of a patient receiving a renal transplant (Alfaadhel *et al,* 2016), and negatively impacts clinical outcomes. Frail patients are increasingly likely to be removed from the waiting list or die while awaiting transplantation (Cheng *et al,* 2019), or experience reduced physical function post transplantation, delayed graft function, increased risk of peri-operative complications and increased mortality risk before and after transplantation (McAdams-DeMarco *et al,* 2013 and 2015).

Several studies have demonstrated that quality of care can positively influence longer-term mortality and hospitalisation rates in dialysis patients (Anvari *et al,* 2013) and outcomes in transplant patients, including quality of life and survival (McAdams-DeMarco *et al,* 2019; Ma *et al,* 2022). Multi-component interventions, including physical activity, nutritional management, educational or psychological interventions, may improve quality of care, prevent nutritional and functional decline, and maintain HRQoL in dialysis patients and renal transplant recipients (Lacson *et al,* 2011; Fischer et al*,* 2016; McAdams-DeMarco *et al,* 2019), although published evidence to support these remains limited at present (Sheshadri and Johansen, 2017; Willingham *et al,* 2019; McAdams-DeMarco *et al,* 2019). However, several single interventions studies focusing on the role of exercise, nutrition, psychological, or education in ESKD have reported positive results, and may be used as a basis for developing multi-component interventions (Campbell *et al,* 2008; Greenwood *et al*, 2012; Young *et al,* 2020).

Interventions to prevent complication of end stage kidney disease

Physical fitness, exercise capacity, muscle strength and endurance

Physical fitness and engagement with exercise is often reduced in patients with ESKD (Wilkinson *et al*, 2021; Walklin *et al,* 2023). Several systematic reviews of studies measuring physical fitness and exercise capacity have showed that any kind of aerobic exercise significantly improved physical fitness and capacity in patients with ESKD (Heiwe and Jacobson, 2011; 2014; Baker *et al,* 2022). Regular physical exercise, regardless of type or intensity of exercise or length of exercise intervention, can also increase muscular strength (Heiwe and Jacobson, 2011; 2014; Golebiowski *et al*, 2012; Greenwood *et al*, 2012; Young *et al*, 2018; Baker *et al*, 2022). These studies involved in-centre exercise programmes, however,

more recently studies exploring the benefit of home-based and digital physical activity interventions have also been published (Nixon *et al,* 2020; Walklin et al, 2023).

Nutritional Status

Protein energy wasting is a significant complication of ESKD, leading to increased morbidity and mortality (Carrero *et al,* 2013). Several studies have investigated the role of nutritional interventions upon nutritional outcomes and HRQoL (Brown *et al,* 2021). In one single-centre randomised controlled trial (RCT) (Campbell *et al,* 2008), Patient-generated Subjective Global Assessment (PG-SGA) was used to assess nutritional status in pre-dialysis patients. Patients who received a 12 week dietetic intervention, that aimed to increase nutritional intake and intensify dietetic input were more likely to demonstrate improvements in nutritional status according to PG-SGA than patients in the control group, where some patients' nutritional status declined. There was a statistically significant difference ($p<0.01$) in change in PG-SGA ratings between the groups. Heiwe and Jacobson (2011) analysed the effect of exercise upon markers of nutritional status in patients with ESKD, although did not find a consistent relationship between any kind of exercise with subjective global assessment (SGA) of nutritional status or protein intake. However, regular exercise of any type was found to significantly increase energy intake. Nutritional interventions exploring nutritional status and undernutrition in kidney transplant recipients are limited, with the majority of interventions focussing on dietary and lifestyle strategies to reduce cardiovascular risk factors (Brown *et al,* 2021).

Frailty

Frailty, classed as increased vulnerability to physical stressors, such as illness, is common in ESKD, and is associated with increased risk of hospitalisation and mortality (Nixon *et al,* 2018; McAdams-DeMarco *et al,* 2019; Young *et al,* 2020). Exercise and nutritional interventions are thought to be useful management strategies in frail patients (Nixon *et al,* 2018). A pilot RCT in pre-frail and frail CKD patients, including some patient with ESKD not on dialysis, reported that a 12 week home-based exercise intervention may be beneficial for improved fitness and strength (Nixon et al, 2021). Intra-dialytic exercise interventions have been shown to be feasible and acceptable in frail haemodialysis (HD) patients (Young *et al,* 2020).

Nutritional status is also associated with frailty. A study by Tseng *et al* (2023) found that frailty was associated with reduced values for markers of nutritional status, including handgrip and dietary protein intake, and higher incidence of PEW as defined by malnutrition inflammation score.

Health related quality of life

Exercise and nutritional interventions in ESKD have been found to impact HRQoL, assessed using several methods including Kidney Disease Quality of Life Short Form tool (KDQoL-SF™ tool) and Hospital Anxiety and Depression Score (HADS) (Campbell *et al,* 2008; Greenwood *et al,* 2012; Young *et al,* 2018). Campbell *et al* (2008) found that well-nourished patients had a higher mean overall score for the KDQoL-SF™ than malnourished patients, indicating an improved patient perception of HRQoL. Higher scores were observed particularly for the symptoms of kidney disease, physical functioning, social function and role emotional domains of the questionnaire. Greenwood *et al* (2012) reported a 16% mean improvement for the HADS anxiety rating and 29% improvement in HADS depression rating following a 12 week programme of combined cardiovascular and resistance training and exercise education.

Young *et al* (2018) found that intra-dialytic exercise was associated with a significant reduction ($p=0.02$) in HADS depression score over a 12 month period.

Anxiety and depression are associated with reduced adherence for pre- and post-transplant medical care, including immunosuppression. A meta-analysis of 27 transplant studies concluded that depression affects post-transplant mortality and increases kidney graft loss (Dew, 2015). Interventions to address this may therefore improve medical care and outcomes post kidney transplantation (De Pasquale *et al,* 2020).

Multi component Interventions

There is a varied body of evidence relating to the impact of exercise and nutritional interventions on physical fitness, exercise capacity, muscle strength, nutritional status, and HRQoL in patients with ESKD with many studies being small, single intervention studies (Willingham *et al,* 2019). The role of a multi-component interventions in preventing functional and nutritional decline, and maintaining quality of life, in patients with ESKD is an emerging area of interest, and patients with ESKD undertaking exercise trials have reported that they would favour multi-component interventions (Young *et al,* 2020). Programmes which include

supervised group exercise and education are well-established in other long-term conditions, such as cardiac disease and chronic obstructive pulmonary disease (*Bolton et al,* 2013; Price *et al*, 2016), and 'prehabilitation' including exercise, nutritional counselling and anxiety management have been shown to improve post-surgical recovery when commenced before surgical intervention for colorectal cancer (Gillis *et al*, 2014; Carli *et al* 2017; Crevenna *et al,* 2021). Although studies are starting to emerge in ESKD patients approaching dialysis and in preparation for renal transplantation (Castle et al, 2023), there is still a significant gap in the current evidence base for multi-component interventions in patients across the spectrum of ESKD.

What would a multi-component 'prehabilitation' programme include?

Any interventions would need to address strategies that could prevent functional and nutritional decline and maintain or improve HRQoL. Therefore, the main strands of such an intervention would include the following components:

- Exercise
- Nutritional assessment and advice
- Educational and/or psychological support.

Additionally, prehabilitation interventions should be delivered for maximal patient benefit, therefore it is proposed that this should be in preparation for dialysis initiation or transplantation.

Exercise intervention

Exercise has wide ranging benefits across the spectrum of ESKD (Wilkinson et al, 2020; Baker *et al,* 2022). The UK Kidney Association guidelines (2021) provide recommendations for exercise targets in CKD, ESKD and kidney transplantation (Table 1). Statistically significant effects upon physical function (Golebiowski *et al,* 2012; Greenwood *et al,* 2012), muscle strength (Golebiowski *et al,* 2012) and quality of life (Greenwood *et al,* 2012) were seen with exercise interventions lasting for at least 12 weeks, therefore this should be recommended as the optimum minimum length of time for any exercise intervention.

Table 1 – UK Kidney Association Guidelines for Exercise in Kidney Disease

Stage of CKD	Frequency	Intensity	Time (minutes)	Type
CKD	Daily	Moderate Vigorous	150 minutes per week 75 minutes per week (vigorous)	Aerobic activity (moderate/ vigorous) Strengthening
Haemodialysis	No recommendation	Moderate Vigorous	150 or 75 minutes per week	Aerobic activity Inter-dialytic Intra-dialytic
Transplantation	No recommendation	Moderate Vigorous	150 or 75 minutes per week	Structured Aerobic activity Strengthening

A supervised group exercise programme, including a low impact aerobic warm up and seated cool down and relaxation, could use an exercise circuit comprising both low impact aerobic activity and weight-based resistance/strengthening exercises to work key muscle groups and improve physical strength and function. Increasing the level of intensity and/or resistance during the programme, where improvements in exercise capacity and strength allow, is thought to beneficial (Willingham *et al,* 2019). Baseline measurements, such as incremental shuttle walk test, one minute sit to stand and short physical performance battery (Segura-Orti *et al,* 2011; Greenwood *et al,* 2012) may be used to determine exercise capacity and functional ability and to devise an individualised exercise plan for the circuit. Encouraging additional exercise at home beyond group sessions will also help patients to achieve activity levels closer to recommended guidance (UK Kidney Association, 2021).

While gym-based interventions are considered effective, as well as providing a safe space with appropriate support to develop exercise confidence (Levett *et al,* 2019), they are more costly than home-based interventions and may present access challenges for patients. Therefore, home-based or digital interventions could also be considered (Walklin *et al,* 2023).

Nutritional assessment and advice

Nutritional assessment and interventions should be evidence-based and, where possible, informed by theoretical frameworks (Michie et al, 2011a). A comprehensive nutritional assessment should include several parameters used to assess nutritional status and

determine body composition, such as SGA of nutritional status (Steiber *et al,* 2007; Cuppari et al, 2014; Kidney Disease Outcomes Quality Initiative (KDOQI), 2020), anthropometric measurements [weight, height, calculation of BMI (kg/m^2), assessment of recent unintentional weight loss (Parenteral and Enteral Nutrition Group [PENG], 2018) mid upper arm circumference (PENG, 2018) and handgrip strength (Norman *et al*, 2011; KDOQI, 2020; Wilkinson *et al,* 2021). Patient self-completed dietary records could be used to estimate nutritional intake, supplemented by appetite assessment using validated appetite questionnaires (Burrowes *et al*, 2005; Dwyer *et al*, 2005).

As individualised nutritional interventions can lead to improvements in nutritional status (Campbell *et al,* 2008; Willingham et al, 2019), they are considered more beneficial than group interventions or non-specific advice. An in-person or remote video consultation with a specialist kidney dietitian can be undertaken to generate a patient-centred nutritional care plan, using results from a baseline core nutritional assessment and further information gained during the consultation. Discussions to explore and address potential barriers may improve the likelihood of successfully achieving nutritional targets, and behaviour change techniques including goal setting, action planning, barrier identification and problem solving may be useful (Michie *et al*, 2011b).

Education/psychological support

Psychological input into prehabilitation programmes may help patients to support their own self-management of their diagnosis and treatment, and in turn improve their quality of life and wellbeing, enhancing self-efficacy and treatment adherence. Patient engagement with prehabilitation is a key driver for efficacy, hence regular face-to-face psychological support, incorporating motivational conversations could be considered to optimise compliance and patient benefit (Levett and Grimmett, 2019).

Summary

This review has outlined the potential role of exercise, nutrition and educational and psychological support in preventing frailty, sarcopaenia and related complications of ESKD. Many single intervention studies have demonstrated beneficial effects, however, multi-component interventions are thought to provide greater benefits in preventing functional and

nutritional decline, maintaining quality of life, and improving survival in patients with ESKD, as has been demonstrated in other clinical conditions. So far, however, few studies have investigated the role of multi-component 'prehabilitation' across the spectrum of CKD, therefore highlighting the need for further research in this important area.

Key Points

- Clinical frailty and sarcopaenia are significant consequences of end stage kidney disease (ESKD) and significantly impact clinical and quality of life outcomes
- Many interventions which aim to prevent frailty, sarcopaenia and related complications of ESKD comprise single interventions (exercise, nutrition or education)
- Multi-component interventions including exercise, nutrition, education and psychology input prior to commencing dialysis or pre-transplantation (prehabilitation) may be more beneficial in improving clinical outcomes and quality of life

CPD Questions

1. Which interventions have been proposed to mitigate against the complications and adverse consequences of end stage kidney disease?
2. Why is there a need to consider multicomponent 'prehabilitation' in end stage kidney disease?
3. How could a multi component 'prehabilitation' be structured and delivered?

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