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Frailty and chronic kidney disease: current evidence and continuing uncertainties

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Abstract

Frailty, the state of increased vulnerability to physical stressors as a result of progressive and sustained degeneration in multiple physiological systems, is common in those with chronic kidney disease (CKD). In fact, the prevalence of frailty in the older adult population is reported to be 11%, whereas the prevalence of frailty has been reported to be greater than 60% in dialysis-dependent CKD patients. Frailty is independently linked with adverse clinical outcomes in all stages of CKD and has been repeatedly shown to be associated with an increased risk of mortality and hospitalization. In recent years there have been efforts to create an operationalized definition of frailty to aid its diagnosis and to categorize its severity. Two principal concepts are described, namely the Fried Phenotype Model of Physical Frailty and the Cumulative Deficit Model of Frailty. There is no agreement on which frailty assessment approach is superior, therefore, for the time being, emphasis should be placed on any efforts to identify frailty. Recognizing frailty should prompt a holistic assessment of the patient to address risk factors that may exacerbate its progression and to ensure that the patient has appropriate psychological and social support. Adequate nutritional intake is essential and individualized exercise programmes should be offered. The acknowledgement of frailty should prompt discussions that explore the future care wishes of these vulnerable patients. With further study, nephrologists may be able to use frailty assessments to inform discussions with patients about the initiation of renal replacement therapy.

Key words: CKD, dialysis, elderly, exercise, frailty, nutrition

Introduction

Frailty is a state of increased vulnerability to physical stressors, such as illness or trauma, with an associated increased risk of poor clinical outcomes [1]. This occurs as the result of a progressive and sustained degeneration in multiple physiological systems and, some would argue, also the result of a decline in psychological health and inadequate social support [1–3]. In isolation these deficits may not be considered severe enough to be classified as a disease state or to require the individual to need additional care [2]. It is the accumulation of multiple deficits across various systems that is thought to be fundamental to the development of

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frailty [2]. In recent years there have been efforts to create an operationalized definition of frailty to aid in its diagnosis and to categorize its severity. Two principal concepts are described: the Fried Phenotype Model of Frailty, which focuses on physical frailty, and the more holistic Cumulative Deficit Model of Frailty, also known as the Frailty Index, which takes into account a broad range of medical and psychological conditions and considers functional impairments [2, 4–8].

Frailty is common in those with chronic kidney disease (CKD). The prevalence of frailty in the community-dwelling older adult population is reported to be 11%, whereas studies have reported a frailty prevalence of $>60\%$ in dialysis-dependent CKD patients [9–11]. The Atherosclerosis Risk in Communities (ARIC) Study demonstrated that frailty is strongly associated with progressive renal impairment [12]. Furthermore, frailty is independently linked with adverse clinical outcomes in all stages of CKD and has been repeatedly shown to be associated with an increased risk of mortality and hospitalization [9, 10, 13–16].

Given the convincing relationship between frailty and adverse outcomes in those with CKD, nephrologists should be more aware of the concept of frailty. This is particularly true during interactions with other health care providers, such as general practitioners and geriatric medicine physicians, who will assess frailty in the renal population and use the diagnosis as part of decision making. The European Renal Best Practice (ERBP) Working Group recently released a clinical practice guideline on the management of older patients with CKD Stage 3b or higher [17]. They emphasized the importance of assessing functional decline in older frail patients with advanced CKD, although they conceded that there was insufficient evidence to recommend a specific frailty scoring tool [17]. So where does this leave the practising nephrologist? How should we screen for frailty in those with CKD? Are scores and tools better than clinical acumen, and if so, which should be used? What's more, if we identify frailty, what can we do for our patients? Here we provide a focused review of frailty in the renal population with an emphasis on learning points for the general nephrologist. We also provide a brief review of the recent literature and highlight areas of uncertainty and controversy with a need for further research.

Why does physical frailty occur in those with CKD?

Patients with advanced CKD often have a reduced energy intake that contributes to sarcopenia and, subsequently, physical frailty [18, 19]. Studies have shown that there is in fact a progressive decline in food intake with deteriorating kidney function [18, 20, 21]. The reduced energy intake is frequently due to anorexia, which is present in up to one-third of patients with end-stage renal disease (ESRD) [18, 22]. The loss of appetite that occurs in CKD is likely multifactorial; potential contributors include the uraemic milieu, inflammation, superimposed illnesses, medications and coexistent low mood [18, 19]. It has been postulated that the accumulation of uraemic toxins may cause defects in the hypothalamic regulation of appetite [18]. Furthermore, cognitive impairment is more common in the CKD population and may lead to reduced food intake [23]. Another dietary challenge for those with CKD is maintaining adequate protein and energy intake while restricting dietary phosphate intake to prevent the development of secondary hyperparathyroidism and CKD–mineral bone disease [24]. This is particularly difficult in those that are dialysis-dependent as there are unavoidable losses of amino acids during the dialysis procedure [25].

Physical activity tends to decrease with ageing and this decline is more marked for individuals with CKD [26–29]. Notably, patients with dialysis-dependent CKD who maintain physical activity have superior gait speed, leg strength and lean body mass [19, 30, 31]. Furthermore, physical inactivity is associated with increased mortality in those with CKD, as in the general population [29, 32]. Hence physical inactivity may be partly responsible for the reduced lean body mass and, in turn, the development of sarcopenia and frailty in patients with CKD.

Studies have demonstrated a correlation between pro-inflammatory cytokines and white blood cell count with frailty in older adults [33–36]. There are increased levels of pro-inflammatory cytokines in CKD, including IL-6 and tumour necrosis factor alpha (TNF-α) [18, 37–39]. This is likely secondary to a combination of impaired clearance of cytokines with progressive renal impairment and exposure to inflammatory stimulants, such as uraemic toxins, dialysis and concomitant infections [19, 37]. The signalling of the anabolic hormones insulin and insulin-like growth factor 1 (IGF)-1 is impaired by these pro-inflammatory cytokines by increasing the activity of glucocorticoids and by directly causing skeletal muscle resistance to insulin and IGF-1 [18, 19, 37, 38, 40]. This incites muscle protein breakdown via the caspase-3 and ubiquitin proteasome system [38]. The inflammatory state is also associated with an increase in resting energy expenditure that may contribute to the imbalance of muscle protein homeostasis and, in turn, the frailty syndrome [18, 19].

Metabolic acidosis develops with progressive renal impairment as the ability of nephrons to excrete the daily acid load is impaired [41]. Metabolic acidosis activates caspase-3 and the ubiquitin proteasome system, inhibits intracellular signalling of insulin and IGF-1 and increases adrenal glucocorticoid production [18, 19, 38]. All of the above result in a state of protein catabolism that, if it persists, can lead to sarcopenia [41].

Prolactin retention occurs with progressive renal impairment [18]. This impairs the production of gonadotropic hormones such as testosterone [18]. Testosterone is an anabolic hormone that promotes muscle protein synthesis [18]. Testosterone deficiency is frequently present in male individuals with ESRD and is independently associated with adverse outcomes [42]. In earlier stages of CKD, testosterone level was an independent predictor of muscle mass and strength [43]. Thus low levels of testosterone in men are likely a factor in the pathophysiology of sarcopenia and, subsequently, frailty.

Low 25-hydroxyvitamin D [25(OH)D] levels are associated with frailty in the older population [35, 44]. 25(OH)D is hydroxylated to the more active 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] in the proximal tubule of the kidney [45]. Levels of $1,25(OH)_2D$ decrease with progressive renal impairment, thus deficiency of $1,25(OH)_2D$ is common in those with CKD [46]. Evidence suggests that vitamin D may act directly on skeletal muscle through genomic and non-genomic pathways, ultimately affecting contractile muscle function and muscle metabolism [45]. Gordon *et al.* [47] demonstrated that $1,25(OH)_2D$ is a determinant of physical function and muscle size in those with CKD. It is therefore conceivable that vitamin D deficiency may be a factor in the development of frailty in CKD, although further study is needed.

Finally, cellular senescence, loss of telomeric structures, mitochondrial dysfunction, increased free radical production and poor DNA repair capability are important in the ageing

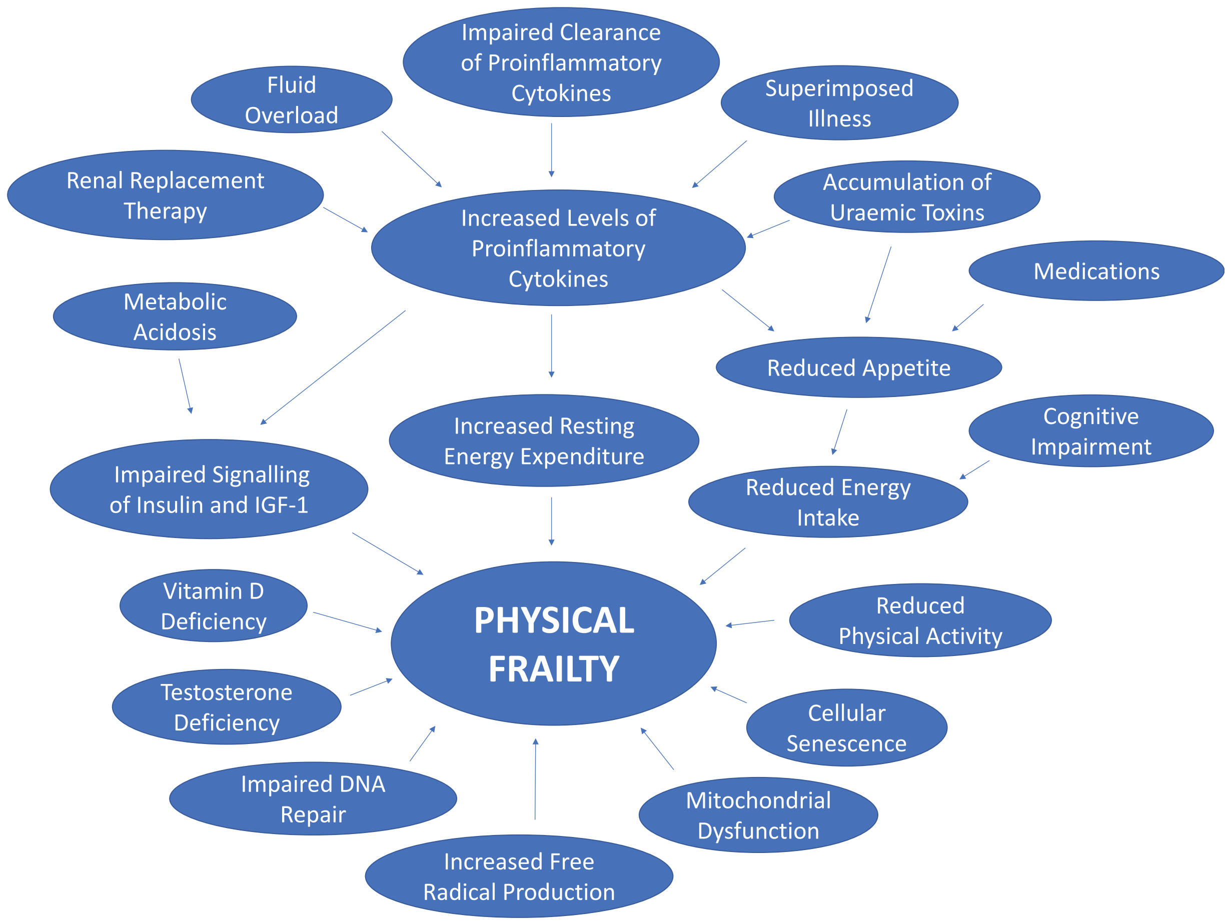

Fig. 1. Putative mechanisms involved in the pathophysiology of physical frailty in CKD.

Table 1. Operationalized definitions of frailty [2, 4–8]

Phenotype model of physical frailty	Cumulative Deficit Model of Frailty
Clinical syndrome involving at least three of the following: 1. Unintentional weight loss 2. Self-reported exhaustion 3. Weakness 4. Slow walking speed 5. Low physical activity	A Frailty Index score is calculated by totaling the number of deficits from a predetermined list of $\geq$ 30 clinical variables including a broad range of medical and psychological conditions and functional impairments.

process and in the development of frailty [48]. These processes occur prematurely in those with CKD and are thought to be the result of the uraemic milieu [49, 50]. They ultimately lead to sarcopenia, vascular dysfunction and progressive organ damage [49, 50]. Although not exhaustive, Figure 1 summarizes fundamental mechanisms involved in the pathophysiology of physical frailty in those with CKD.

Frailty assessment for the nephrologist

In their seminal paper, Fried *et al.* [4] described the Frailty Phenotype (FP) as 'a clinical syndrome involving at least three of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed and low physical activity' (Table 1). They demonstrated that their definition of physical frailty, although having some overlap with disability and comorbidity, was a distinct syndrome and independently predictive of adverse outcomes, including falls, hospitalization and death [4]. Furthermore, the presence of one or two of their frailty criterion, termed intermediate frailty (or pre-frailty), was predictive of becoming frail over the subsequent 3–4 years [4].

The FP has been used in several studies involving patients with CKD. Roshanravan *et al.* [51] reviewed the outcomes for those categorized as frail by the FP in patients with CKD Stages 1–4. They established that the FP is associated with a 2.5-fold [95% confidence interval (CI) 1.4–4.4] increased risk of death or requiring dialysis in those with CKD [51]. Bao *et al.* [9] evaluated the outcomes of those diagnosed as frail at dialysis initiation. They demonstrated that frailty at dialysis initiation was associated with an increased risk of mortality [hazard ratio [HR] 1.57 (95% CI 1.25–1.97)] [9]. They also determined that frailty at dialysis initiation was an independent risk factor for first hospitalization [HR 1.26 (95% CI 1.09–1.45)] [9]. McAdams-DeMarco *et al.* [13] assessed the association between frailty and mortality and hospitalization risk in those established on dialysis. The authors categorized participants as either non-frail, intermediately frail or frail [13]. They found that the proportion of participants admitted to hospital on two or more occasions over the subsequent year after enrolment was 43% for frail dialysis-dependent CKD patients compared with 28% for non-frail dialysis-dependent CKD patients [13]. They also showed that the 3-year mortality was 40% for frail dialysis-dependent CKD patients [13]. Notably, 34% of those categorized as intermediately frail died within the 3-year follow-up period, compared with only 16% of those that were categorized as non-frail [13]. This study thus suggests that differentiating degrees of frailty may offer even greater clinical utility. In an additional study, McAdams-DeMarco *et al*. [52] reviewed the number of falls occurring over a 6.7-month follow-up period of 95 dialysis-dependent CKD patients. They used the phenotype definition of frailty and demonstrated that frailty predicted a 3.09-fold (95% CI 1.38–6.90) greater number of falls in a dialysis-dependent CKD population [52]. There was no difference in the association between frailty and falls for younger and older participants [52].

Notwithstanding the value of the FP, the measures of weakness and walking speed present practical issues, specifically the time and equipment needed to complete the assessments. Therefore, several studies of CKD populations have used modified versions of the FP, often substituting questionnaire-based assessments for the objective measures of weakness and slowness [9, 10, 53–55]. It has been suggested that questionnaire-based methods of assessing frailty are more likely to overestimate the prevalence of frailty, although they still appear to be predictive of outcomes [56–58]. Johansen *et al*. [10] reviewed the outcomes of those fulfilling the criteria of a modified version of the FP with dialysis-dependent CKD. They demonstrated that a modified FP was independently associated with an increased mortality risk in dialysis-dependent CKD [HR 2.24 (95% CI 1.60–3.15)] [10]. They also demonstrated that frailty was associated with an increased risk of the combined endpoint of hospitalization or death [HR 1.56 (95% CI 1.36–1.79)] [10]. Interestingly, these outcomes were unrelated to participant age [10]. Mansur *et al*. [53] reviewed the association of frailty with quality of life in CKD patients. They used a modified version of the phenotype definition of frailty that relied on self-reporting of all domains. They demonstrated that frailty correlated with poorer health-related quality of life as measured by the 36-item Short Form Health Survey (SF-36) [53]. Lee *et al*. [59] performed a similar cross-sectional study in 2015. They also demonstrated that a modified version of the FP was associated with lower health-related quality of life scores as assessed using the SF-36 [59].

Mitnitski *et al*. [7] described a contrasting and more holistic approach to assessing frailty in the general older patient, namely the Cumulative Deficit Model of Frailty. Rockwood *et al*. [5] further developed this model, including a total of 70 variables consisting of a variety of medical and psychological conditions and functional impairments. The total number of deficits for an individual patient was divided by all the predetermined clinical variables to calculate a Frailty Index (FI) score [5]. Rockwood *et al*. [6] subsequently compared the FI with the FP. They performed both measures on 2305 individuals $\geq$70 years of age from the Canadian Study of Health and Aging [6]. They demonstrated that these operational definitions of frailty correlated moderately well with each other [6]. They categorized participants as robust, pre-frail (intermediate frailty) and frail as per the FP [6]. They demonstrated that increasing FI scores correlated with worse outcomes, specifically with respect to survival and institutionalization [6]. The FI accurately predicted outcomes within categories of the FP, suggesting that the FI may be a more precise measure [6]. Hubbard *et al*. [60] demonstrated that frailty can be measured in CKD using an FI. Within their study there was agreement between an FI and a modified version of the FP [60]. The FI is challenging to implement into routine clinical care, as at least 30 variables are required to calculate the score [61–64]. However, with the advent of electronic patient records it may be possible to overcome this challenge. Clegg *et al*. [65] demonstrated that data from primary health care electronic records can be used to create a FI that is predictive of mortality, hospitalization and nursing home admission.

Clinicians' perception of frailty does not correlate well with measured frailty, therefore there definitely is merit in formally assessing frailty [66]. Unfortunately, it has not been agreed what precise operational definition of frailty should be adopted. There is certainly overlap between both these concepts of frailty. However, in the general older population and in the CKD population, the prevalence of frailty differs depending on the approach employed [11, 67]. A study performed by Drost *et al*. [68] effectively demonstrated the inconsistencies in frailty identification when using different operational definitions of frailty. Their study population included 95 patients that were either dialysis-dependent or who had advanced CKD not yet necessitating dialysis [68]. They demonstrated a frailty prevalence of 37% when using the FI and 27% when using the FP criteria, perhaps because the FI is a more holistic approach to the concept of frailty [68]. There have been more CKD studies to date that assess frailty using the FP rather than the Cumulative Deficit Model of Frailty [67]. There is some progress towards a consensus in gerontology, namely that it is useful to identify physical frailty for which a targeted management plan can be developed [69, 70]. Given that currently there is no overall agreement as to which concept of frailty is superior and as both approaches are associated with clinical outcomes, arguably it is more important that efforts are made to identify frailty, regardless of the adopted methodology.

Several frailty screening tools have been developed, although not all have been used in CKD cohorts [61, 71–77]. Following on from their work with the FI, Rockwood *et al*. [5] developed the Clinical Frailty Scale (CFS), which is a frailty screening tool that relies on clinical judgement alone. In its original form, the CFS was a 7-point scale with descriptors for levels of frailty [5]. It has since been updated to include nine descriptors (Figure 2) [61]. In their 2005 study, Rockwood *et al*. [5] demonstrated that the CFS correlated well with the FI in the general population. Higher scores on the CFS were also associated with an increased risk of death [HR 1.30 (95% CI 1.27–1.33)] and institutionalization [HR 1.46 (95% CI 1.39–1.53)] [5]. Alfaadhel *et al*. [76] demonstrated that CFS scores at dialysis initiation are associated with mortality. A subsequent study showed that the CFS performed in patients pre-dialysis is an independent predictor of mortality [78]. Iyasere *et al*. [75] performed the CFS within their study that compared the quality of life and physical function in older patients on assisted peritoneal dialysis and haemodialysis. The authors demonstrated that higher CFS scores are associated with worse health-related quality of life scores [75]. We believe that the CFS is a promising frailty screening tool that could be incorporated into routine clinical nephrology care. Further research is required to establish the construct validity and interrater reliability of the CFS within CKD populations given the inherent subjective nature of the tool.

How should we care for the frail patient with CKD?

The management of frailty is multifaceted and multidisciplinary given that frailty is the result of multiple deficits. A cornerstone

Fig. 2. The 9-point Clinical Frailty Scale was adapted from the 7-point scale used in the Canadian Study of Health and Aging [5] and has been reprinted with permission of Geriatric Medicine Research, Dalhousie University, Halifax, Nova Scotia, Canada.

of the management of frailty is a holistic medical review. Within gerontology, the Comprehensive Geriatric Assessment (CGA) is advocated [1, 79–82]. The CGA is a multidisciplinary, systematic approach to identify the medical, psychosocial and functional needs of older adults [79–81]. This allows the formulation of a targeted management plan that should address current medical conditions and include a medication review, fall prevention measures and anticipatory care planning (Table 2) [79–83]. The use of the CGA in the management of older adults has been associated with improved outcomes, both in terms of physical function and survival [79–81]. Recent studies have demonstrated that it is feasible to use a CGA within nephrology care, although further research is required to assess outcomes [84, 85]. We encourage nephrology services to consider the development of management pathways with local gerontology departments so that patients identified as frail receive specialist geriatric assessment.

Undernutrition is a key contributor to the development of sarcopenia and frailty in those with CKD [18, 19, 70]. First and foremost, it is important to address possible causes for reduced appetite, including medications, uraemia, metabolic acidosis, intercurrent illness and comorbid conditions such as depression [24]. Nutritional supplementation may enhance protein anabolism in the general older patient [86, 87]. A Cochrane review illustrated that calorie supplementation in older adults does lead to a modest but consistent gain in weight [88]. Cheu *et al.* [89] demonstrated that oral nutritional supplementation is associated with positive outcomes, specifically, fewer hospital admissions, in those with ESRD and hypoalbuminaemia, although they did not show any significant effect on survival. The risks of undernutrition and protein-energy wasting may

Table 2. Approach to the management of frail patients with CKD

Practice points

1. Holistic assessment and targeted management strategy, including:
   - Treatment of symptomatic medical conditions
   - Medication review
   - Falls prevention measures
   - Anticipatory care planning
2. Nutrition
   - Consider causes of reduced appetite
   - Dietetic assessment and dietary advice focused on maintaining nutritional status
3. Timely care of complications of CKD
   - Metabolic acidosis
   - Fluid overload
   - Uraemia
4. Individualized exercise training programme
5. Shared decision with the patient regarding the appropriateness of renal replacement therapy

outweigh the benefits of strict phosphate control in the frail CKD cohort, therefore dietary phosphate restriction should be individualized to allow adequate nutritional intake [17, 90–93]. In fact, recent guidelines state that 'preserving nutritional status should prevail over any other dietary restriction' [17]. There is a need for further research that investigates the benefits of phosphate and potassium restriction compared with dietary advice more focused at maintaining adequate nutrition.

Intradialytic parenteral nutrition has been used in dialysis-dependent CKD, although the evidence to date is limited [19, 24, 94, 95]. It may improve nutritional status, but it has yet to be shown to have any beneficial effects on survival [19, 24, 94, 95].

Good and timely care of the complications of CKD is essential to limit the propagation of protein-energy wasting, sarcopenia and frailty [19]. As mentioned earlier, metabolic acidosis develops as renal function declines and is thought to contribute to the development of sarcopenia [41]. Oral sodium bicarbonate treatment in those with mild acidosis is associated with an improvement in nutritional parameters and in muscle strength [96, 97]. Most guidelines currently recommend administering oral sodium bicarbonate when the serum bicarbonate concentration falls below 22 mmol/L, though the target serum bicarbonate level is not well-defined [41, 98]. It is also important to avoid periods of significant fluid overload that can stimulate the inflammatory cascade and subsequent protein catabolism [24]. This requires judicious fluid management that may include fluid restriction, diuretic therapy and renal replacement therapy [24]. Lastly, uraemia leads to protein catabolism and subsequent sarcopenia, therefore the timing of dialysis is likely important—this is discussed in more detail below [18, 19].

Exercise has well-established, multifaceted benefits for patients with all stages of CKD, including improvements in muscle strength, cardiovascular function, physical function and health-related quality of life [99–101]. Aerobic, resistance and combined exercise programmes have been investigated and all have demonstrated benefits for those with CKD [102–112]. Several studies have examined the effects of intradialytic exercise programmes [104, 106, 108, 109, 112]. For example, Konstantinidou *et al.* [104] examined the effect of different programmes and concluded that exercising during non-dialysis days was most effective, but exercising during dialysis was both effective and preferable. So it seems that regardless of the form or mode of exercise, exercise is beneficial for those with CKD. Exercise training is also associated with improved functional performance in frail older adults [113–117]. Although studies to date have not directly targeted frailty status as a primary outcome in frail adults with CKD, it is conceivable that exercise may improve physical frailty in this patient group, provided there is appropriate consideration of the individual patient's medical condition and functional needs. Further work is required to explore the feasibility of a targeted exercise program for frail patients with CKD.

There are potential pharmacological options for frailty under investigation in those with CKD, although further evidence is required before they can be recommended in routine clinical practice [109, 118–123]. Vitamin D replacement is currently recommended for those that are frail and vitamin D deficient, although a randomized controlled trial has not yet been performed [70, 123]. The evidence so far has demonstrated that vitamin D supplementation for those with native vitamin D deficiency is associated with improved outcomes in the elderly, including a reduced risk of falls and risk of hip fractures, improved muscle strength and balance and reduced mortality [70, 124–128]. Vitamin D supplementation in a CKD cohort was also linked with an improvement in physical performance [129].

Finally, how does dialysis affect the trajectory of frailty and should this influence the timing of dialysis or indeed the decision to commence dialysis at all? Kurella Tamura *et al.* [130] assessed the functional status of elderly nursing home residents before and after commencing dialysis. They demonstrated that dialysis was associated with a sustained decline in functional ability rather than an improvement that would be expected if uraemia alone was thought to be the cause of their poor performance status [130]. van Loon *et al.* [131] also demonstrated that physical performance declines while on haemodialysis, especially for older patients. These reports appear at odds with a study by John *et al.* [132] that demonstrated that muscle loss is more pronounced pre-dialysis and that this actually may be ameliorated once dialysis has been established. One of the main difficulties in establishing how dialysis affects the trajectory of frailty is that few studies to date have measured frailty directly and over a sustained period before and after dialysis initiation. A recent study by Johansen *et al.* [133] directly assessed frailty, although participants were already established on dialysis at the time of assessment. They demonstrated that there is variability in frailty scores over time, with a roughly equal difference in those whose frailty scores improved and those that worsened [133]. It thus remains unclear precisely how dialysis affects the trajectory of frailty in patients with advanced CKD. Moreover, in the absence of randomized controlled trials, it is unclear if dialysis, regardless of the modality, offers a significant survival benefit over conservative management for frail older patients with advanced CKD [17, 134, 135]. We recommend that future studies involving patients with advanced CKD assess the FP so that more direct comparisons and more definite conclusions can be made. For the time being, the decision to commence renal replacement therapy should be made in collaboration with the individual patient, outlining the perceived risks and benefits within the context of the limited evidence currently available. If a patient opts for renal replacement therapy, with the lack of a clear consensus, the choice of modality should be governed by patient preference and individual circumstances. We believe that the acknowledgement of frailty in these discussions provides a meaningful opportunity to discern future care wishes of these vulnerable patients.

Conclusion

Frailty is not just a problem faced by geriatricians. Frail patients with CKD are more likely to require hospitalization and more likely to die than their non-frail counterparts. Therefore, nephrologists should actively attempt to identify these vulnerable patients. With no agreement on which frailty assessment approach is superior, for the time being emphasis should be placed on any efforts to identify frailty. Recognizing frailty should prompt a holistic assessment of the patient to address risk factors that may exacerbate its progression and to ensure they have appropriate psychological and social support. Adequate nutritional intake is essential and individualized exercise programmes should be offered. In the same way that the assessment of frailty may be used to guide chemotherapy decisions, with further study nephrologists may be able to use frailty assessments to inform discussions with patients about dialysis initiation [136, 137]. Finally, acknowledging frailty should prompt discussions with patients that establish future care wishes.

Conflict of interest statement

None declared. The views expressed are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health.

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