Renal Replacement Therapy

REVIEW

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Physical function management for elderly dialysis patients: prevention and improvement of frailty and disability

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Abstract

Frailty has become an emerging public health problem in the aging society and is regarded as a state of vulnerability to developing increased dependency and/or mortality when exposed to a stressor. As the proportion of elderly dialysis patients is increasing worldwide, frailty has recently influenced on the clinical outcomes among those patients also caused great attention. The prevalence of frailty among dialysis patients has ranged from 3.0- to 10-fold higher than in community-dwelling elderly. Since frailty has been found to be associated with higher mortality, independent of clinical characteristics and comorbidity, interventions to improve frailty have the potential to contribute to better quality of life and lower mortality among dialysis patients. Moreover, clinical research should be focused on the possibility that early rehabilitation of dialysis patients might improve poor outcomes. Current clinical question should aim to take an appropriate strategy to address frailty, including identifying the optimal timing for intervention.

Keywords Frailty, Chronic kidney disease, Dialysis, Mortality, Intervention

Introduction

Since it is known that the highest life expectancy and a persistently low birth rate have been reported in Japan, and is aging more rapidly than that of any other country [1]. Recent systematic review and meta-analysis [2] have shown five studies including 11,940 Japanese people aged 65 years or older living in the community and demonstrated that the pooled prevalence of frailty, pre-frailty, and robustness based on the Fried criteria, were 7.4%, 48.1%, and 44.4%, respectively. Stratified analyses reported that the prevalence of frailty in women was greater than that of men and that increased with age. Currently, there is still limited data concerning the clinical features of frailty and its association with adverse outcomes.

The population undergoing dialysis is aging worldwide, particularly in Japan. The number of prevalent dialysis patients in Japan was 327,336 in 2018 [3], and the mean age of those dialysis patients was 68.75 years (Fig. 1). It is, therefore, becoming urgent for dialysis staff to recognize frailty, which is popular in elderly dialysis patients in Japan.

A particular problematic issue plaguing the elderly dialysis population is the clinical condition of frailty. Frailty has been recognized as a loss of functional, physiologic and cognitive reserves that leads to a vulnerable state [4]. Frailty is also considered to indicate the end of healthy life expectancy and develops as a consequence of the age-related decline in physiological systems, and it increases the risk of adverse outcomes, including falls, delirium, and disability [5]. An urgent perspective for therapeutic clue to frailty is to examine

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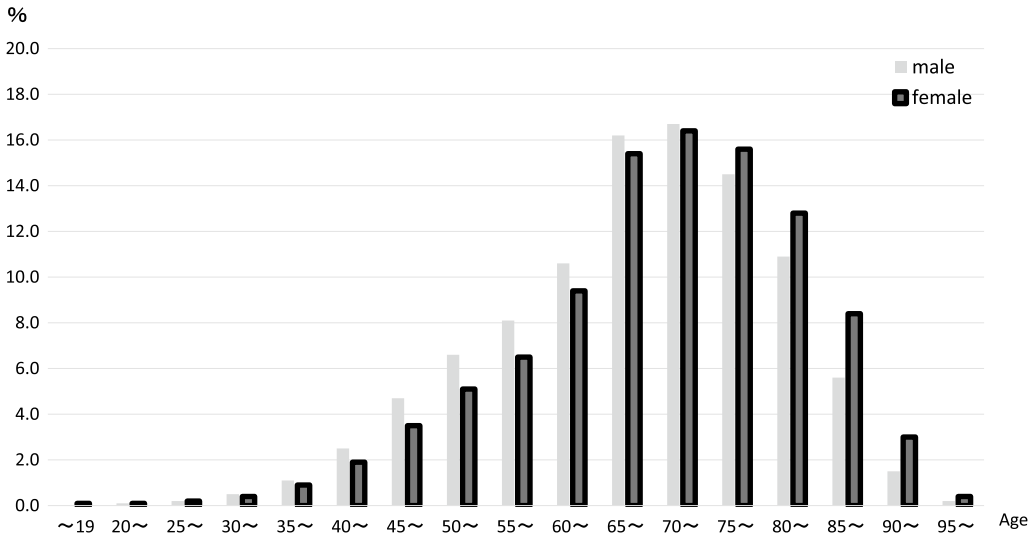

Fig. 1 Distribution of dialysis patients according to age in the Annual Report of the Japanese Society for Dialysis Therapy as of 31 December 2018

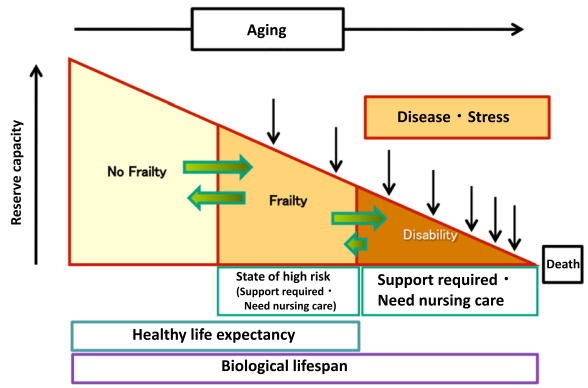

Fig. 2 Gradual progression of disability

how the complex mechanism of aging promotes the cumulative decline of multiple physiological systems, consequent disturbance of homeostatic reserves, and vulnerability to disproportionate changes in health status in response to relatively minor stressor events (Fig. 2).

Potential pathophysiological factors of frailty present in patients with chronic kidney disease (CKD), and the protein energy wasting (PEW), uremic toxins, inflammation, and oxidative stresses, accelerates the aging process in CKD patients [6]. The combination of these risk factors may explain why the frailty phenotype is much more common in the CKD population irrespective of dialysis therapy. The Japanese Society of Renal Rehabilitation published a clinical practice guideline for renal rehabilitation targeting patients who were non-dialysis- and dialysis-dependent and renal transplant recipients in 2019 [7].

Frailty has been reported to be associated with nutritional conditions. PEW is a state of nutritional and metabolic disorders in patients with CKD and end-stage renal disease (ESRD) characterized by the simultaneous loss of systemic body protein and energy storage [8]. PEW is defined as (1) abnormal serum chemistry such as hypoalbuminemia; (2) a loss of body mass; (3) a loss of muscle mass; (4) a decrease in the creatinine production rate, and a decrease in dietary intake. PEW is diagnosed when there is at least one item in > three of the four categories. We should consider the presence of PEW as a risk factor for frailty in elderly dialysis patients.

This article reviews the recent frailty consensus in older adults and how to apply it to the dialysis population.

Definition of frailty

Fried et al. [4] developed a frailty phenotype as a convenient definition of frailty, consisting of at least three of the following unintentional weight loss, exhaustion, physical inactivity, slow gait speed, and weak grip strength. According to this definition, approximately 7% of community-dwelling elderly in a large United States cohort study were frail, and frailty was significantly associated with female sex, older age, and higher comorbidity burden. In order to apply the concept of frailty to patients with CKD or ESRD, the frailty phenotype has been applied in different fashions, the most common of which is to substitute patients' self-report of physical functioning for direct measures of physical performance [9, 10].

To define physical frailty, two ways of approach have become common. The first model consists of adding together an individual's number of impairments and conditions to create a Frailty Index [11]. The second model

was originally defined as a specific physical phenotype consisting of a constellation of 5 possible components: weight loss, exhaustion, weakness, slowness, and reduced physical activity, which marked an underlying physiologic state of multisystem and energy dysregulation [12]. Both of these definitions are currently used to define a frail state and a prefrail state, a condition between the frail state and non-frail state. Many other definitions of frailty have been proposed, but the heterogeneity of definitions may have contributed to the inability to agree on a single operational definition of frailty that satisfies all experts.

A recent consensus conference of European and American frailty experts defined frailty as a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability to developing increased dependency and/or to death [13]. The consensus conference showed 4 recommendations; (1) physical frailty is an important medical syndrome, (2) simple screening tests are available to be used by physicians to recognize frail persons and identify persons with physical frailty or at risk of frailty, (3) physical frailty is a manageable condition, and (4) all persons older than 70 years should be screened for frailty. Since aging and chronic diseases are likely contribute to the development of frailty through mechanisms that include oxidative stress, inflammation, and reductions in serum anabolic hormone levels [11], it is not surprising that CKD, which itself can lead to all of the above, is associated with a higher prevalence of frailty in community-dwelling elderly [14]. However, the definition or the diagnostic criteria of 'Frailty' have not gained the broad consensus.

Prevalence of frailty in the pre-dialysis and dialysis population

CKD patients have numerous metabolic disturbance, accompanied by malnutrition, and it is easy to cause premature occurrence of age-related alterations. The combined effect of aging and CKD may represent a frequent pathophysiological changes [14]. An occurrence of frailty in pre-dialysis CKD has recently considered. A systematic review of frailty in CKD found that several studies have shown a significant relationship between worsening kidney function and poor performance on physical function tests [15]. In a large study of pre-dialysis CKD patients enrolled in the third National Health and Nutrition Evaluation Survey, increasing severity of pre-dialysis CKD patients was frequently associated with appearance of frailty [16], suggesting that more severe metabolic abnormalities carried by worsening kidney function lead to more significant grades of frailty.

Dialysis patients are particularly susceptible to frailty. Using a self-report-based definition of frailty, Johansen et al. assessed the prevalence and characteristics of frailty among the 2275 dialysis patients participating in the Dialysis Morbidity and Mortality Wave 2 study [10]. They revealed that two-thirds of the patients were identified as frail, including those who were under the age of 65 years. A multivariable logistic regression analysis suggested that older age, female sex, and hemodialysis were independently associated with frailty. A Cox proportional hazards model indicated that frailty was independently associated with higher risk of death (adjusted hazard ratio [HR] 2.24, 95% confidence interval [CI] 1.60–3.15) and with a combined outcome of death and hospitalization (adjusted HR 1.63, 95% CI 1.41–1.87). Thereafter, the Fried frailty criteria has been applied to prevalent dialysis populations in the United States [17, 18]. The 30–40% prevalence of frailty in the study cohort was more than Four–sixfold higher than community-dwelling elders. The prevalence of frailty among ESRD patients has varied with the cohorts, probably as a result of differences between the methods used to assess frailty [19]. Differences in patient characteristics, such as dialysis vintage and severity of comorbidities, probably contribute to the variation. Nevertheless, all studies have indicated a significantly higher prevalence of frailty among ESRD patients than among community-dwelling elderly.

Because of the high prevalence of comorbidity in dialysis patients and the high overall mortality, it is important to evaluate whether frailty provides prognostic information in this population. If various comorbidity illness exists already in the dialysis population, the presence of frailty may not improve prediction of adverse outcomes. However, frailty has been shown to be independently related to higher mortality in all studies that have examined the relationship between frailty and mortality to date. Frailty has also been found to be associated with higher risk of falls and fractures [20, 21]. There is an ongoing debate about the value of frailty assessment in dialysis populations and the methods by which frailty should be assessed [22, 23], and longitudinal studies are needed to provide the answers.

Screening and management of frailty

There is general consensus that a geriatric assessment is the good systematic approach for the identification of frailty. Recent information is accumulated for the performance of frailty screening of persons 70 years of age and older by health care providers. Simple rapid screening tests that allow physicians to rapidly identify frail persons have been developed and validated. Examples of some commonly used and validated frailty tools are the FRAIL (Table 1) [24] and the Clinical Frailty Scale (Table 2) [25].

Table 1 The simple "FRAIL" questionnaire screening tool

3 or greater = frailty; 1 or 2 = prefrail
Fatigue: Are you fatigued?
Resistance: Cannot walk up 1 flight of stairs?
Aerobic: Cannot walk 1 block?
Illnesses: Do you have more than 5 illnesses?
Loss of weight: Have you lost more than 5% of your weight in the past 6 months?

A screening approach is also being carried out widely in Japan, and interventions suggested by the consensus group have been provided successfully [26]. They compared the comprehensive geriatric assessment (CGA) between specified elderly individuals at risk of requiring long-term care insurance and uncertified elderly people, and also compared CGA between the risk group and non-risk group, in subcategories of the modified "Kihon Checklist", including the physical strength, nutrition/oral function, overall low score on questions 1–20, houseboundness, cognitive function, and depression risk (Fig. 3). They concluded that the assessments of physical strength and cognitive function were more useful as means of identifying frail elderly.

Several recent studies that specifically examined frailty in dialysis patients suggested that in the absence of intervention, the functional status of elderly patients declines further after initiating dialysis [27, 28]. Thus, treatments or interventions to reverse this downward trajectory must be considered. Because the definition of frailty includes physical inactivity, interventions that increase activity may reverse frailty directly or indirectly if they also improve physical performance or the symptoms of fatigue and exhaustion. Some studies have reported that hemodialysis patients are extremely inactive [29–31] and that their low physical activity is associated with poorer physical performance [32] and lower survival rates

Table 2 The clinical frailty scale (CFS)

CFS score	Interpretation
1	Very fit: robust, active, energetic, motivated, and fit; fittest in their age group
2	Well: without active disease but not as fit as those in category 1
3	Well: with treated comorbid disease
4	Apparently vulnerable: not dependent but has symptoms from comorbid disease (such as being slowed up)
5	Mildly frail: limited dependence on others for instrumental activities of daily living
6	Moderately frail: help is needed for instrumental activities of daily living and activities of daily living
7	Severely frail: completely dependent on others for instrumental activities of daily living and activities of daily living or terminally ill
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

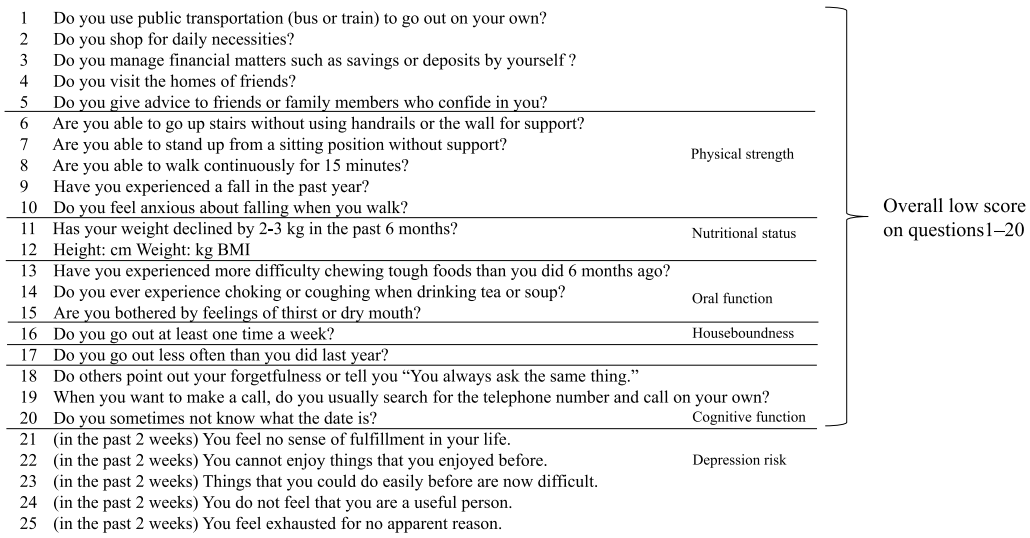

Fig. 3 Modified Kihon Checklist of 25 items and seven categories for screening "specified elderly" individuals for frailty

[33, 34]. Although few studies to date have focused on increasing habitual physical activity in the different dialysis population [35, 36], this strategy seems promising and warrants further investigation. Even in the absence of solid evidence for such benefit, dialysis patients should be encouraged to follow physical activity guidelines for elderly dialysis patients.

Several studies have focused on active exercise training programs designed to increase the exercise capacity or physical performance of dialysis patients [37]. Although many of the study cohorts were small and/or of low quality, aerobic exercise training would seem to have the potential to improve frailty, given that most of the patients showed improvements and that patients with lower baseline functional activities showed greater benefits in one of the largest of these exercise intervention studies [38]. However, the vigorous nature of such training programs has led to large numbers of hemodialysis patients being excluded from such studies, and frail patients are more likely to meet exclusion criteria. Also, a large proportion of patients decline to participate in such programs [37], suggesting that fear or reluctance to engage in vigorous activity is a barrier to patients' adoption of exercise programs. Thus, the extent to which aerobic exercise training during dialysis or at some other time can reverse frailty remains to be determined.

Because muscle weakness is part of frailty, and muscle atrophy is a key underlying mechanism [39], resistance exercises or other anabolic interventions might be valuable options for ameliorating frailty in the dialysis population [40]. Indeed, resistance training has been shown to increase muscle strength in both hemodialysis patients [39] and institutionalized nonagenarians [41], demonstrating that such programs are not only possible but that they can also be beneficial in extremely low functioning patients. Referral of frail individuals for physical therapy and strength training should therefore be considered when muscle weakness or frailty is detected.

Interventions for frail elderly

Early identification of poor physical function and physical inactivity is essential to the comprehensive management of patients on hemodialysis. Strategies such as community-based interventions need to be developed to reduce the risk of disability, including physical frailty, worldwide. Physical frailty is bidirectional and potentially reversible. Therefore, interventions have been developed to address certain conditions, and exercise has been shown to exert a positive functional effect on physical frailty [42]. For elderly adults at high risk of disability, although interventions comprising exercise, nutrition and/or education can improve their quality of life, there is little evidence as to whether these interventions reduce the onset of disability with physical frailty [43]. However, recently, Makizato et al. [44] reported the potential for a community disability prevention program to reduce the disability among frail elderly individuals, aged 65 years or older, living in the community.

A recent systematic review reported that exercise interventions are beneficial, feasible, and can be performed safely in patients with ESRD [45]. Both aerobic and resistance exercise interventions provided in a dialysis facility or elsewhere led to improvements in physical activity [46]. However, some uncertainties remain about provision for dialysis patients, including indefinite bias about the appropriate modality and grade of exercise, the optimal timing of intervention, safety and health concerns, and frequent hospitalizations and changes in clinical condition that can interrupt training. Consensus has been difficult to reach because of the heterogeneity of the ESRD population, the presence of various comorbidities, and the difficulty in providing long-term intervention due to a high drop-out rate in the studies to date and high mortality among these patients.

Recently, a clinical algorithm for managing physical frailty in patients who require hemodialysis therapy was reported by Matsuzawa et al. [47]. The algorithm is based on an understanding of the patient's physical function, physical activity level, and exercise interventions. The study also evaluated the effects on all-cause mortality and cardiovascular events of participation in a program aimed at regular management of physical frailty, which consists of routine assessment of physical function and activity with feedback [48]. Participants with lower rates of program attendance had increased risks of mortality and cardiovascular events compared with those with regular attendance.

Participation in any exercise intervention has been reported to modify various risk factors for sarcopenia and physical frailty in general. A report on the EXCITE trial—a multicenter, randomized trial in patients on dialysis—revealed that a simple, personalized, low-intensity, home-based exercise program could improve functional status, including muscle strength and exercise capacity, in dialysis patients compared with standard care [49]. In addition, an analysis restricted to those patients who completed the 6-months intervention program revealed that hospitalization-free survival was significantly lower in the exercise group than in the control group. Recently, Matsuzawa has shown the results of exercise intervention in dialysis patients [50].

Nutritional intervention is important to prevent the onset and progression of frailty. However, it remains controversial to decide ideal dietary protein intake in elderly frail dialysis patients. Usually, 1.0–1.2 g/kg/day is recommended for dialysis patients to preserve muscle mass

[51]. When focusing on maintenance of skeletal muscle in dialysis patients, amino acid supplementation is reasonable. Amino acids are not only precursors for muscle protein synthesis but also stimulators of intracellular signaling. Among essential amino acids, leucine has a distinct anabolic action [52]. A recent systematic review reported no effects of supplementation with essential amino acids on muscle mass, muscle strength, or physical performance, whereas a significant effect of leucine on muscle mass was shown in subjects with sarcopenia as compared with healthy subjects [53]. Following exercise or physical activity, nutritional supplementation should be able to provide synergistic beneficial effects on maintenance of skeletal muscle in dialysis patients [54].

Conclusion

Frailty is often seen in the elderly dialysis patients and is associated with adverse outcomes, including disability, death, hospitalization, falls, and fractures. Studies are required to determine whether interventions can improve frailty. The potential association between frailty of pre-dialysis patients and higher risk of ESRD would suggest that early intervention may be effective, but it is also important to consider the dialysis patients whose current functional activity is extremely impaired.

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KN planned the review, searched the literature, and prepared the article. NH searched the literature and assisted in writing the article. KT planned the context of this article and assisted in writing the article. All authors read and approved the final manuscript.

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