

Nixon, Andrew C. ORCID: <https://orcid.org/0000-0002-4093-6204> , Bampouras, Theodoros ORCID: <https://orcid.org/0000-0002-8991-4655> , Pendleton, Neil, Woywodt, Alexander, Mitra, Sandip and Dhaygude, Ajay (2018) Frailty and chronic kidney disease: current evidence and continuing uncertainties. *Clinical Kidney Journal*, 11 (2). pp. 236-245.

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## CKJ REVIEW

# Frailty and chronic kidney disease: current evidence and continuing uncertainties

Andrew C. Nixon<sup>1,2</sup>, Theodoros M. Bampouras<sup>3</sup>, Neil Pendleton<sup>4</sup>, Alexander Woywodt<sup>1</sup>, Sandip Mitra<sup>5</sup> and Ajay Dhaygude<sup>1,2</sup>

<sup>1</sup>Department of Renal Medicine, Lancashire Teaching Hospitals NHS Foundation Trust, Preston, UK, <sup>2</sup>Division of Cardiovascular Sciences, University of Manchester, Manchester, UK, <sup>3</sup>Active Ageing Research Group, University of Cumbria, Carlisle, UK, <sup>4</sup>Division of Neuroscience and Experimental Psychology, University of Manchester, Manchester, UK and <sup>5</sup>Manchester Academy of Health Sciences Centre and NIHR Devices for Dignity, Health Technology Cooperative, Manchester, UK

Correspondence and offprint requests to: Andrew C. Nixon; E-mail: andrew.nixon@lthtr.nhs.uk

## 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- $\alpha$ ) [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)<sub>2</sub>D] in the proximal tubule of the kidney [45]. Levels of 1,25(OH)<sub>2</sub>D decrease with progressive renal impairment, thus deficiency of 1,25(OH)<sub>2</sub>D 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)<sub>2</sub>D 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

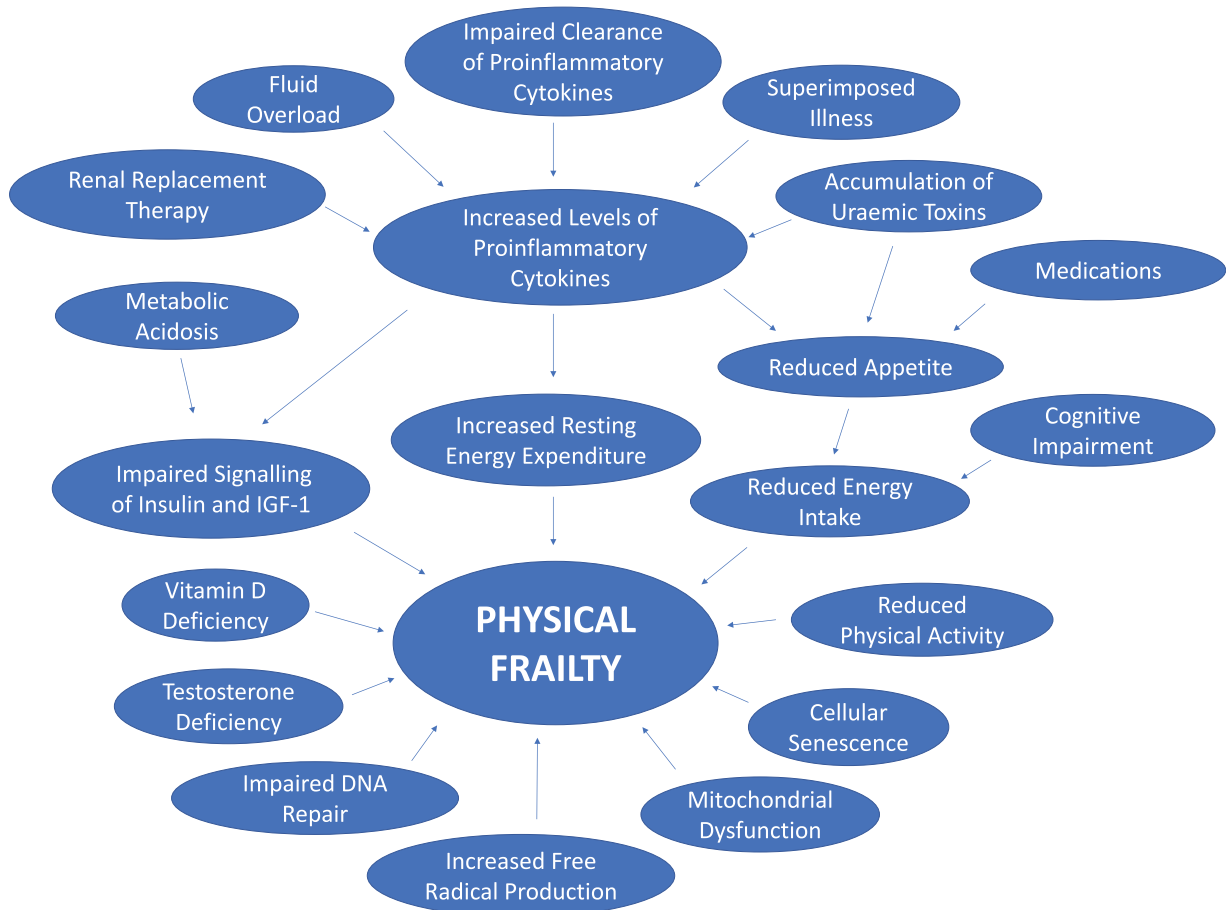


Fig. 1. Putative mechanisms involved in the pathophysiology of physical frailty in CKD.

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: <ol style="list-style-type: none"> <li>1. Unintentional weight loss</li> <li>2. Self-reported exhaustion</li> <li>3. Weakness</li> <li>4. Slow walking speed</li> <li>5. Low physical activity</li> </ol>	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

## Clinical Frailty Scale\*



**1 Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.



**2 Well** – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.



**3 Managing Well** – People whose **medical problems are well controlled**, but are **not regularly active** beyond routine walking.



**4 Vulnerable** – While **not dependent** on others for daily help, often **symptoms limit activities**. A common complaint is being “slowed up”, and/or being tired during the day.



**5 Mildly Frail** – These people often have **more evident slowing**, and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.



**6 Moderately Frail** – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.



**7 Severely Frail** – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).



**8 Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.



**9. Terminally Ill** - Approaching the end of life. This category applies to people with a **life expectancy <6 months**, who are **not otherwise evidently frail**.

### Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

\* 1. Canadian Study on Health & Aging, Revised 2008.

2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489-495.

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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.

## References

1. Clegg A, Young J, Iliffe S *et al.* Frailty in elderly people. *Lancet* 2013; 381: 752–762

2. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci* 2007; 62: 722–727
3. Levers MJ, Estabrooks CA, Ross Kerr JC. Factors contributing to frailty: literature review. *J Adv Nurs* 2006; 56: 282–291
4. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56: M146–M156
5. Rockwood K, Song X, MacKnight C et al. A global clinical measure of fitness and frailty in elderly people. *Can Med Assoc J* 2005; 173: 489–495
6. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. *J Gerontol A Biol Sci Med Sci* 2007; 62: 738–743
7. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Sci World J* 2001; 1: 323–336
8. Walston JD, Bandeen-Roche K. Frailty: a tale of two concepts. *BMC Med* 2015; 13: 185
9. Bao Y, Dalrymple L, Chertow GM et al. Frailty, dialysis initiation, and mortality in end-stage renal disease. *Arch Intern Med* 2012; 172: 1071–1077
10. Johansen KL, Chertow GM, Jin C et al. Significance of frailty among dialysis patients. *J Am Soc Nephrol* 2007; 18: 2960–2967
11. Collard RM, Boter H, Schoevers RA et al. Prevalence of frailty in community-dwelling older persons: a systematic review. *J Am Geriatr Soc* 2012; 60: 1487–1492
12. Ballew SH, Chen Y, Daya NR et al. Frailty, kidney function, and polypharmacy: the atherosclerosis risk in communities (ARIC) study. *Am J Kidney Dis* 2016; 67: 218–226
13. McAdams-DeMarco MA, Law A, Salter ML et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. *J Am Geriatr Soc* 2013; 61: 896–901
14. Kallenberg MH, Kleinvelde HA, Dekker FW et al. Functional and cognitive impairment, frailty, and adverse health outcomes in older patients reaching ESRD—a systematic review. *Clin J Am Soc Nephrol* 2016; 11: 1624–1639
15. Walker SR, Gill K, Macdonald K et al. Association of frailty and physical function in patients with non-dialysis CKD: a systematic review. *BMC Nephrol* 2013; 14: 228
16. Shen Z, Ruan Q, Yu Z et al. Chronic kidney disease-related physical frailty and cognitive impairment: a systemic review. *Geriatr Gerontol Int* 2017; 17: 529–544.
17. Farrington K, Covic A, Aucella F et al. Clinical practice guideline on management of older patients with chronic kidney disease stage 3b or higher (eGFR <45 mL/min/1.73 m<sup>2</sup>). *Nephrol Dial Transplant* 2016; 31(Suppl 2): ii1–ii66
18. Carrero JJ, Stenvinkel P, Cuppari L et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). *J Ren Nutr* 2013; 23: 77–90
19. Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. *J Am Soc Nephrol* 2013; 24: 337–351
20. Ikizler TA, Greene JH, Wingard RL et al. Spontaneous dietary protein intake during progression of chronic renal failure. *J Am Soc Nephrol* 1995; 6: 1386–1391
21. Duenhas MR, Draibe SA, Avesani CM et al. Influence of renal function on spontaneous dietary intake and on nutritional status of chronic renal insufficiency patients. *Eur J Clin Nutr* 2003; 57: 1473–1478
22. Bossola M, Tazza L, Giungi S et al. Anorexia in hemodialysis patients: an update. *Kidney Int* 2006; 70: 417–422
23. Berger I, Wu S, Masson P et al. Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med* 2016; 14: 206
24. Ritter CS, Slatopolsky E. Phosphate toxicity in CKD: the killer among us. *Clin J Am Soc Nephrol* 2016; 11: 1088–1100
25. Ikizler TA, Cano NJ, Franch H et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. *Kidney Int* 2013; 84: 1096–1107
26. Johansen KL, Chertow GM, Ng AV et al. Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int* 2000; 57: 2564–2570
27. Johansen KL, Chertow GM, Kutner NG et al. Low level of self-reported physical activity in ambulatory patients new to dialysis. *Kidney Int* 2010; 78: 1164–1170
28. Bowlby W, Zelnick LR, Henry C et al. Physical activity and metabolic health in chronic kidney disease: a cross-sectional study. *BMC Nephrol* 2016; 17: 187
29. Beddhu S, Baird BC, Zitterkoph J et al. Physical activity and mortality in chronic kidney disease (NHANES III). *Clin J Am Soc Nephrol* 2009; 4: 1901–1906
30. Majchrzak KM, Pupim LB, Sundell M et al. Body composition and physical activity in end-stage renal disease. *J Ren Nutr* 2007; 17: 196–204
31. Kutsuna T, Matsunaga A, Matsumoto T et al. Physical activity is necessary to prevent deterioration of the walking ability of patients undergoing maintenance hemodialysis. *Ther Apher Dial* 2010; 14: 193–200
32. Roshanravan B, Robinson-Cohen C, Patel KV et al. Association between physical performance and all-cause mortality in CKD. *J Am Soc Nephrol* 2013; 24: 822–830
33. Ershler WB, Keller ET. Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu Rev Med* 2000; 51: 245–270
34. Leng SX, Hung W, Cappola AR et al. White blood cell counts, insulin-like growth factor-1 levels, and frailty in community-dwelling older women. *J Gerontol A Biol Sci Med Sci* 2009; 64: 499–502
35. Puts MT, Visser M, Twisk JW et al. Endocrine and inflammatory markers as predictors of frailty. *Clin Endocrinol* 2005; 63: 403–411
36. Schaap LA, Pluijm SM, Deeg DJ et al. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. *J Gerontol A Biol Sci Med Sci* 2009; 64: 1183–1189
37. Carrero JJ, Stenvinkel P. Inflammation in end-stage renal disease—what have we learned in 10 years? *Semin Dial* 2010; 23: 498–509
38. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. *Nat Rev Nephrol* 2014; 10: 504–516
39. Domański M, Ciechanowski K. Sarcopenia: a major challenge in elderly patients with end-stage renal disease. *J Aging Res* 2012; 2012: 754739
40. Hu Z, Wang H, Lee IH et al. Endogenous glucocorticoids and impaired insulin signaling are both required to stimulate muscle wasting under pathophysiological conditions in mice. *J Clin Invest* 2009; 119: 3059–3069
41. Kraut JA, Madias NE. Metabolic acidosis of CKD: an update. *Am J Kidney Dis* 2016; 67: 307–317
42. Carrero JJ, Qureshi AR, Nakashima A et al. Prevalence and clinical implications of testosterone deficiency in men with



- end-stage renal disease. *Nephrol Dial Transplant* 2011; 26: 184–190
43. Cigarran S, Pousa M, Castro MJ *et al*. Endogenous testosterone, muscle strength, and fat-free mass in men with chronic kidney disease. *J Ren Nutr* 2013; 23: e89–95
  44. Bruyere O, Cavalier E, Buckinx F *et al*. Relevance of vitamin D in the pathogenesis and therapy of frailty. *Curr Opin Clin Nutr Metab Care* 2017; 20: 26–29
  45. Molina P, Carrero JJ, Bover J *et al*. European Renal Nutrition (ERN) and Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Working Groups of the European Renal Association-European Dialysis Transplant Association (ERA-EDTA). Vitamin D, a modulator of musculoskeletal health in chronic kidney disease. *J Cachexia Sarcopenia Muscle* 2017; 8: 686–701
  46. Górriz JL, Molina P, Bover J *et al*. Characteristics of bone mineral metabolism in patients with stage 3–5 chronic kidney disease not on dialysis: results of the OSERCE study. *Nefrologia* 2013; 33: 46–60
  47. Gordon PL, Doyle JW, Johansen KL. Association of 1, 25-dihydroxyvitamin D levels with physical performance and thigh muscle cross-sectional area in chronic kidney disease stage 3 and 4. *J Ren Nutr* 2012; 22: 423–433
  48. Walston J, Hadley EC, Ferrucci L *et al*. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 2006; 54: 991–1001
  49. Kooman JP, Kotanko P, Schols AM *et al*. Chronic kidney disease and premature ageing. *Nat Rev Nephrol* 2014; 10: 732–742
  50. Kooman JP, Broers NJH, Usvyat L *et al*. Out of control: accelerated aging in uremia. *Nephrol Dial Transplant* 2013; 28: 48–54
  51. Roshanravan B, Khatri M, Robinson-Cohen C *et al*. A prospective study of frailty in nephrology-referred patients with CKD. *Am J Kidney Dis* 2012; 60: 912–921
  52. McAdams-DeMarco MA, Suresh S, Law A *et al*. Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. *BMC Nephrol* 2013; 14: 224
  53. Mansur HN, Colugnati FA, Grincenkova FR *et al*. Frailty and quality of life: a cross-sectional study of Brazilian patients with pre-dialysis chronic kidney disease. *Health Qual Life Outcomes* 2014; 12: 27
  54. Delgado C, Grimes BA, Glidden DV *et al*. Association of frailty based on self-reported physical function with directly measured kidney function and mortality. *BMC Nephrol* 2015; 16: 203
  55. Delgado C, Shieh S, Grimes B *et al*. Association of self-reported frailty with falls and fractures among patients new to dialysis. *Am J Nephrol* 2015; 42: 134–140
  56. Painter P, Kuskowski M. A closer look at frailty in ESRD: getting the measure right. *Hemodial Int* 2013; 17: 41–49
  57. Johansen KL, Dalrymple LS, Glidden D *et al*. Association of performance-based and self-reported function-based definitions of frailty with mortality among patients receiving hemodialysis. *Clin J Am Soc Nephrol* 2016; 11: 626–632
  58. Johansen KL, Dalrymple LS, Delgado C *et al*. Comparison of self-report-based and physical performance-based frailty definitions among patients receiving maintenance hemodialysis. *Am J Kidney Dis* 2014; 64: 600–607
  59. Lee SJ, Son H, Shin SK. Influence of frailty on health-related quality of life in pre-dialysis patients with chronic kidney disease in Korea: a cross-sectional study. *Health Qual Life Outcomes* 2015; 13: 70
  60. Hubbard RE, Peel NM, Smith M *et al*. Feasibility and construct validity of a frailty index for patients with chronic kidney disease. *Australas J Ageing* 2015; 34: E9–12
  61. Moorhouse P, Rockwood K. Frailty and its quantitative clinical evaluation. *J R Coll Physicians Edinb* 2012; 42: 333–340
  62. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011; 27: 17–26
  63. Searle SD, Mitnitski A, Gahbauer EA *et al*. A standard procedure for creating a frailty index. *BMC Geriatr* 2008; 8: 24
  64. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc* 2010; 58: 681–687
  65. Clegg A, Bates C, Young J *et al*. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing* 2016; 45: 353–360
  66. Salter ML, Gupta N, Massie AB *et al*. Perceived frailty and measured frailty among adults undergoing hemodialysis: a cross-sectional analysis. *BMC Geriatr* 2015; 15: 52
  67. Chowdhury R, Peel NM, Krosch M *et al*. Frailty and chronic kidney disease: a systematic review. *Arch Gerontol Geriatr* 2016; 68: 135–142
  68. Drost D, Kalf A, Vogtlander N *et al*. High prevalence of frailty in end-stage renal disease. *Int Urol Nephrol* 2016; 48: 1357–1362
  69. Rodríguez-Mañas L, Féart C, Mann G *et al*. Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. *J Gerontol A Biol Sci Med Sci* 2013; 68: 62–67
  70. Morley JE, Vellas B, Abellan van Kan G *et al*. Frailty consensus: a call to action. *J Am Med Assoc* 2013; 309: 392–397
  71. van Loon IN, Goto NA, Boereboom FTJ *et al*. Frailty screening tools for elderly patients incident to dialysis. *Clin J Am Soc Nephrol* 2017; 12: 1480–1488
  72. Bohm C, Storsley L, Tangri N. The assessment of frailty in older people with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2015; 24: 498–504
  73. Clegg A, Rogers L, Young J. Diagnostic test accuracy of simple instruments for identifying frailty in community-dwelling older people: a systematic review. *Age Ageing* 2015; 44: 148–152
  74. van Munster BC, Drost D, Kalf A *et al*. Discriminative value of frailty screening instruments in end-stage renal disease. *Clin Kidney J* 2016; 9: 606–610
  75. Iyasere OU, Brown EA, Johansson L *et al*. Quality of life and physical function in older patients on dialysis: a comparison of assisted peritoneal dialysis with hemodialysis. *Clin J Am Soc Nephrol* 2016; 11: 423–430
  76. Alfaadhel TA, Soroka SD, Kiberd BA *et al*. Frailty and mortality in dialysis: evaluation of a clinical frailty scale. *Clin J Am Soc Nephrol* 2015; 10: 832–840
  77. de Vries NM, Staal JB, van Ravensberg CD *et al*. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev* 2011; 10: 104–114
  78. Pugh J, Aggett J, Goodland A *et al*. Frailty and comorbidity are independent predictors of outcome in patients referred for pre-dialysis education. *Clin Kidney J* 2016; 9: 324–329
  79. Stuck AE, Siu AL, Wieland GD *et al*. Comprehensive geriatric assessment: a meta-analysis of controlled trials. *Lancet* 1993; 342: 1032–1036

80. Ellis G, Whitehead MA, Robinson D et al. Comprehensive geriatric assessment for older adults admitted to hospital: meta-analysis of randomised controlled trials. *BMJ* 2011; 343: d6553
81. Welsh TJ, Gordon AL, Gladman JR. Comprehensive geriatric assessment—a guide for the non-specialist. *Int J Clin Pract* 2014; 68: 290–293
82. Turner G, Clegg A. Best practice guidelines for the management of frailty: a British Geriatrics Society, Age UK and Royal College of General Practitioners report. *Age Ageing* 2014; 43: 744–747
83. Fit for Frailty, Part I: Consensus best practice guidance for the care of older people living in community and outpatient settings—a report from the British Geriatrics Society 2014. [http://www.bgs.org.uk/campaigns/fff/fff\\_full.pdf](http://www.bgs.org.uk/campaigns/fff/fff_full.pdf) (12 October 2017, date last accessed)
84. Parlevliet JL, Buurman BM, Pannekeet MMH et al. Systematic comprehensive geriatric assessment in elderly patients on chronic dialysis: a cross-sectional comparative and feasibility study. *BMC Nephrol* 2012; 13: 30
85. Hall RK, Haines C, Gorbalkin SM et al. Incorporating geriatric assessment into a nephrology clinic: preliminary data from two models of care. *J Am Geriatr Soc* 2016; 64: 2154–2158
86. Paddon-Jones D, Rasmussen BB. Dietary protein recommendations and the prevention of sarcopenia. *Curr Opin Clin Nutr Metab Care* 2009; 12: 86–90
87. Paddon-Jones D, Short KR, Campbell WW et al. Role of dietary protein in the sarcopenia of aging. *Am J Clin Nutr* 2008; 87: 1562s–1566s
88. Milne AC, Potter J, Vivanti A et al. Protein and energy supplementation in elderly people at risk from malnutrition. *Cochrane Database Syst Rev* 2009; 2: CD003288
89. Cheu C, Pearson J, Dahlerus C et al. Association between oral nutritional supplementation and clinical outcomes among patients with ESRD. *Clin J Am Soc Nephrol* 2013; 8: 100–107
90. Kalantar-Zadeh K, Tortorici AR, Chen JLT et al. Dietary restrictions in dialysis patients: is there anything left to eat? *Semin Dial* 2015; 28: 159–168
91. Lertdumrongluk P, Rhee CM, Park J et al. Association of serum phosphorus concentration with mortality in elderly and nonelderly hemodialysis patients. *J Ren Nutr* 2013; 23: 411–421
92. Shinaberger CS, Greenland S, Kopple JD et al. Is controlling phosphorus by decreasing dietary protein intake beneficial or harmful in persons with chronic kidney disease? *Am J Clin Nutr* 2008; 88: 1511–1518
93. Lynch KE, Lynch R, Curhan GC et al. Prescribed dietary phosphate restriction and survival among hemodialysis patients. *Clin J Am Soc Nephrol* 2011; 6: 620–629
94. Cano NJM, Fouque D, Roth H et al. Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. *J Am Soc Nephrol* 2007; 18: 2583–2591
95. Dukkipati R, Kalantar-Zadeh K, Kopple JD. Is there a role for intradialytic parenteral nutrition? A review of the evidence. *Am J Kidney Dis* 2010; 55: 352–364
96. Abramowitz MK, Melamed ML, Bauer C et al. Effects of oral sodium bicarbonate in patients with CKD. *Clin J Am Soc Nephrol* 2013; 8: 714–720
97. de Brito-Ashurst I, Varaganam M, Raftery MJ et al. Bicarbonate supplementation slows progression of CKD and improves nutritional status. *J Am Soc Nephrol* 2009; 20: 2075–2084
98. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42(Suppl 3): S1–201
99. Heiwe S, Jacobson SH. Exercise training in adults with CKD: a systematic review and meta-analysis. *Am J Kidney Dis* 2014; 64: 383–393
100. Heiwe S, Jacobson SH. Exercise training for adults with chronic kidney disease. *Cochrane Database Syst Rev* 2011; 10: CD003236
101. Segura-Orti E. [Exercise in haemodialysis patients: a literature systematic review]. *Nefrologia* 2010; 30: 236–246
102. Leehey DJ, Moinuddin I, Bast JP et al. Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study. *Cardiovasc Diabetol* 2009; 8: 62
103. Koufaki P, Mercer TH, Naish PF. Effects of exercise training on aerobic and functional capacity of end-stage renal disease patients. *Clin Physiol Funct Imaging* 2002; 22: 115–124
104. Konstantinidou E, Koukouvou G, Kouidi E et al. Exercise training in patients with end-stage renal disease on hemodialysis: comparison of three rehabilitation programs. *J Rehabil Med* 2002; 34: 40–5
105. DePaul V, Moreland J, Eager T et al. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. *Am J Kidney Dis* 2002; 40: 1219–1229
106. van Vilsteren MC, de Greef MH, Huisman RM. The effects of a low-to-moderate intensity pre-conditioning exercise programme linked with exercise counselling for sedentary haemodialysis patients in The Netherlands: results of a randomized clinical trial. *Nephrol Dial Transplant* 2005; 20: 141–146
107. Rossi AP, Burris DD, Lucas FL et al. Effects of a renal rehabilitation exercise program in patients with CKD: a randomized, controlled trial. *Clin J Am Soc Nephrol* 2014; 9: 2052–2058
108. Cheema B, Abas H, Smith 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
109. Johansen KL, Painter PL, Sakkas GK et al. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. *J Am Soc Nephrol* 2006; 17: 2307–2314
110. Castaneda C, Gordon PL, Parker RC et al. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis* 2004; 43: 607–616
111. Watson EL, Greening NJ, Viana JL et al. Progressive resistance exercise training in CKD: a feasibility study. *Am J Kidney Dis* 2015; 66: 249–257
112. Segura-Orti E, Kouidi E, Lisón JF. Effect of resistance exercise during hemodialysis on physical function and quality of life: randomized controlled trial. *Clin Nephrol* 2009; 71: 527–537
113. Singh NA, Quine S, Clemson LM et al. Effects of high-intensity progressive resistance training and targeted multidisciplinary treatment of frailty on mortality and nursing home admissions after hip fracture: a randomized controlled trial. *J Am Med Assoc* 2012; 307: 24–30
114. Theou O, Stathokostas L, Roland KP et al. The effectiveness of exercise interventions for the management of frailty: a systematic review. *J Aging Res* 2011; 2011: 569194

115. de Labra C, Guimaraes-Pinheiro C, Maseda A et al. Effects of physical exercise interventions in frail older adults: a systematic review of randomized controlled trials. *BMC Geriatr* 2015; 15: 154
116. Binder EF, Schechtman KB, Ehsani AA et al. Effects of exercise training on frailty in community-dwelling older adults: results of a randomized, controlled trial. *J Am Geriatr Soc* 2002; 50: 1921–1928
117. Marijke JM, Paw MCA, de Jong N, Stevens M et al. Development of an exercise program for the frail elderly. *J Aging Phys Activity* 2001; 9: 452–465
118. Ottenbacher KJ, Ottenbacher ME, Ottenbacher AJ et al. Androgen treatment and muscle strength in elderly men: a meta-analysis. *J Am Geriatr Soc* 2006; 54: 1666–1673
119. Iglesias P, Diez JJ, Fernandez-Reyes MJ et al. Recombinant human growth hormone therapy in malnourished dialysis patients: a randomized controlled study. *Am J Kidney Dis* 1998; 32: 454–463
120. Fouque D, Peng SC, Shamir E et al. Recombinant human insulin-like growth factor-1 induces an anabolic response in malnourished CAPD patients. *Kidney Int* 2000; 57: 646–654
121. Niemczyk S, Sikorska H, Wiecek A et al. A super-agonist of growth hormone-releasing hormone causes rapid improvement of nutritional status in patients with chronic kidney disease. *Kidney Int* 2010; 77: 450–458
122. Basaria S, Coviello AD, Travison TG et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010; 363: 109–122
123. Stenvinkel P, Carrero JJ, von Walden F et al. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. *Nephrol Dial Transplant* 2016; 31: 1070–1077
124. Murad MH, Elamin KB, Abu Elnour NO et al. Clinical review: the effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011; 96: 2997–3006
125. Bischoff-Ferrari HA, Willett WC, Orav EJ et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med* 2012; 367: 40–49
126. Rejnmark L, Avenell A, Masud T et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. *J Clin Endocrinol Metab* 2012; 97: 2670–2681
127. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc* 2011; 59: 2291–2300
128. Gillespie LD, Robertson MC, Gillespie WJ et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2012; 15: CD007146
129. Taskapan H, Baysal O, Karahan D et al. Vitamin D and muscle strength, functional ability and balance in peritoneal dialysis patients with vitamin D deficiency. *Clin Nephrol* 2011; 76: 110–116
130. Kurella Tamura M, Covinsky KE, Chertow GM et al. Functional status of elderly adults before and after initiation of dialysis. *New Engl J Med* 2009; 361: 1539–1547
131. van Loon L, Hamaker ME, Boereboom FTJ et al. A closer look at the trajectory of physical functioning in chronic hemodialysis. *Age Ageing* 2017; 6: 1–6
132. John SG, Sigrist MK, Taal MW et al. Natural history of skeletal muscle mass changes in chronic kidney disease stage 4 and 5 patients: an observational study. *PLoS One* 2013; 8: e65372
133. Johansen KL, Dalrymple LS, Delgado C et al. Factors associated with frailty and its trajectory among patients on hemodialysis. *Clin J Am Soc Nephrol* 2017; 12: 1100–1108
134. O'Connor NR, Kumar P. Conservative management of end-stage renal disease without dialysis: a systematic review. *J Palliat Med* 2012; 15: 228–235
135. Foote C, Kotwal S, Gallagher M et al. Survival outcomes of supportive care versus dialysis therapies for elderly patients with end-stage kidney disease: a systematic review and meta-analysis. *Nephrology* 2016; 21: 241–253
136. Handforth C, Clegg A, Young C et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 2014; 26: 1091–1101
137. Rodriguez Villarreal I, Ortega O, Hinostroza J et al. Geriatric assessment for therapeutic decision-making regarding renal replacement in elderly patients with advanced chronic kidney disease. *Nephron Clin Pract* 2014; 128: 73–78