Recent Advances of Sarcopenia and Frailty in CKD

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Preface

There is increasing interest in actively addressing sarcopenia and frailty in the field of CKD. Experimental studies have demonstrated that uraemia facilitates skeletal muscle wasting via multiple mechanisms such as increased inflammatory cytokines, reactive oxidative species, insulin resistance, metabolic acidosis and accumulated uremic toxin. Recent advances have focused on skeletal muscle renewal, the role of mitochondrial pathophysiology and exercise mimetics. Skeletal muscle progenitor cells, termed as satellite cells, provide new nuclei to myofibres, thus contributing to the increase and maintenance of muscle mass. Abnormalities of mitochondrial structure, function and composition are also observed in muscular cells in uraemia.

The prevalence of sarcopenia and frailty increases substantially in the advanced CKD stages. Sarcopenia and frailty are closely associated with adverse outcomes such as falls, bone fracture, cognitive impairment, major cardiovascular events and mortality. The frailty syndrome is also related to the risk of advancing to end-stage kidney disease.

Recent clinical guidelines have recommended the interventions of regular exercise/physical activity and nutritional support in the prevention and treatment of sarcopenia and frailty. However, there is still debate about the best therapeutic approaches, as well as the impact on outcomes of current approaches based on different exercise and nutritional programmes.

In this eBook, we aim to clarify the recent advances of diagnoses, epidemiology and clinical outcomes of sarcopenia and frailty in CKD patients. We further provide a better understanding of the prevention and management of sarcopenia and frailty in CKD patients to improve renal and overall health, as well as directions for future basic and clinical research.

Lastly, we sincerely thank all the authors for writing the chapters despite limited time due to their busy clinical, educational and research work schedule.

Hamamatsu, Japan — Akihiko Kato

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Epidemiology of Sarcopenia and Frailty in CKD

1

Akihiko Kato

Abstract

Chronic kidney disease (CKD) is very common in the elderly. CKD-related metabolic derangements increase the risk of skeletal muscle wasting, so the prevalence of sarcopenia and frailty are substantially higher in CKD patients compared to the general population. Sarcopenia is defined according to the Asian Working Group for Sarcopenia (AWGS), while frailty according to the Japanese version of the Cardiovascular Health Study (J-CHS) in Japan. Sarcopenia and frailty are closely associated with protein-energy wasting. Frailty is also more prevalent in female than in male in CKD patients.

Sarcopenia and frailty are both related to survival prognosis and accelerated progression to end-stage kidney disease in patients with non-dialysis-dependent CKD. In dialysis patients, low muscle strength rather than muscle mass volume is more strongly associated with physical inactivity, inflammation, and total mortality. Frailty is also an independent predictor of cognitive impairment, hospitalization, and mortality in the dialysis population.

Given the convincing relationship between sarcopenia, frailty, and adverse clinical outcomes, we should be more aware of the concept of sarcopenia and frailty and prevent their progressions especially in older patients with advanced CKD.

Keywords

CKD prevalence · Definition · Protein-energy wasting · Renal outcome · Mortality

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1.1 Introduction

Sarcopenia is a progressive and generalized "skeletal muscle disease" that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality. In contrast, frailty is "a geriatric syndrome" that is observed as the decline over a lifetime in multiple physiological systems, resulting in negative consequences to physical, cognitive, and social dimensions.

In this chapter, demonstrating after the current trends of CKD epidemiology, I review the epidemiology of sarcopenia and frailty in patients with non-dialysis and dialysis-dependent CKD.

1.2 Current trends in CKD epidemiology

1.2.1 Renal Replacement Therapy (RRT)

More than 2 million people worldwide are being treated for end-stage renal disease (ESRD). The global incidence of dialysis more than doubled from 44 incidents per million people (pmp) in 1990 to 93 pmp in 2010 [1]. The global prevalence of maintenance dialysis has also increased 1.7 times, from 165 pmp in 1990 to 284 pmp in 2010. A systematic review [2] also estimates that 2.6 million people received RRT worldwide in 2010, whereas the number of patients requiring RRT is between 4.9 and 9.7 million. This review also points out that, with rising global incomes, worldwide use of RRT will be more than double to 5.4 million people in 2030, with the most growth in Asia (1.0 million to a projected 2.2 million) and most rapid relative increase projected in Latin America (from 0.37 million in 2010 to 0.90 million by 2030).

In contrast, in already developed nations that provide universal access to maintenance dialysis, there has been a plateauing in rates of ESRD, with recent declines in incidence. In the USA, ESRD incidence adjusted for age, sex, and race/ethnicity was 386 pmp in 2003, but decreased to 356, 352, and 351 pmp in 2011, 2012, and 2013, respectively [3]. In Japan, the actual number of new dialysis patients with diabetic nephropathy has almost been unchanged for the recent few years [4].

1.2.2 Non-dialysis CKD

A meta-analysis of 44 country prevalence studies [5] have demonstrated that the worldwide prevalence of CKD at 13.4% in 2010 (95% confidence interval [95% CI], 11.7–15.1%). A survey of 33 prevalence studies [6] also estimates worldwide prevalence of CKD at 10.4% in men (95%CI, 9.3–11.9%) and at 11.8% in women (95%CI, 11.2–12.6%), with a 15% higher prevalence in low- and middle-income countries compared with high-income countries. The Global Burden of Disease study [7] predicts that there were 21 million incident case of CKD

per year, 276 million prevalent cases, and nearly 1.2 million death and 35 million years of healthy life lost due to CKD in 2016.

The prevalence of CKD is especially high in the elderly. Analyses of recent data from the US National Health and Nutrition Examination Survey (NHANES) demonstrated that the crude prevalence of CKD at stages G3 (eGFR from 30 to 59 ml/min/1.73 m^2) and G4 (eGFR from 15 to 29 ml/min/1.73 m^2) were 4.1% in subjects aged 20–39 years and 10.8% in those aged 40–64 years, while it reached 31.5% in those aged 65–79 years and 65.0% in those over 80 years [8]. Similarly, in Japan, prevalence rates of stage G3 and G4 CKD have been estimated at 43.1% in males and 44.5% in females aged over 80 years old [9].

1.2.3 Clinical Outcomes of CKD

In addition to being a precursor to ESRD, CKD is a potent risk factor for other adverse outcomes, such as acute kidney injury, cardiovascular disease, and mortality. The risk of ESRD, or death related to CKD comorbidities prior to dialysis initiation, varies by age. Analyses of data from a cohort of US veterans [10] demonstrated that younger patients (18–44 years old) were at risk of reaching ESRD before death at eGFR <45 ml/min/1.73 m^2, whereas for older patients (65–84 years old), the risk of ESRD first exceeded death at an eGFR of <15 ml/min/1.73 m^2. It was also demonstrated that the risk of death always exceeded the risk of ESRD among those 85 years or older. Among patients with CKD stage G4 who were referred to nephrologists, the rate of death without requiring RRT increased from the age of 50 years onwards, and exceeded that of RRT in incident patients aged ≥80 years old [11]. Specifically, older patients with low-grade proteinuria were more likely to die before requiring RRT [11]. A retrospective review of CKD in stage G3 to G5 patients also demonstrated that younger individuals are at higher risk of ESRD, whereas older individuals are more likely to die prior to developing ESRD [12]. The review found that the risk of death prior to ESRD relative to the onset of ESRD was about threefold higher for CKD stage G3, while equal for stage G4, and lower for stage G5, after adjusting for age and other cofounders [12]. It follows from these studies, therefore, that the oldest CKD patients almost died before the initiation of RRT.

In Japan, a cohort study in 461 referred CKD patients (mean age: 67.0 years) demonstrated that the incidence of death before RRT was 2.8/100 patient-years and none had ESRD among CKD stage 3 patients older than 65 years without overt proteinuria during median follow-up was 3.2 years [13]. Newly visiting CKD patients with normal-range proteinuria also did not exhibit a decline of kidney function even in advanced CKD stages 4–5 under specialized nephrology care [14]. The observations suggest that elderly CKD patients with normal-range proteinuria may not exhibit CKD progression even in advanced CKD stage. Therefore, elongation of a healthy life expectancy is more complicated than simply slowing eGFR decline in the elderly with CKD stage G3 and G4.

1.3 Epidemiology of Sarcopenia in CKD

1.3.1 Definition of Sarcopenia

Sarcopenia originally refers to the age-related reduction of appendicular skeletal muscle mass volume. However, in recognition that loss of strength or physical function often accompanies loss of muscle mass, it has been defined to include both low muscle mass and compromised functionality, such as reduced handgrip strength and/or slower gait speed.

Recently, the European Working Group on Sarcopenia in Older People (EWGSOP2) [15] updates the original definition in order to reflect scientific and clinical evidence that has built over the last decade. The working group recognizes sarcopenia, i.e., muscle failure, as "a muscle disease" rooted in adverse muscle changes across a lifetime that may be acute or chronic. Sarcopenia is defined by low levels of measures for three parameters in numerical order: (1) muscle strength, (2) muscle quantity/quality, and (3) physical performance as an indicator of severity (Table 1.1). They also recommend an algorithm for case-finding, diagnosis, and severity determination for systematic and consistent identification of people with sarcopenia or its risk.

In Asia, the Asian Working Group for Sarcopenia (AWGS) [16] defined the cutoff values for muscle mass measurements (7.0 kg/m^2 for men and 5.4 kg/m^2 for women by using dual X-ray absorptiometry, and 7.0 kg/m^2 for men and 5.7 kg/m^2 for women by using bioimpedance analysis), handgrip strength (<26 kg for men and <18 kg for women), and usual gait speed (<0.8 m/s) for the elderly. A revised consensus paper of AWGS (AWGS2019) has been recently published (Chen LK, et al. J Am Med Dir Assoc, in press). In this revision, calf circumference (<34 cm for men and <33cm for women) is available for the screening of sarcopenia. In addition, the cutoff of handgrip strength for men is elevated to <28 kg. Low physical perfomance can be diagnosed by either usual gait speed (<1.0 m/s), 5 sit to stand test (> or = 12 sec), or short physical perfprmance battery (< or = 9 points).

Table 1.1 EWGSOP2 sarcopenia cutoff points

Test	Cutoff points for men	Cutoff points for women
Low strength by chair stand and grip strength		
Grip strength	<27 kg	<16 kg
Chair stand	>15 s for five rises	
Low muscle quantity		
ASM	<20 kg	<15 kg
ASM/height^2	<7.0 kg/m^2	5.5 kg/m^2
Low performance		
Gait speed	≤0.8 m/s	
SPPB	≤8 point score	
TUG	≥20 s	
400 m walk test	Non-completion or ≥6 min for completion	

ASM appendicular skeletal muscle mass, *SPBB* short physical performance battery, *TUG* timed-up-and-go test

1.3.2 Sarcopenia in Non-dialysis CKD

The prevalence of sarcopenia is higher among adult patients with non-dialysis-dependent CKD compared to the general population, ranging from 5.9 to 50.0% [17–21] (Table 1.2). Sarcopenia is more prevalent in men than in women [19, 20]. An increased risk of sarcopenia is associated with age, body mass index, diabetes mellitus, and loop diuretic use [20].

Sarcopenia is related to survival prognosis [17] and GFR decline [19]. A lower bilateral psoas mass area at CT slice is an independent predictor of major adverse cardiovascular events in CKD patients [22].

1.3.3 Sarcopenia in Dialysis Patients

Dialysis patients exhibit more functionally muscle wasting than patient with CKD stage G4 [23]. The prevalence of sarcopenia is substantially high among hemodialysis (HD) patients, ranging from 9.5 to 37.1% (Table 1.3) [24–29]. The prevalence of sarcopenia was 8.4% in Japanese peritoneal dialysis (PD) patients using the AWGS criteria [30].

Low muscle strength rather than muscle mass volume was more strongly associated with physical inactivity, inflammation, and mortality than low muscle mass in incident dialysis patients [24]. Physical performance measures, including slow gait speed and weak grip strength, were also associated with mortality even after adjustment for

Table 1.2 Prevalence of sarcopenia in CKD patients not yet on dialysis

N	Age (years)	Mean eGFR (ml/min/1.73 m^2)	Definition	Prevalence of sarcopenia (%)	Reference
287	59.9 ± 10.5 (Brazil)	25.0 ± 15.8	Handgrip (<30th percentile of a reference population adjusted for sex and age) ASM/height^2 (BIA) (Male <10.76, Female <6.76 kg/m^2)	5.9	[17]
100	73.6 ± 9.2 (Brazil)	36.0 ± 16.0	EWGSOP FNIH	11.9 28.7	[18]
148	66 [19–87] (Sweden)	22.5 ± 8.2	EWGSOP	13.5	[19]
260	79 [69–80] (Japan)	31.5 ± 12.9	AWGS	25.0	[20]
80	73.7 ± 7.2 (Italy)	28.3 ± 9.8	EWGSOP	12.5 (60–74 years) 50.0 (≥75 years)	[21]

ASM appendicular skeletal muscle mass, *EWGOP* European Working Group on Sarcopenia in Older people, *FNIH* Foundation for the National Institutes of Health, *AWGS* Asian Working Group for Sarcopenia, *BIA* bioelectrical impedance analysis

Table 1.3 Prevalence of sarcopenia in dialysis patients

N	Age (years) (country) [reference]	Sample characteristics	Cutoff values		Prevalence of sarcopenia (%)
			Appendicular SMI (kg BW/height m^2)	Handgrip (kg)	
330	53 ± 13 (Sweden) [24]	Incident (HD 100%)	DEX Male <7.3 Female <5.5	Male <30 Female <20	20.6
95	64 ± 10 (South Korea) [25]	Prevalent (HD 57%)	BIA (2SDs below the sex-specific mean of young adults)		9.5
102	71 ± 7 (Brazil) [26]	Prevalent (HD 73.5%)	1. DEX 2. BIA (2SDs below the sex-specific mean of young adults)		1. 30.6 2. 12.7
111	77.5 (71–85) (France) [27]	Prevalent (HD 100%)	BIA Male <8.87 Female <6.42		31.5
645	56.7 ± 14.5 (USA) [28]	Prevalent (HD 100%)	BIS-derived total-body muscle mass to $height^2$, BW, BSA, and BMI (2SDs below the sex-specific mean of young adults)	Male <26 Female <16	$Height^2$: 3.9 BW: 11.4 BSA: 15.9 BMI: 14.0
170	70 ± 7 (Brazil) [29]	Prevalent (HD 100%)	DEX (2SDs below the sex-specific mean of young adults)	Male <30 Female <20	37.1

HD hemodialysis, *SMI* skeletal muscle mass index, *DXA* dual energy X-ray absorptiometry, *BIA* bioelectrical impedance analysis, *BIS* bioelectrical impedance spectroscopy, *BSA* body surface area, *BW* body weight, *BMI* body mass index

muscle size and other confounders in prevalent HD patients [28]. Low muscle strength was associated with worse quality of life (QOL) domains [29]. So, functional limitations (in strength or speed) are mainly associated with mortality, whereas muscle size appeared to be less important with regard to survival among dialysis patients.

Sarcopenia is also related to accelerated changes of arteriosclerosis. Reduced thigh muscle mass area is independently related to arteriosclerotic parameters such as carotid artery intima-medial thickness, brachial-ankle pulse wave velocity, and ankle-brachial pressure index, indicating that thigh sarcopenia is closely associated with systemic changes of arteriosclerosis in HD patients [31].

1.4 Epidemiology of Frailty in CKD

1.4.1 Definition of Frailty

Frailty is "a multidimensional geriatric syndrome" that is characterized by cumulative decline in multiple body systems or functions. Frailty increases

vulnerability to poor health outcomes such as disability, hospital admission, reduced QOL, and even death.

There are two approaches to assessing frailty: one is phenotype model [32] and the other is accumulated deficit model [33]. The physical phenotype of frailty, originally described by Fried and co-workers [32], is characterized by the phenotype according to limitations in three or more of the following five conditions based on Cardiovascular Health Study (CHS): slow gait speed, weakness, exhaustion, low activity, and weight loss. This criteria overlaps with sarcopenia; low grip strength and slow gait speed are characteristic of both.

In contrast, frailty index, a typical accumulated deficit model, is to count deficits in health (which can be symptoms, signs, diseases, disabilities or laboratory, radiographic or electrocardiographic abnormalities) on the grounds that the more deficits a person has, the more likely that person is to be frail. This index is often expressed as a ratio of deficits present to the total number of deficits considered [34].

To date, fundamental differences in the conceptualization of frailty among these approaches result in long-standing hurdles to uniform agreement on a single definition that can be used for identifying those who are at high risk and in need of comprehensive care.

1.4.2 Modified Definition of Frailty in Japan

The Kihon Check List (LCL), which consists of 25 questions to screen participants who require care prevention, is used as a screening tool to assess frailty in Japan [35]. KCL is divided into the eight domains: instrumental activities of daily living (ADL), social ADL, exercise, falling, nutrition, oral function, cognitive function, and depression. Participants are asked to respond either "negative" (score: 1) or "positive" (score: 0), for a total score of 25. Frailty is evaluated by the total points as follows: frail, 8–25 points; pre-frail, 4–7 points; and robust, 0–3 points [35].

Frailty can be also diagnosed by the Japanese version of the Cardiovascular Health Study (J-CHS) [36]. Slow gait speed is established based on a cutoff of <1.0 m/s. Weakness is defined using maximum grip strength and was established according to a sex-specific cutoff (<26 kg for men and <18 kg for women), identical to AWGS criteria [16]. Exhaustion is considered present if a participant responded "yes" to the following question included in the KCL: "In the last 2 weeks, have you felt tired without a reason?" Physical activity is evaluated by asking the following questions about the time spent engaged in exercise: "Do you engage in low levels of physical exercise aimed at health?" If participants answered "no" to the questions, we classified them to the low activity category. Weight loss was assessed by a response of "yes" to the question, "Have you lost 2 kg or more in the past 6 months?". Participants who do not have any of these components are considered as non-frail (robust), and those with one or two components were considered as pre-frail.

1.4.3 Frailty in Non-dialysis CKD

The prevalence of frailty defined by the Fried phenotype [32] ranges from 7 to 20.9% in pre-dialysis patients [37]. Frailty phenotypes such as body weight loss, low physical activity, and slow gait speed are independently associated with CKD progression and/or total mortality in CKD stages G1 to G4 patients [38]. Physical function such as gait speed and handgrip decreases in ambulant patients with CKD stage 4 or 5 than those with CKD stage 2 or 3 [39].

In community-dwelling Japanese older adults, participants with CKD stage 4 or 5 were more frail (odds ratio [OR] 1.90, 95% confidence interval [CI] 1.01–3.59). In addition, the individuals with a history of diabetes (OR 2.76, 95% CI 1.21–8.24), hypertension (OR 2.53, 95% CI 1.45–5.12), or both (OR 3.67, 95% CI 1.13–14.1) showed a significantly higher risk of frailty [40]. In addition, reduced kidney function (CKD stage 4–5) was associated with a higher risk of weight loss, low physical activity, and slowness [41].

The frailty phenotype was associated with an estimated 2.5 (95% CI, 1.4–4.4)-fold greater risk of death or incident dialysis therapy [42]. Frailty is independently linked to adverse outcomes such as lower physical and metal QOL [43], and limited activity of daily life (ADL) [44].

1.4.4 Frailty in Dialysis Patients

The prevalence of frailty is high in the dialysis populations, ranging from 24 to 78% [37]. However, since several studies have made modification to the frailty phenotype originally proposed, reported prevalence changes depending on the method of frailty assessment [37]. The prevalence of pre-frailty and frailty based on J-CHS criteria [36] was 52.6 and 21.4% in prevalent 413 Japanese HD patients (mean age 67.2 ± 11.9 years old). The 56.6% of the patients were categorized as pre-frailty and 32.7% as frailty among those aged over 75 years old ($n = 113$) [45]. The prevalence of frailty is reported as 10.9% when diagnosed using the Clinical Frailty Scale [30] in Japanese PD patients.

Frailty is an independent predictor of mortality and hospitalization in maintenance dialysis patients [46]. All five phenotype components are associated with higher mortality, and gait speed was the strongest individual predictor. The number of frailty components met was associated with mortality in a gradient that ranged from a hazard ratio of 2.73 for one component to 10.07 for five components met [47], indicating that measurement of all components was exclusively essential for optimal mortality prediction.

Frailty is also associated with impaired cognitive function using the Modified Mini-Mental State test and Trail Making Tests A and B among patients new to HD [48].

Table 1.4 Criteria for the clinical diagnosis of PEW in CKD

Serum chemistry
Serum albumin<3.8 g/dL (Bromocresol green assay)
Serum transthyretin <30 mg/dL (for maintenance dialysis patients only)
Serum cholesterol<100 mg/dL
Body mass
Body mass index (BMI) <23 kg/m^2
Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
Total body fat percentage <10%
Muscle mass
Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months
Reduced mid-arm muscle circumference area (reduction >10% in relation to 50th percentile of reference population)
Creatinine appearance
Dietary intake
Unintentional low daily protein intake <0.80 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients with CKD stages 2–5
Unintentional low daily energy intake <25 kcal/kg/day for at least 2 months

Incident dialysis patients self-reporting frailty experienced nearly twice the risk of medically urgent falls or fractures compared to those who did not report frailty [49].

1.5 Association of Protein-Energy Wasting with Sarcopenia, and Frailty Phenotype

Protein-energy wasting (PEW) is defined by an expert panel of the International Society of Renal Nutrition and Metabolism (ISRNM) in 2008 as the loss of somatic and circulating body protein and energy reserves [50]. PEW develops as the consequence of a combination of insufficient, uremic toxins, systematic inflammation, and superimposed catabolism. PEW can be diagnosed if at least 3 of the 4 listed categories (and at least one test in each of the selected category) are satisfied (Table 1.4).

A systematic review [51] reported that PEW prevalence ranges 11–54% in patients with CKD stages G3 to G5, and 28–54% in dialysis patients. About 15.3–17.1% of Japanese HD patients have PEW based on the ISRNM criteria [52, 53]. Since the hazard ratio for mortality became maximal at BMI <20 kg/m^2 in Japanese HD patients, a lower BMI may be more suitable to diagnose the presence of PEW in the Asia population.

Decreased muscle mass is the same category in sarcopenia and PEW, while anthropometric measurements are different. Unintentional loss of body weight is also applied in the phenotype of frailty and PEW (Fig. 1.1).

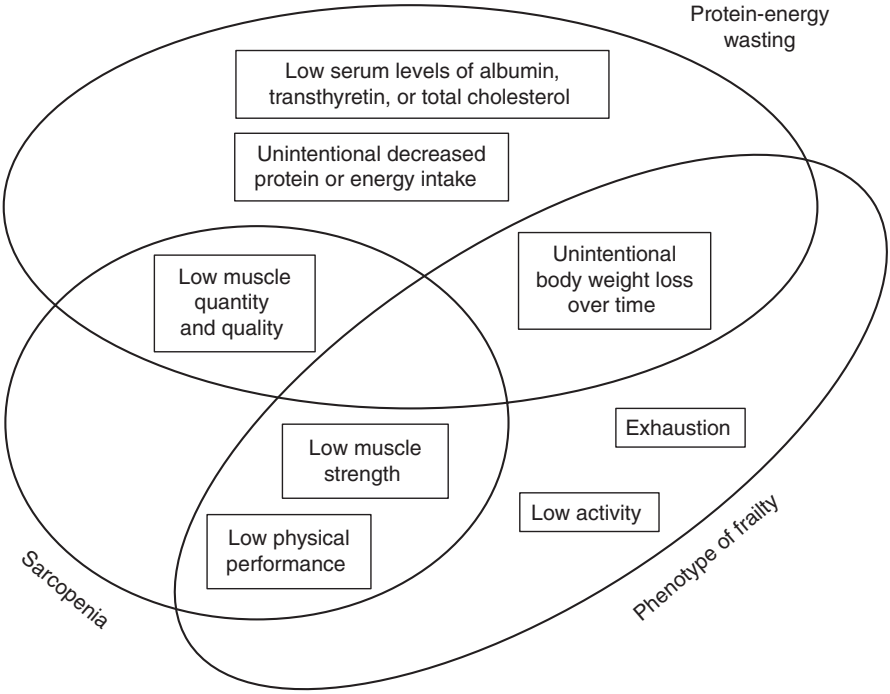

Fig. 1.1 Comparison of protein-energy wasting, sarcopenia, and phenotype of frailty

1.6 Conclusion

Currently, over 850 million people have been suffering from some form of kidney disease in the world. CKD is a potent risk for fatal cardiovascular events. Annual costs per one patient for HD are expensive, thereby imposing a heavy financial burden on healthcare budgets.

CKD is a predominant disease of the elderly. So, we need to consider the influence of aging, lifestyle, and social factors on renal and overall health, as well as CKD-related comorbidities and complications (Fig. 1.2). Especially, sarcopenia and frailty are very common. Given the convincing relationship between sarcopenia, frailty, and adverse clinical outcomes, we should be more aware of the concept of sarcopenia and frailty in older patients with advanced CKD.

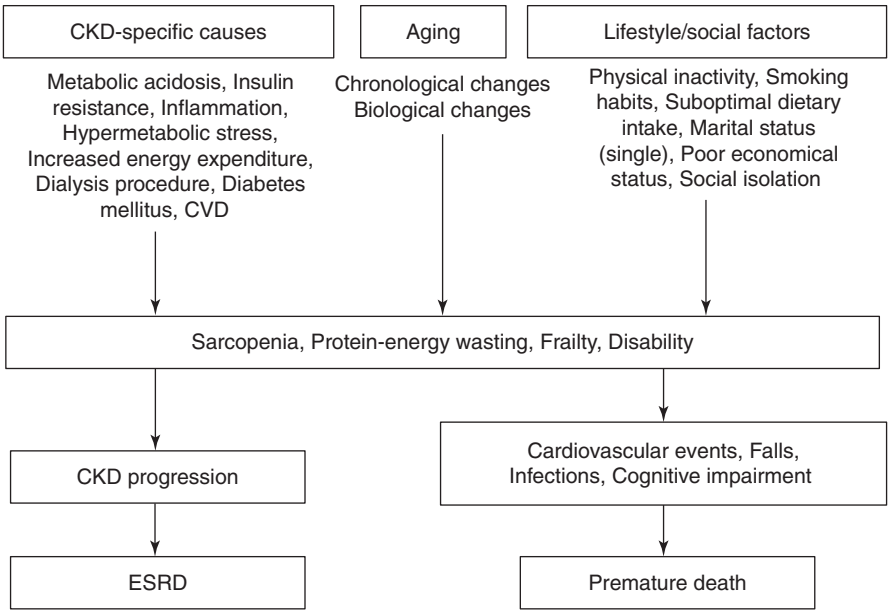

Fig. 1.2 Association of chronic kidney disease-related causes, aging, and lifestyle/social-related factors with clinical outcomes. *CKD* chronic kidney disease, *CVD* cardiovascular disease, and *ESRD* end-stage renal disease

Disclosures I declare that I have no competing interests.

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Molecular Mechanism of Muscle Wasting in CKD

2

Hiroshi Watanabe, Yuki Enoki, and Toru Maruyama

Abstract

Chronic kidney disease (CKD), a chronic catabolic condition, is characterized by muscle wasting and a decreased muscle endurance. Many insights have made into the molecular mechanisms of muscle atrophy in CKD. A persistent imbalance between protein synthesis and degradation causes a loss of muscle mass. A decrease in insulin/IGF-1-Akt-mTOR signaling and an increased ubiquitin-proteasome system (UPS) have emerged as inducers of muscle loss. During muscle wasting, abnormal levels of reactive oxygen species (ROS) and inflammatory cytokines are detected in skeletal muscle. These increased ROS and inflammatory cytokine levels induce the expression of myostatin. The binding of myostatin to its receptor ActRIIB stimulates the expression of Foxo-dependent atrogenes. An impaired mitochondrial function also contributes to reduced muscle endurance. Increased glucocorticoid, angiotensin II, parathyroid hormone, and protein-bound uremic toxin levels that are observed in CKD all have a negative effect on muscle mass and endurance. The loss of skeletal muscle mass during the progression of CKD further contributes to the development of renal failure. Some potential therapeutic approaches based on the molecular mechanisms of muscle wasting in CKD are currently in the testing stages using animal models and clinical settings.

Keywords

Atrogene · Myostatin · Mitochondria · Oxidative stress · Inflammation · Uremic toxin

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2.1 Introduction

Skeletal muscle atrophy, referred to as sarcopenia, and decreased exercise endurance are frequently observed in chronic kidney disease (CKD) and are correlated with the risk of morbidity and mortality in such patients [1–5]. Therefore, maintaining physical performance is considered to be an essential factor for improving the prognosis of CKD patients. Muscle tissue functions as a protein reservoir and a source of amino acids that can be used for energy production by various tissues during catabolic conditions. In catabolic conditions such as CKD, persistent imbalances between protein synthesis and degradation result in a substantial loss of muscular protein mass (cachexia). Impaired mitochondrial function also contributes to reducing muscle endurance. This chapter explores the available evidence for the molecular mechanism of muscle wasting and potential therapeutic agents that might be used to counteract muscle atrophy in CKD.

2.2 Molecular Mechanism of Muscle Atrophy in CKD

2.2.1 Protein Degradation in Muscle

2.2.1.1 Atrogenes: Atrogin-1, MuRF-1, and Autophagy-Related Genes

A balance between protein synthesis and degradation is important for the maintenance of muscle mass. Therefore, the decrease in muscle mass can be attributed to either an increase in protein degradation or a decrease in protein synthesis. Several molecular mechanisms have been proposed to explain CKD-induced skeletal muscle atrophy in which multiple intracellular signaling pathways stimulate the expression of atrogenes such as atrogen-1 (known as muscle atrophin F-box (MAFbx)) and muscle ring factor 1 (MuRF-1, known as TRIM63), a member of the muscle-specific ubiquitin ligase family, in addition to autophagy-related genes (Fig. 2.1) [6–8]. The increased expression of these atrogenes induces protein degradation via the activation of the ubiquitin-proteasome system (UPS) and autophagy. In a catabolic state such as CKD, increased oxidative stress, inflammation, the production of glucocorticoids, angiotensin II, parathyroid hormone, and defective insulin signaling can initiate these pathways [6–9]. Hemodialysis procedures can also reduce protein synthesis and stimulate protein degradation [10].

2.2.1.2 Myostatin and TGF-β

Myostatin, a member of the TGF-β family and an autocrine inhibitor of muscle growth, is produced predominantly in skeletal muscle and functions as a negative regulator of muscle growth [11, 12]. It binds to the activin A receptor type IIB (ActRIIB) followed by activation of the downstream pathway in which Smad2 and Smad3 are factors that mediate the effects of myostatin on muscle (Fig. 2.1) [13, 14]. In a study of the skeletal muscle of patients with CKD, Verzola et al. reported

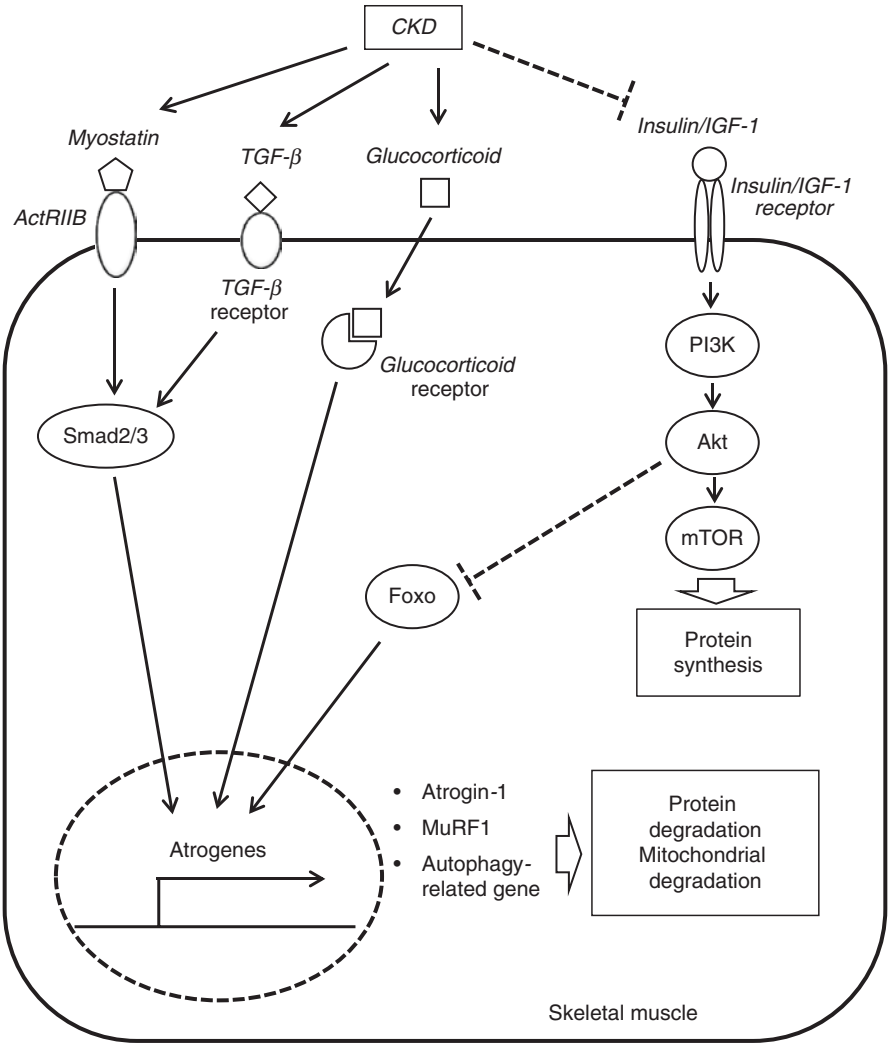

Fig. 2.1 Proposed molecular mechanisms for the muscle atrophy that develops in CKD. In a catabolic condition such as CKD, increased myostatin, TGF-β, and glucocorticoid levels induce atrogenes such as atrogin-1, MuRF1, and autophagy-related genes. The reduction in insulin/IGF-1-Akt-mTOR activity then results in a decrease in protein synthesis

that the mRNA expression of myostatin were upregulated [15]. Zhang et al. reported that the expression of myostatin in muscle was also increased in five-sixth nephrectomized mice (CKD mice) as well as CKD patients [16], and that the administration of an anti-myostatin anti-peptide to these mice suppressed the reduction in muscle mass [17]. Myostatin expression is enhanced by oxidative stress, inflammation, and glucocorticoids [18–20] through the forkhead box protein O (Foxo), NF-κB [21], and Smad2/3.

TGF-β also functions as a potent inducer of muscle wasting. In fact, Mendias et al. reported that the administration of TGF- β induced muscle atrophy and fibrosis through the induction of atrogin-1 [22]. TGF-β binds to TGF-β type II and type I receptors, which activate the Smad2/3 and TAK1/p38 MAPK signaling pathways to induce atrogenes (Fig. 2.1).

2.2.2 Protein Synthesis in Muscle

2.2.2.1 Akt-mTOR Signaling and Foxo Activation

The insulin or insulin-like growth factor (IGF-1)-PI3K-Akt pathway plays important roles in skeletal muscle hypertrophy by increasing muscle protein synthesis via mTOR and decreasing protein degradation via the inactivation of the Foxo family [8, 23–26]. Lee et al. reported that muscle atrophy was increased under conditions where insulin responsiveness was impaired, and suppressing PI3K activity increased atrogin-1 activity [27]. Sandri et al. reported that a decrease in Akt activity led to the activation of Foxo transcription factors and atrogen-1 induction. In addition, an IGF-1 treatment or the overexpression of Akt suppressed the expression of Foxo and atrogen-1 [28]. In this scenario, the expression of atrogenes such as atrogin-1, MuRF-1, and autophagy-related genes is suppressed by Akt via the inactivation of Foxo, a negative regulator of transcriptional factors for atrogenes [26–28].

2.2.3 Mitochondria

It is well known that exercise capacity is strongly related to mitochondrial function in skeletal muscle [29]. The amount of mitochondria is regulated by both mitochondrial biosynthesis and degradation [30, 31]. Tamaki et al. recently reported that muscle mitochondria and running distance were decreased in the early-stage of CKD model mice and that it was correlated with increased oxidative stress and inflammatory responses [32]. In fact, oxidative stress and inflammation cause the expression of the peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α), a master regulator for mitochondrial biosynthesis, to be reduced and to an increase in autophagy, a mitochondria degradation system. Interestingly, Brault et al. demonstrated that the overexpression of PGC-1α caused a resistance to muscle atrophy that was induced by denervation or fasting [33]. Similarly, Wenz et al. also showed that the overexpression of PGC-1α in mice prevented muscle atrophy, resulting in an extended life span [34]. In patients with stage 3~4 CKD, Balakrishnan et al. reported that the numbers of mitochondria in skeletal muscle were decreased [35]. They also demonstrated that the exercise increased the mitochondria content in skeletal muscle of CKD patients. Therefore, a decrease in the number of mitochondria in muscle appears to play a critical role in muscle endurance in CKD patients.

2.3 Initiating Factors Responsible for the Onset and Progression of Muscle Atrophy in CKD

2.3.1 Oxidative Stress and Inflammation

During muscle wasting, abnormally high levels of reactive oxygen species (ROS) and inflammatory cytokines are produced in skeletal muscle [21, 36]. Zhang et al. previously reported that an increase in ROS-induced TNF-α expression triggers myostatin production via a NF-κB dependent pathway, which further stimulates the production with the release of IL-6 in muscle tissue [16]. Sriram et al. also demonstrated that myostatin-induced TNF-α production via NF-κB signaling resulted in a further increase in ROS levels through the activation of NADPH oxidase [21]. Therefore, increased ROS production results in a feed forward loop that further increases the expression of myostatin via the NF-κB signaling of TNF-α.

Inflammatory cytokines such as TNF-α and IL-6, which were known to cause skeletal muscle breakdown, were also increased in muscle tissue of CKD mice [3, 37], whereas the inhibition of myostatin reduced the levels of these cytokines in the blood circulation [17]. In addition, Cheung et al. demonstrated that the infusion of TNF-α and IL-6 into mice resulted in the development of muscle atrophy, while it was attenuated by the neutralization of these cytokines [38]. Zhang et al. also reported that TNF-α activates myostatin, which further accelerates UPS-mediated catabolism [17]. Similar to myostatin, atrogin-1 was also found to be regulated by oxidative stress and inflammatory cytokines. These findings point to the conclusion that the development of skeletal muscle atrophy is mutually linked with myostatin, atrogenes, oxidative stress, and inflammation [21, 39–43].

2.3.2 Glucocorticoids

Increased levels of circulating glucocorticoids are associated with muscle atrophy. Watson et al. tested the direct contribution of a glucocorticoid receptor in skeletal atrophy by creating muscle-specific glucocorticoid receptor knockout mice. They subsequently showed that the knockout mice were resistance to glucocorticoid-induced muscle atrophy [44], suggesting that the glucocorticoid receptor was essential for muscle atrophy in response to glucocorticoids. Several reports have shown that myostatin expression is increased in the presence of glucocorticoids [45–48], thereby inducing protein breakdown by enhancing atrogenes (atrogine-1 and MuRF1) expression and decreasing protein synthesis by inhibiting the mTOR pathway. In particular, in the case of the IGF-1-PI3K-Akt-mTOR pathway, glucocorticoids were found to inhibit IGF-1 production [49, 50], accelerate the degradation of insulin receptor growth factor (IRS-1), followed by reducing PI3K activity [51–54]. Frost and Lang et al. showed that the constitutively activated form of Akt suppressed the negative effects of glucocorticoids on protein synthesis [55] and muscle mass [19]. Glucocorticoids also caused an increase in Foxo gene

expression [46, 56]. It therefore appears that glucocorticoid receptors and Foxo synergistically contribute to the upregulation of atrogene expression [57]. Glucocorticoid-induced muscle atrophy is characterized by fast-twitch (type II muscle fiber) atrophy and reduced protein mass in muscle [58]. On the other hand, it was also reported that the administration of glucocorticoid paradoxically exerted a positive effect on muscle function, probably due to suppressing inflammatory cytokine expression [59].

2.3.3 Angiotensin II

Increased levels of circulating angiotensin II are associated with the loss of lean body mass in CKD. Brink et al. reported that angiotensin II infusion to rats induced cachexia [60]. They found that, when rats were infused with angiotensin II, muscle mass became decreased but kidney and left ventricular weights were increased (Brink [61]. In these experimental conditions, circulating IGF-1 levels were reduced by about 30% in angiotensin II-treated rats. Zhang et al. also demonstrated that the infusion of angiotensin II increased the levels of circulating IL-6 and its hepatic production [62]. In addition, the infusion of angiotensin II stimulates the suppressor of cytokine signaling (SOCS3) in muscle which led to a loss of the insulin receptor substrate 1 (IRS-1), thus impairing insulin/IGF-1 signaling [62]. Benigni et al. reported that the mouse homolog of antgiotensin II type 1 (AT_1) knockout mice (agtr1a$^{-/-}$) showed a decrease in oxidative stress and an increase in the number of mitochondria. In addition, the mice had a prolonged life span [63]. Yabumoto et al. recently reported that the administration of irbesartan, an AT_1 receptor blocker, improved muscle repair and regeneration through the downregulation of the aging promoting C_{1q}-Wnt/β-catenin signaling pathway [64]. These data indicate that angiotensin II can stimulate muscle atrophy through a defect in insulin/IGF-1 signaling and an inflammatory mechanism via an AT_1 receptor.

2.4 Molecular Mechanism of Uremic Toxin-Induced Muscle Wasting

2.4.1 Uremic Toxin

Uremic toxins accumulate in the body under CKD conditions and exert biological actions. Among the uremic toxins, the presence of protein-bound uremic toxins, such as indoxyl sulfate, indole acetic acid, *p*-cresyl sulfate, hippuric acid, kynurenic acid, and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, etc., has been reported, due to the difficulty associated with their removal by hemodialysis because of their strong binding to serum albumin [65–68]. An accumulation of evidence has clarified that protein-bound uremic toxins are related to renal toxicity and CKD complications, including cardiovascular damage caused by enhanced oxidative

stress and inflammation [69–74]. In addition, Tamaki et al. reported that feeding a high protein diet not only exacerbates impaired renal function but also reduces exercise endurance in CKD mice [75], which is accompanied by an increased production of protein-bound uremic toxins [76]. These bodies of experimental evidence led us to hypothesize that protein-bound uremic toxins play an important role in the muscle atrophy and reduced endurance.

Several mechanisms have been proposed to explain the harmful actions of protein-bound uremic toxins. For example, protein-bound uremic toxins enter the target cell via specific transporters, such as an organic anion transporter (OAT) [77–83], and they then exert their toxicity via the activation of cellular NADPH oxidase, which results in the overproduction of ROS and inflammatory cytokines [71–73]. In addition, recent reports have shown that indole containing toxins, especially indoxyl sulfate, act as aryl hydrocarbon receptor (AHR) ligands and exert their toxicity via AHR [84, 85]. Interestingly, Ohake et al. reported that AHR functions as a component of the ubiquitin ligase complex [86]. We recently demonstrated that, among the protein-bound uremic toxins, indole containing compounds, namely, indoxyl sulfate, contributed to skeletal muscle wasting [87, 88].

2.4.2 The Distribution of Indoxyl Sulfate in Muscle Tissue

OAT such as Oat1 and Oat3 is responsible for the uptake of indoxyl sulfate by cells [77–79]. Western blotting analyses showed the mouse Oat1 and Oat3 are expressed in C2C12 mouse myoblast cells. In addition, when half-nephrectomized mice are administered indoxyl sulfate, the indoxyl sulfate is distributed to skeletal muscle (gastrocnemius) [87]. At the same time, the pattern of the immunostaining image of indoxyl sulfate was similar to that for ROS production, suggesting that indoxyl sulfate induces ROS production in skeletal muscle in vivo (Fig. 2.2).

2.4.3 Redox Properties of Indoxyl Sulfate in Skeletal Muscle

Indoxyl sulfate inhibits the proliferation and myotube formation in C2C12 myoblast cells. In addition, indoxyl sulfate caused an increased ROS production and inflammatory cytokine expression (TNF-α, IL-6, and TGF-β1) in C2C12 cells. It also enhances the expression of myostatin and atrogin-1. These effects which are induced by indoxyl sulfate were suppressed in the presence of an antioxidant, inhibitors of the Oat and AHR, or in the presence of siAHR. The chronic administration of indoxyl sulfate to half-nephrectomized mice significantly reduced their body weights and this reduction was accompanied by a loss in skeletal muscle weight. In these mice, indoxyl sulfate induced the expression of myostatin and atrogin-1, in addition to increasing the production of inflammatory cytokines by enhancing oxidative stress in skeletal muscle [87]. Indoxyl sulfate also induced mitochondrial dysfunction by decreasing the expression of PGC-1α and inducing autophagy (Fig. 2.2) [88].

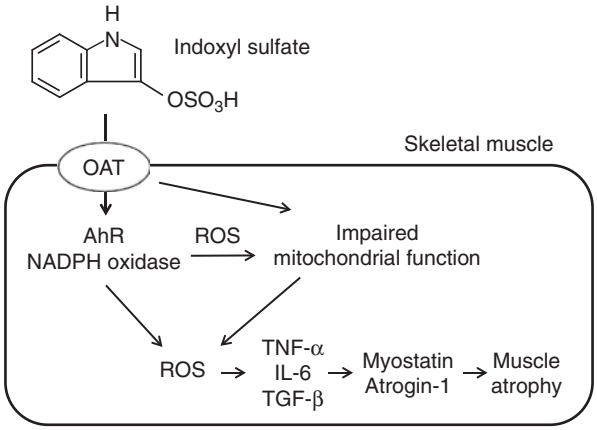

Fig. 2.2 Proposed mechanism for indoxyl sulfate-induced muscle atrophy. Indoxyl sulfate accumulates in muscle cells via Oat where indoxyl sulfate activates the AHR pathway and NADPH oxidase to cause increased ROS production. The enhanced ROS production, in turn, triggers the production of inflammatory cytokines to induce the expression of myostatin and atrogin-1, which are involved in muscle wasting. Indoxyl sulfate also impairs mitochondrial function

2.4.4 Effect of *p*-Cresyl Sulfate on Insulin Signaling in Skeletal Muscle

Koppe et al. demonstrated that, when mice are treated with *p*-cresyl sulfate, insulin signaling is altered in skeletal muscle where *p*-cresyl sulfate inhibited insulin-stimulated glucose uptake and decreased insulin signaling pathways through the activation of the ERK kinase [89]. Regarding the downstream pathway of insulin signaling, *p*-cresyl sulfate suppressed the insulin-induced phosphorylation of Akt. Since indoxyl sulfate had no effect on Akt phosphorylation [87], the effect of indoxyl sulfate or *p*-cresyl sulfate on muscle atrophy appears to be independent of each other (Fig. 2.3).

2.5 Muscle–Kidney Crosstalk: Skeletal Muscle Affects the Renal Pathology

Hanatani and Izumiya et al. investigated the effects of muscle growth on kidney disease using muscle-specific Akt transgenic mice [90]. They showed that unilateral ureteral obstruction (UUO)-induced renal interstitial fibrosis was significantly diminished in Akt transgenic mice via mediation by an increased level of eNOS signaling in the kidney. In a recent study, Peng et al. reported that the overexpression of muscle-specific PGC-1α resulted in reduced kidney damage and fibrosis in a mouse model of kidney disease [91]. These data suggest that skeletal muscle loss during kidney disease can affect the further progress of renal failure [90–92].

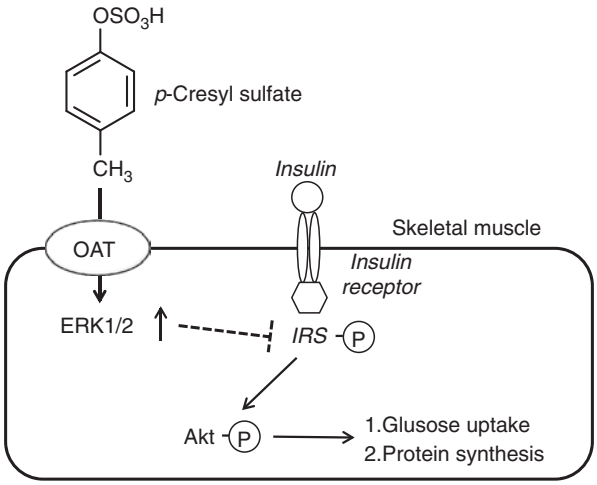

Fig. 2.3 Proposed mechanism for *p*-cresyl sulfate-induced insulin resistance. *p*-cresyl sulfate accumulates in muscle cells via Oat. *p*-Cresyl sulfate induces a resistance to insulin in muscle, accompanied by a decrease in insulin/IGF-1-Akt-mTOR activity through ERK1/2 activation

2.6 Kidney–Fat–Muscle Crosstalk: Parathyroid Hormone (PTH) Contributes to Muscle Atrophy Via PTH Receptor Expressed in Fat Tissue

Kir et al. demonstrated that the parathyroid hormone (PTH) is involved in stimulating the expression of thermogenic gene, such as UCP1, in five-sixth nephrectomized CKD mice [9]. In this mouse model, the expression of the atrogine-1, MuRF1, and myostatin genes was increased in gastrocnemius muscle tissue, whereas IGF-1 expression was decreased. Interestingly, they also showed that the loss of PTH receptors in fat tissue blocked the upregulation of thermogenic genes and prevented muscle atrophy. These data indicate that PTH/PHR receptor signaling in fat tissue is an important player in muscle atrophy in CKD.

2.7 Potential Therapeutic Interventions for CKD-Associated Sarcopenia in the Animal Model

2.7.1 Blocking Myostatin-ActRIIB Signaling

Myostatins are negative regulators of skeletal muscle mass, which are known to signal via the ActRIIB receptor on skeletal muscle, thereby inducing muscle wasting [11]. Morvan et al. recently showed that bimagrumab, acting as a human dual-specific anti-ActRIIA/ActRIIB antibody, neutralized muscle atrophy [93]. The activin decoy receptor ActRIIB also prevented skeletal muscle pathophysiology

[94, 95]. Endogenous circulating proteins such as follistatin and follistatin-like proteins are known to inhibit the binding of myostatin to ActRIIB [96, 97]. Lee et al. reported that transgenic mice expressing high levels of follistatin showed an increased muscle mass [98]. Chang et al. also demonstrated that the overexpression of muscle-specific follistatin enhanced skeletal muscle growth, due, at least in part, to myofiber hypertrophy [99]. Follistatin gene therapy against sporadic inclusion body myositis or facioscapulohumeral muscular dystrophy improved functional outcomes such as the distance traveled in a 6-min walk test [100]. Follistatin delivery systems such as nanoparticles and Fc fusion systems, etc. are under development in clinical settings [101–103]. In addition, the anti-myostatin peptibody that binds myostatin or blocks its receptor is also under development [17]. These data suggest that molecules that block myostatin-ActRIIB signaling would be potentially useful for enhancing muscle growth.

2.7.2 L-Carnitine

In CKD patients, restricted protein intake, decreased L-carnitine biosynthesis, and the easy removal of L-carnitine by dialysis result in an L-carnitine deficiency. Such a deficiency results in a decline in muscle power, the development of fatigue, non-ketotic hypoglycemia, or myocardial myopathy, while L-carnitine supplementation is effective for myopathy and for a decrease in muscle mass and power [104, 105]. An L-carnitine treatment ameliorates muscle atrophy and exercise capacity in CKD mice without affecting their renal function or the indoxyl sulfate levels in both plasma and muscle [88]. This can be attributed to the inhibition of mitochondrial dysfunction and decreased numbers of type I slow twitch fibers (Enoki [88].

2.7.3 DPP-4 Inhibitor

Teneligliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, has therapeutic potential for the treatment of CKD-induced muscular dysfunction without causing changes in indoxyl sulfate accumulation [88]. The DPP-4 enzyme catalyzes the degradation of incretin hormones such as GLP-1 and glucose-dependent insulinotropic polypeptide [106]. Kang et al. recently reported that GLP-1 increased mitochondrial membrane potential and oxygen consumption in addition to increasing PGC-1α expression [107]. Fukuda-Tsuru et al. reported that a teneligliptin treatment suppressed mitochondrial dysfunction in the livers of mice that had been fed a high-fat diet [108]. GLP-1 also ameliorated insulin resistance via the activation of the PI3K-Akt signal pathway in skeletal muscle [109]. In addition, Kimura et al. reported that teneligliptin acts as a hydroxyl radical scavenger [110]. Using human proximal tubular cells, Wang et al. also reported that diportin, another DPP-4 inhibitor, inhibited cell injury via the inhibition of indoxyl sulfate-induced ROS/p38MAPK/ERK activity, and the recovery of the PI3K-Akt signaling pathway without involving the

action of GLP-1[111]. Taking these findings into consideration, a DDP-4 inhibitor may exert cytoprotective activities not only indirectly via GLP-1 but also via its direct action against CKD-induced muscle atrophy.

2.7.4 AST-120

In clinical settings, AST-120 is used to suppress the progression of renal failure in CKD patients via inhibiting the accumulation of protein-bound uremic toxins. The administration of AST-120 to CKD mice resulted in a significant decrease in the plasma and muscular levels of indoxyl sulfate, which resulted in exercise capacity, muscle weight, and the number of type I slow twitch fibers to be restored and mitochondrial dysfunction was suppressed [88]. Nishikawa et al. also showed that the administration of AST-120 improved exercise capacity and mitochondrial biogenesis of skeletal muscle via reducing oxidative stress in CKD mice [112].

2.7.5 Ghrelin

Tamaki et al. reported that the administration of acylated ghrelin to five-sixth nephrectomized CKD mice increased muscle mass and muscle mitochondrial content through increasing PGC-1α expression [75, 113]. It has also been reported that the non-peptidergic ghrelin receptor agonist counteracts cachectic body weight loss under inflammatory conditions [114–116].

2.7.6 Blockade of Leptin Activity

Elevated serum leptin levels are correlated with changes in lean body mass in patients with CKD, suggesting that leptin signaling could be an important cause of CKD-induced muscle loss [3, 117]. Cheung et al. reported that a pegylated leptin receptor antagonist attenuated CKD-induced muscle loss [118]. Interestingly, they also found the pegylated leptin receptor antagonist was able to cross the blood–brain barrier.

2.7.7 Others

Increased miR27a/b was reported to negatively regulate the expression of myostatin [119]. Wang et al. investigated the role of miR-23a and miR-27a in the regulation of muscle mass. The injection of an adeno-virus encoding miR-23a and miR-27a or the overexpression of miR-23a and miR-27a in CKD mice suppressed muscle loss through increasing Akt phosphorylation [120]. miR1 is a muscle-specific microRNA which induces muscle atrophy by regulating HSA70. The antagonism of miR1 may be beneficial during muscle atrophy [121]. Hu et al. reported that a low frequency

electrical stimulation ameliorates CKD-induced muscle atrophy by upregulating the IGF-1 signaling pathway through decreasing the expression of miR1 and miR206 [122]. Interestingly, low frequency electrical stimulation induced the activation of M2 macrophage [122].

2.8 Conclusions

This chapter summarizes the available evidence for the molecular mechanism of muscle wasting in CKD. It is noteworthy that oxidative stress and inflammation appear to be strong contributors to the muscle atrophy caused by a decrease in muscle mass and mitochondrial dysfunction. Increased levels of glucocorticoids, angiotensin II, parathyroid hormone, and uremic toxin also contribute to this type of muscle atrophy and reduced muscle endurance. These data point to the importance of developing potential therapeutic agents for counteracting the muscle atrophy that is associated with CKD.

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Protein Energy Wasting in Chronic Kidney Disease

3

Eiichiro Kanda

Abstract

Chronic kidney disease (CKD) patients are increasing in number globally because kidney function is affected by aging and lifestyle habits. Malnutrition, muscle weakness, and a decline in activities of daily living (ADL) are often observed in elderly CKD patients and dialysis patients, and are related to their CKD prognosis and life prognosis. Chronic inflammation and atherosclerotic disease are associated with malnutrition. Because malnutrition and its related factors affect their prognosis, it is necessary to find and treat patients with malnutrition at an early stage. The state in which the storage of protein and energy source accompanying CKD is decreased is called protein energy wasting (PEW). PEW is diagnosed on the basis of biochemical tests finding such as hypoalbuminemia, physique, muscle mass, and loss of dietary intake. For evaluating PEW, a complex nutritional index taking into account the pathophysiology specific to CKD patients is useful. Because PEW involves various factors such as nutritional status, muscular strength, ADL, and social life, the combined effect of various problems exacerbates PEW and affects life prognosis of CKD patients and dialysis patients. Taking these factors into consideration, not only nutritional therapy but also exercise therapy is necessary to stop the vicious cycle related to the decline of PEW and ADL.

Keywords

Chronic kidney disease · Dialysis · Protein energy wasting · Inflammation · Malnutrition · Albumin

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3.1 Introduction

Kidney function is affected by aging and lifestyle habits. Currently, Japan and Europe have aging population, and it is expected that the number of chronic kidney disease (CKD) patients will increase in the future. CKD is a risk factor not only for end-stage-kidney disease (ESKD) but also for cardiovascular disease (CVD) and death [1].

The risk factors for CVD include aging, gender, hypertension, diabetes, dyslipidemia, and smoking. In addition to these risk factors in CKD patients, uremia, renal anemia, CKD-mineral and bone disorder (CKD-MBD), malnutrition, nitric oxide production disorder, and chronic heart failure also exist as specific risk factors that increase the risks of CVD and death. Hemodialysis patients have arteriovenous fistula, which increases cardiac output. They also have abrupt changes in body fluid volume before and after dialysis, hypotension, reduced coronary arterial blood flow, and a high risk of CVD.

For elderly CKD patients, it is important to prevent the progression of CKD. Problems such as complications, malnutrition, decline in activities of daily living (ADL), and nursing care are more frequently found in elderly CKD patients and dialysis patients than in healthy elderly persons [2]. Moreover, in elderly CKD patients, ADL declines after dialysis and mortality rate increases [3]. In dialysis patients, malnutrition, loss of appetite, and low ADL level are risk factors for death [4–6]. To prevent the progression of CKD in elderly patients, it is necessary to consider nutrition and ADL simultaneously.

From the above, CKD, malnutrition, ADL, and life prognosis are closely related to each other. Moreover, inflammation is involved in malnutrition, which worsens not only the prognosis of life but also ADL owing to a decrease in muscular strength.

3.2 Characteristics of Nutritional Status of CKD Patients

Malnutrition in CKD patients is characterized by the involvement of inflammation unlike in ordinary malnutrition caused by, for example, starvation with low nutritional intake. In the case of malnutrition in CKD patients, hypercatabolism occurs owing to the induction of inflammatory cytokines such as interleukins (ILs)-6, -8, -1B, -18, tumor necrosis factor (TNF)-α. Chronic inflammation and arteriosclerotic disease often develop as complications and together characterize the so-called malnutrition inflammation atherosclerosis (MIA) syndrome, in which CVD and death are likely to occur.

As CKD progresses, chronic inflammation continues and arteriosclerosis develops. In CKD patients, the functions of redox control and the antioxidant system and the control mechanism of oxidative stress degrade, resulting in oxidative stress enhancement [7]. In dialysis patients with diabetes, the oxidation and degradation of glucose occur owing to uremia and oxidative stress, which result in the increase in the levels of advanced glycation end products (AGEs). AGEs act on AGE receptors on endothelial cells and monocytes and increase the production of inflammatory cytokines and reactive oxygen [8]. Chronic inflammation is associated with

abnormal levels of anti-inflammatory factors and the progression of MIA syndrome [9]. Abnormal levels of anti-inflammatory cytokines such as IL-10 are associated with CVD in dialysis patients [10]. Moreover, oxidative stress causes the denaturation of high-density lipoprotein (HDL) cholesterol, which has the anti-arteriosclerotic effect, resulting in the development of malnutrition and CVD [11].

Hypernutrition is related to CVD development in the general population, but in dialysis patients, the incidence of CVD and the risk of death increase with the decrease in body mass index (BMI) and total cholesterol level. This is called reverse epidemiology [12, 13]. In a cohort study of hemodialysis patients, the group with malnutrition and inflammation showed reverse epidemiology, but the group without malnutrition and inflammation did not [12]. According to the Okinawa Dialysis Study, the first cause of death among dialysis patients with a total cholesterol level of 220 mg/dL or higher was heart disease, whereas the first cause of death among those with a total cholesterol level below 140 mg/dL was infection [14]. Because malnutrition and inflammation may affect the relationship between total cholesterol level and the risk of death, it is necessary to establish strategies for examination and treatment of malnutrition according to the presence of malnutrition and inflammation.

Malnutrition in CKD patients is a state in which the amounts of proteins, such as those in muscle, and fat and energy storage decrease. The International Society of Renal Nutrition and Metabolism (ISRNM) defined such type of malnutrition as protein energy wasting (PEW) [15]. PEW is diagnosed on the basis of the following categories [1]: serum chemistry tests to identify abnormalities such as hypoalbuminemia (serum albumin level <3.8 g/dL), serum prealbumin <30 mg/dL, and serum cholesterol level <100 mg/dL [2]. The category of body mass includes, BMI < 23 kg/m^2, unintentional weight loss over time (5% over 3 months or 10% over 6 months), and total body fat percentage <10% [3]. The category of muscle mass includes muscle wasting (reduced muscle mass 5% over 3 months or 10% over 6 months), reduced midarm muscle circumference area (reduction >10% in relation to 50th percentile of reference population), and reduced creatinine appearance. And [4] the category of dietary intake includes unintentional low DPI (dialysis patients, <0.80 g/kg/day for at least 2 months; and CKD stages 2–5 patients, <0.6 g/kg/day for at least 2 months) and unintentional low dietary energy intake <25 kcal/kg/day for at least 2 months.

Each category of item contains test items, and if there are three or more test items with abnormal results in at least one category, PEW is diagnosed. PEW is observed in 18–45% of patients with CKD stages G3 to G5 and in 75% of dialysis patients [15, 16].

3.3 Evaluation of Nutritional Status Based on PEW Diagnostic Criteria

Nutrition assessment is essential for the early detection of PEW and the control of nutrition. There are various indices used to evaluate nutrition (Table 3.1). Among these indices, serum albumin level is frequently used and included in the diagnostic

Table 3.1 Nutritional indices

Medical examination
• Nutritional intake: dietary protein intake, salt intake, dietary energy intake
• Anthropometry: height, weight, BMI, decrease in body weight, skinfold thickness, arm muscle area, grip strength
• Blood examinations: complete blood count; and albumin, prealbumin, creatinine, transferrin, cholesterol, and triglyceride levels
• Urine examinations: urinary biochemistry, creatinine, urea nitrogen
• Dialysis-related factors: nPCR, % creatinine production rate
• Indirect calorimetry
• Multiple indices: SGA, MIS, GNRI, SI

BMI body mass index, *nPCR* normalized protein catabolic rate, *SGA* subjective global assessment, *MIS* malnutrition-inflammation score, *GNRI* geriatric nutritional risk index, *SI* survival index

criteria of PEW [15]. Hypoalbuminemia is a risk factor for death in dialysis patients [17–19]. However, because serum albumin level is affected by various factors such as inflammation, liver injury, malignancies, urine protein, and it does not always reflect nutritional status [20]. When hypoalbuminemia is observed in a patient, it is necessary to evaluate the patient's condition from both aspects of malnutrition and inflammation [21]. For this purpose, we must evaluate blood cell counts (white blood cells and lymphocytes) and C-reactive protein (CRP) level together.

Because in hemodialysis patients, the body water volume is larger at prehemodialysis than at posthemodialysis, the blood test values are underestimated. Therefore, it is not clear whether the nutritional condition is accurately evaluated. Therefore, it is necessary to compare test values at prehemodialysis with those at posthemodialysis, which more correctly reflects nutritional conditions. In a large-scale cohort study of hemodialysis patients in Japan using the Japanese Society for Dialysis Therapy (JSDT) Renal Data Registry (JRDR) data, the relationship between the life prognosis of hemodialysis patients and the test values at pre- and posthemodialyses was evaluated [22]. The risk of death after 1 or 5 years on hemodialysis is more accurately predicted by the BMI at posthemodialysis than that at prehemodialysis, and is also accurately predicted by serum albumin and creatinine levels at prehemodialysis than those at posthemodialysis. And subanalysis of groups of diabetes and elderly patients showed similar results. It was considered that the BMI at posthemodialysis and the serum albumin and creatinine levels at prehemodialysis are appropriate indices for the evaluation of PEW.

BMI is an item in the body mass category for as the diagnosis criteria of PEW. The body weight of dialysis patients decreases by 2–5 kg after dialysis, so it has to be evaluated by dry weight. It is also necessary to regularly watch unintentional weight loss.

For the evaluation of muscle mass measurements of the arm muscle circumference and arm muscle area, bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry, computed tomography (CT), and magnetic resonance imaging (MRI) are usually carried out. In addition, grip strength, serum creatinine level, and creatinine production rate are also measured. The muscle mass of the thighs and grip strength are related to the prognosis of dialysis patients [23, 24]. Body fat mass is generally measured as the subcutaneous fat thickness under the triceps brachii

and shoulder blades. In BIA, the resistance of the body is measured by applying a weak current that does not affect the human body. BIA is based on the fact that current flowability differs depending on the water content of body tissue, and it is used to evaluate body composition. Multifrequency BIA is used to estimate the total body water content, which is used to estimate fat-free body mass and body fat. Weight scales capable of measuring body composition with BIA are used for dialysis patients. Because the results of BIA are influenced by body fluid volume, BIA should be performed after dialysis.

In CKD patients, 24-h-urinary-creatinine excretion level is an indicator of muscle mass. In CKD patients, a decrease in 24-h-urinary-creatinine excretion level is related to the worsening of life prognosis [25, 26]. In an anuric dialysis patient, the serum creatinine level and creatinine production rate at predialysis are indicators of skeletal muscle mass.

To maintain a patient's nutritional status, adequate intake of both protein and energy is necessary. Therefore, the dietary intake of protein and energy should be monitored by patients and dieticians by recording. Dietary intake is evaluated from records, interviews, and normalized protein catabolic rate (nPCR). As recording methods, 24-h recall, food recording, and food frequency questionnaire are used. In the 24-h recall, patients are asked about the food they took during 24 h through interview. In food recording, patients record in detail the type and amount of food they ingested over 3–7 days. Food frequency questionnaire is a large list of commonly eaten food items with multiple choices for the frequency of food ingested.

3.3.1 Multiple Assessment of Nutritional Status

Evaluation of nutritional status is indispensable for nutritional control in CKD patients. Therefore, a nutritional index that can be used for accurately evaluating the prognosis and nutritional status of CKD patients should be developed. The index should be easily measured by anyone with a small measurement error between assessors.

Serum albumin level, inflammatory marker level, nPCR, imaging diagnosis, subjective global assessment (SGA), malnutrition inflammation score (MIS), and geriatric nutritional risk index (GNRI) are often used [27–29]. However, since serum albumin level is affected by the inflammatory state, it does not always reflect a patient's nutritional status [20]. Therefore, when hypoalbuminemia is observed, it is necessary to evaluate the condition from aspects of both malnutrition and inflammation [21].

SGA and MIS are nutritional indices including multiple items and are widely used. SGA is used to assess nutritional status on the basis of the features of medical history and physical examination [27]. This assessment formalizes information of patients' medical history and physical features. Medical history includes weight changes, dietary intake changes, gastrointestinal symptoms, functional capacity, and disease and its relationship with nutritional requirements. Physical examination includes evaluations of the loss of subcutaneous fat (triceps, chest), muscle wasting

(quadriceps, deltoids), ankle edema, sacral edema, and ascites. On the basis of SGA, a patient is determined to be well nourished, moderately malnourished, or severely malnourished.

MIS is a modification of SGA, and includes a patient's (A) related medical history, (B) physical examination items, (C) body mass index, and (D) laboratory parameters [29]. (A) A patient's related medical history includes [1] changes in postdialysis dry weight, [2] dietary intake, [3] gastrointestinal symptoms, [4] functional capacity, and [5] comorbidity. (B) Physical examination items include [6] decreased fat stores or loss of subcutaneous fat, and [7] signs of muscle wasting. (D) Laboratory parameters include [9] serum albumin level and [10] serum total iron binding capacity or serum transferrin level.

GNRI is calculated from serum albumin level and body weight and is calculated as follows [30].

$$\text{GNRI} = 1.489 \times \text{Alb}\left(\text{g/dL}\right) + 41.7 \times \text{body weight / ideal body weight}$$

To evaluate the nutritional status of dialysis patients, complications must be analyzed in addition to the test items for the diagnostic criteria for PEW. For this purpose, a multiple nutritional index that can be used to evaluate nutritional status and complications is necessary. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), which a global cohort study of dialysis patients, survival index (SI), which is a novel nutrition assessment index, was developed using data of hemodialysis patients [31]. SI is a multiple nutritional index calculated as follows:

$$\begin{aligned}\text{SI} = 10 &- \left(0.4 \times \text{Age}\right) + \left(0.3 \times \text{BMI}\right) + \left(0.7 \times \text{Cr}\right) + \left(6 \times \text{Alb}\right) + \left(0.03 \times \text{Tchol}\right) \\ &- \left(\text{P}\right) - \left(2 \times \text{CVDs}\right) + \left(2 \times \text{AVF}\right),\end{aligned}$$

where Age is in years; BMI is in kg/m^2; Cr = serum creatinine level (mg/dL); Alb = serum albumin level (g/dL); Tchol = serum total cholesterol level (mg/dL); *P* = serum phosphorus level (mg/dL); CVDs = cardiovascular diseases as comorbid conditions, Yes = 1, No = 0; AVF = arteriovenous fistula use, Yes = 1, No = 0.

SI had higher predictive potential for mortality and diagnosis of PEW than a single index (e.g., age, BMI, serum albumin level, or serum creatinine level) and GNRI.

3.4 Importance of Unique Index for Each Country

To identify patients with malnutrition and treat them accordingly, it is necessary to increase the accuracy of nutritional indices. These indices such as GNRI are not developed for CKD patients and dialysis patients. Therefore, rather than using an index as it is, it is necessary to examine the components of the index before using it.

Let us consider the diagnostic criteria for PEW. The criteria based on the serum chemistry category include a serum albumin level of less than 3.8 g/dL and a serum cholesterol level of less than 100 mg/dL. According to the Annual Dialysis Data

Report 2014 of JRDR, which was a nationwide renal data registry and contained data of all dialysis patients (n = 358,775) in Japan in the year 2014, the mean serum albumin and cholesterol levels in dialysis patients were 3.60 ± 0.44 g/dL and 154.7 ± 35.3 mg/dL, respectively [32]. Assuming that these nutritional factors show normal distributions, it can be estimated that 67.5% of the patients had serum albumin levels of less than 3.8 g/dL and 6.1% had serum cholesterol levels of less than 100 mg/dL. The difference in the distribution of the patients between the two criteria suggests that the patients may be differently diagnosed as having PEW on the basis of each criterion. Because the cutoff levels of the criteria may not be applicable to Japanese patients for the correct diagnosis of PEW and to estimate Asian hemodialysis patients with PEW, reference values of the criteria for PEW diagnosis of Asian hemodialysis patients are required.

3.5 Relationship Between PEW, Sarcopenia, and Frailty

The loss of appetite and reduced ADL are prognostic risk factors for CKD patients and dialysis patients [5]. In elderly CKD patients, ADL decreases after the start of dialysis, and their mortality rate increases [3]. Thus, CKD, malnutrition, ADL, and prognosis are closely related to each other. We summarize the concepts of PEW, sarcopenia, and frailty (Table 3.2).

Various factors affect PEW, which is not only malnutrition but also uremic toxin, inflammation, catabolism, metabolic acidosis, decreased physical activity, dialysis, and complications. As mentioned above, the categories for diagnosis include (1) biochemical test (serum chemistry), (2) body mass, (3) muscle mass, and (4) dietary intake.

Sarcopenia is muscle loss due to aging. According to the definition of the European Working Group on Sarcopenia in Older People, sarcopenia represents a state in which muscle mass reduction and muscle weakness accompany physical dysfunction [33]. According to the Asian Working Group for Sarcopenia, it is diagnosed when decreases in grip strength, physical function, and a decrease in muscle mass are observed [34].

Frailty is a state that is likely to be a health impairment due to the deterioration of energy reserve capacity due to aging [35, 36]. Basically, ADL indicates independence, and if there is a functional failure, ADL decreases indicating disability. The

Table 3.2 Differences in the criteria for PEW, sarcopenia, and frail

	Biochemistry	Loss of appetite	Decrease in weight	Decrease in muscle mass	Muscle weakness	Decrease in physical function	Fatigue
PEW	Yes	Yes	Yes	Yes			
Sarcopenia				Yes	Yes	Yes	
Frail					Yes	Yes	Yes

"Yes" indices that the item is included in the criteria.

indices of frailty include body weight, fatigue, muscular strength, walking speed, and activity level. That is, frailty includes not only muscle strength but also elements of psychophysiological aspects such as physical activity and depression, which reflect conditions requiring nursing care and support.

PEW is determined from biochemical test results, not from muscle strength or physical activity (Table 3.2). Sarcopenia and frailty are not determined from biochemical test results, but from a decrease in muscular strength and physical function. These concepts are complementary, and it is important to multilaterally evaluate the nutrition and activity of elderly CKD patients.

3.6 Causes of PEW

Various causes of PEW are known. Reduction in dietary intake, inflammatory cytokines, CKD, uremic toxins, complications (CVD, diabetes, depression), fluid overload, decrease in muscle mass, and dialysis-related factors. Decreased dietary energy intake (DEI) and dietary protein intake (DPI) are associated with loss of appetite, dietary restriction, depression, dysphagia, uremic substances, acidosis, inflammation, and dialysis.

As kidney function decreases, hormonal imbalance occurs, which results in decreases in appetite and muscle mass, and malnutrition. Insulin resistance occurs at the early stage of CKD, and glucose metabolism and insulin sensitivity are reduced [37]. Because of insulin resistance, protein catabolism is accelerated and muscle mass decreases [38]. In addition, insulin resistance is also involved in kidney hypofunction [39].

Loss of appetite is often observed in CKD patients, which involves endocrine abnormalities. Insulin and leptin levels are elevated in CKD patients, which lower appetite and increase energy expenditure [40]. The inflammatory cytokines IL-6 and TNF-α are also associated with loss of appetite [40]. Ghrelin is a hormone that stimulates appetite and is secreted from the stomach during fasting [41]. Ghrelin has three different forms with different functions in appetite. An interventional study showed that administration of ghrelin to CKD patients improves dietary intake and body weight [42, 43]. Ghrelin is expected as a new treatment for PEW.

Dialysis-related factors include fatigue associated with dialysis, loss of amino acids in dialysate, and uremia due to insufficient dialysis. Because blood comes in contact with the dialyze membrane, inflammation is induced, various dialyzer membranes have been developed. The amount of loss of albumin varies depending on the type of dialyzer membrane used. A cohort study using JRDR data showed that the type of dialyzer membrane affects the prognosis of hemodialysis patients [44]. Multiple studies have shown that dialysis dose affects nutritional status and that nutritional status improves when dialysis is performed more frequently [45–47].

For hemodialysis patients and peritoneal dialysis patients, the amount of amino acids lost is 4–8 g/day [48, 49]. In hemodialysis patients, the use of bioincompatible membrane leads to further losses of amino acids. A study showed that 20 g of protein is lost when using a reused dialyzer cleaned with bleach after 1 session [49]. On

the other hand, another study showed that more frequent dialysis does not deteriorate nutritional status [50]. The amount of amino acids lost may vary depending on the dialysis method. For dialysis patients, a protein intake of 1.2 g/kg/day or more is recommended to compensate for the amount of amino acids lost in dialysate [51]. However, when taking a high-protein diet, the serum phosphorus level increases, which worsens CKD-MBD; therefore, serum phosphorus level must be controlled using phosphate binders. According to an interventional study of dialysis patients, serum albumin levels were improved by a high-protein diet while controlling serum phosphorus levels by administration of lanthanum carbonate [52]. Because appetite may be reduced owing to the side effects of phosphate binders, care is needed, when applying these strategies.

Metabolic acidosis enhances muscle catabolism. Keeping the level of serum hydrogen carbonate within the normal range by administration of sodium bicarbonate prevents the decrease in renal function, improves serum albumin level, and maintains muscle mass [53]. Dietary acid load also affects metabolic acidosis. A diet loads acid or base, which affects endogenous acid production. The induction of nonvolatile acids from foods ingested and cellular metabolism is called endogenous acid production (EAP). EAP minus the amount of gastrointestinal alkali absorbed gives the net endogenous acid production (NEAP). Observational studies in the USA and Japan have shown that as the amount of dietary acid load (i.e., NEAP) increases the kidney function of CKD patients tends to decrease [54–56].

Because inflammation in CKD patients is related to uremic substances, its control is often difficult. Chronic inflammation decreases albumin production and causes PEW and hypoalbuminemia due to anorexia and reduction of dietary intake [57]. In dialysis patients, the levels of inflammatory cytokines may be decreased by changing the type of dialyzer used, long-time dialysis, and online hemodiafiltration (HDF) [58–60].

CKD is also related to digestion and absorption. The intestinal microbial flora changes in CKD patients and affects chronic inflammatory states. In ESKD patients, the number of bacteria and their types decrease [61]. This decrease in the intestinal microbial flora increases the productions of uremia-related substances such as indoxyl sulfate, *p*-cresyl sulfate, amines, and ammonia. These substances are absorbed into the body, resulting in inflammation, endothelial injury, and CVD [62, 63]. Normalization of the intestinal flora may be useful to control chronic inflammation.

In CKD patients, decrease in gastrointestinal motility (i.e., gastroparesis) is observed [64, 65], which is associated with gastrointestinal hormones such as gastrin, cholecystokinin, and gastric inhibitory polypeptide. Gastroparesis causes loss of appetite, bloating, early satiety, vomiting, and gastroesophageal reflux [64]. Treating gastroparesis may improve nutritional status [66].

Owing to the effects of above-mentioned factors, the balance between muscle synthesis and degradation breaks down due to malnutrition, resulting in a decrease in muscle mass. These result in the reduction in the levels of testosterone, estrogen, growth hormone, and other anabolic hormones, thereby worsening the nutritional condition.

3.7 Dietary Therapy for CKD Patients

Dietary therapy plays an important role in the prevention of the onset and progression of CKD. Dietary therapy, which is the core of CKD treatment, is focused on the restriction of DPI, and its main purpose is to protect kidney function. Clinical studies on the suppression of glomerular filtration rate (GFR) decline have been carried out [67, 68]. For the meta-analysis (mean age 55 ± 18 years) in relation to the prevention of GFR decline by dietary therapy, the decrease in the estimated GFR (eGFR) decline rate of the entire CKD patients was statistically significant: −0.95 mL/min/1.73 m^2/year (95% CI: −1.790, −0.11) $p = 0.03$ [69]. In addition, a statistically significant effect was observed in subanalyses when the observation period was 24 months or less, when the patients' eGFR were less than 60 mL/min/1.73 m^2, or when patients' ages were 45 years or older. Furthermore, suppression of GFR decline caused by CKD was statistically significant in nondiabetic CKD patients and type 1 diabetic nephropathy, but not in type 2 diabetic nephropathy. Therefore, the preventive effect of low-protein diet on eGFR decline is not strong in type 2 diabetic nephropathy, but effective in nondiabetic CKD and type 1 diabetic nephropathy. In meta-analyses of RCT in CKD stages G4 to G5, low-protein diet has been reported to reduce the incidence of ESKD by 32% [70]. Therefore, it can be considered that low-protein diet can suppress the progression of CKD.

In a cohort study of CKD patients in the USA, eGFR at the start of observation for all ages has a negative relationship with death and ESKD [71]. In elderly CKD patients, the risk of death is higher and the risk of ESKD is lower than those in young CKD patients. In elderly CKD patients, the risk of death tends to be higher than that of ESKD. Because low-protein diet is aimed at preventing the decline in kidney function and reducing the risk of ESKD, it is not appropriate to uniformly recommend this diet for elderly CKD patients.

In elderly CKD patients, after comparing between the risk of ESKD and the risk of death, and when it is judged that the former is higher, excessive intake of protein should be avoided to prevent CKD progression. Because the recommended DPI is less than that for healthy elderly people, it is necessary to always keep in mind the risk of developing PEW and frailty in elderly CKD patients.

3.8 Strategy Against PEW

The strategy to prevent and treat PEW is as follows (Fig. 3.1) [1]. Screening for malnutrition and [2] nutrition assessment of patients with malnutrition are conducted periodically [3]. If PEW is found, nutritional intervention is considered. Since PEW includes not only malnutrition but also a decrease in muscle mass as a diagnostic criterion, physical rehabilitation is also required to increase muscle mass [4]. If nutritional status improves, [1] is conducted again. However, [5] if nutritional status did not improve, [3] nutritional intervention should be conducted again.

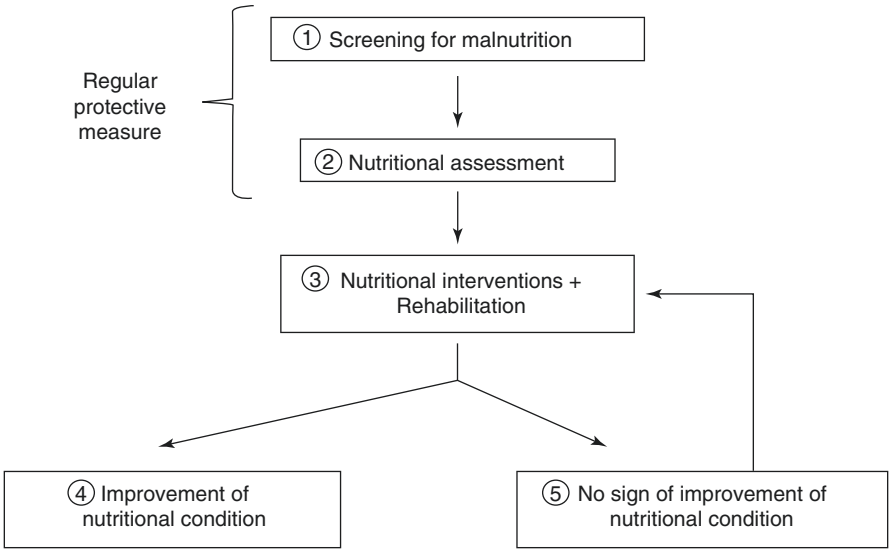

Fig. 3.1 Monitoring of nutritional condition

The specific items of each step are as follows: [1] Serum albumin level, body weight, BMI, MIS, DPI, and DEI are periodically monitored [2]. For a nutrition assessment, serum albumin level, subjective global assessment (SGA), and physical measurement results are evaluated. Preventive measures are carried out such as dietary counseling, appropriate renal replacement therapy, and management of complications (acidosis, diabetes, inflammation, heart failure, and depression) [3]. Nutritional intervention is given when indicated after an evaluation. The conditions, for which nutritional intervention is applicable, are loss of appetite, decrease in DPI and DEI, weight loss, and deterioration of nutritional index [4]. The targets for nutritional status improvement are nutritional indicators such as serum albumin levels of >4.0 g/dL, serum prealbumin level of >30 mg/dL, and achievement of sufficient DPI and DEI [5]. If nutritional status is not improved, nutritional intervention should be conducted. For example, after reviewing dialysis therapy, increase in nutritional intake and nutritional administration during dialysis are considered.

3.9 Dietary Counseling

For the prevention and treatment of PEW in elderly CKD patients, the nutritional characteristics of the elderly CKD patients are evaluated regularly. First, the presence or absence of obesity and weight loss are evaluated at physical examination, and complications such as diabetes and hypertension are diagnosed. When a CKD patient has dementia, the types of foods eaten tend to be unbalanced, and food

intake may extremely decrease. Confirmation of dietary habits and types of food eaten are important. Recording dietary intake and 24-h urinalysis are useful to check the current state of intakes of nutrients. Because individual differences of nutritional characteristics are large among elderly CKD patients unlike young CKD patients, individualized responses are preferable to uniform guidance.

The standard DEI is in the range from 25 to 35 kcal/kg/day for CKD patients and 30–35 kcal/kg/day for dialysis patients; therefore, to ensure sufficient energy, dietary therapy is prescribed according to each patient's condition [72–74]. If a patient does not need to lose weight because the patient has normal body weight, the current weight is maintained. However, there are some cases in which patients misunderstand dietary therapy as weight loss and limit unnecessary energy intake. In the case of unintentional weight loss, hunger and feeling cold are observed: it is necessary to confirm whether energy intake is insufficient. In the case of obesity, DEI should be reduced to attain a BMI 25 kg/m^2. However, because rapid weight loss may lead to a decrease in kidney function, it would be better to reduce weight to be about 5% of body weight in 3–6 months [75, 76].

Low-protein diet of 0.6–0.8 g/kg/day is recommended for CKD patients and that of 0.9–1.2 g/kg/day for dialysis patients [72–74]. However, in the case of elderly people, since their actual DPI is already within this range, it is necessary to confirm their DPI. In CKD patients, DPI can be inferred from Maroni's equation developed from accumulated data.

$$\begin{aligned}&\text{Maroni's equation}: \mathrm{DPI}\left(\mathrm{g/day}\right)\\&=\left[\text{urea nitrogen in urine}\left(\mathrm{g/day}\right)+0.031\times\text{weight}\left(\mathrm{kg}\right)\right]\times 6.25\end{aligned}$$

If their DPI are not sufficient, it is necessary to explain it so as to increase their intakes to the target range.

According to a cross-sectional study of nondiabetic hemodialysis patients in Japan, in patients with a DPI of 0.9 g/kg/day or more, their femoral muscle area and abdominal muscle area were maintained [77]. In another similar cross-sectional study, the body cell mass index, which is the sum total of all the cells of the body, was maintained in the high-DEI group (30 kcal/kg/day or more) regardless of DPI [78]. Moreover, it was shown that the muscle mass was decreased in the group with low DEI (less than 30 kcal/kg/day) and low DPI (less than 1.0 g/kg/day). It can be considered that for hemodialysis patients, muscle mass is less likely to decrease with the recommended DPI if there is sufficient DEI.

Moreover, according to the cross-sectional study in Japan mentioned above, the abdominal-subcutaneous-fat area and the abdominal-visceral-fat area tend to increase when DPI is 1.3 g/kg/day or more, and the serum potassium level is high [77]. According to a cohort study of hemodialysis patients, the relationship between DPI and the risk of death was U-shaped, and the risk of death was higher at DPI of less than 0.9 g/kg/day and 1.3 g/kg/day and higher [79]. Even in patients with hypoalbuminemia (serum albumin level less than 3.5 g/dL), the risk of death was higher at DPI of 1.3 g/kg/day. Considering the above studies, high DPI may increase muscle mass, but there is a risk of increase in visceral fat and hyperkalemia.

Regarding intervention, there was a randomized controlled trial (RCT) in which hemodialysis patients are given proteins (whey protein, soybean protein) during hemodialysis [80]. Walking speed did not improve in the control group, but in the whey-protein and the soy-protein groups, their walking speed increased. Another study showed that when nutritional supplements are administered to malnourished hemodialysis patients for 6 months, their serum albumin level, body weight, and muscle mass increased [81]. Observational studies of hemodialysis patients indicate that life prognosis may be improved oral nutritional supplementation [82]. On the basis of these lines of evidence, nutritional support is effective for improving a patient's life prognosis, but care should be taken to avoid excessive intake of protein.

3.10 Important Points of Dietary Therapy

The amounts of nutrients including amino acids in foods vary, and foods containing protein are rich in the vitamin B group, carnitine, and minerals. The balance of food taken affects the patients' nutritional conditions. Because CKD patients are prone to develop PEW, if their dietary intake is lowered, the types of food they eat become unbalanced, the shortage of high-quality protein intake continues, and nutrient shortage will occur. That is, under low-protein dietary therapy, the restriction of not only DPI but also nutrients in food should be considered.

For dialysis patients, the nutrients removed by dialysis such as amino acids, the vitamin B group, and carnitine should be calculated. In addition, it is necessary to plan dietary intake and contents to prevent PEW and maintain or improve nutritional status and physical condition. If patients cannot achieve the target range of nutritional intake by oral intake of foods alone, nutritional supplementation such as supplementary drugs and administration of nutritional drip injection during dialysis may be effective.

Amino acids that cannot be synthesized in the body and need to be supplemented from food are called essential amino acids. Amino acids with a branched carbon skeleton are called branched-chain amino acids (BCAAs), among which valine, leucine, and isoleucine constitute nearly half of muscle proteins. Many amino acids are metabolized in the liver, but BCAAs are metabolized in muscle. Among BCAAs, leucine promotes the synthesis of proteins through the mammalian target of rapamycin (mTOR) and suppresses degradation [83, 84]. Ingestion of BCAAs may be effective for PEW prevention and treatment.

An interventional study showed that administration of essential amino acids including leucine to the elderly for 16 weeks improved their walking speed [85]. It has been reported that muscle mass is improved by administrating essential amino acids including leucine, but not the muscle strength [86]. Another study showed that both muscle mass and muscle strength are not improved by leucine [87]. From these results, although leucine promotes the synthesis of muscle protein, it may not increase muscle mass and muscle strength. Because the subjects of these studies are healthy individuals, different results will be obtained in CKD patients. Because

various factors such as growth factors, hormones, and exercise are involved in the metabolism of muscles, improvement of muscle mass and strength will be expected with administration of BCAAs and exercise.

Carnitine is synthesized mainly from the essential amino acids, lysine and methionine in the liver and kidney, and 98% of it is in skeletal muscle and cardiac muscle. Meat contains carnitine. More than 90% of carnitine is filtered by glomeruli and reabsorbed by renal tubules, but synthesis and reabsorption of carnitine is reduced owing to decrease in the kidney function. Furthermore, owing to restricted protein diet, loss of dietary intake, and loss of carnitine due to dialysis, CKD patients and dialysis patients tend to be deficient in carnitine [88]. Carnitine deficiency is associated with anemia, dyslipidemia, muscle weakness, and heart failure. Studies showed that the nutritional status of hemodialysis patients was improved by administration of L-carnitine, and prevention and treatment of PEW are expected in the use of carnitine supplementation [89–91].

According to a cohort study in the USA, treatment before and after dialysis initiation affects the life prognosis of dialysis patients, but the effect of the treatment before dialysis initiation is statistically significantly stronger than the treatment after dialysis initiation [92]. Among the treatments of CKD, nephrologist guidance and dietary guidance affect life prognosis after dialysis initiation. Considering these results, the purpose of diagnosis and treatment for elderly CKD patients includes not only the prevention of CKD progression but also improvement of life prognosis after dialysis initiation and improvement of their physical functions and QOL. In other words, a consistent medical care system including CKD and dialysis is necessary, and dietary therapy will play a part of it. Dietary therapy for patients with CKD requires a viewpoint from total life support that takes into consideration of their life prognosis and social life. In other words, taking into account the guidelines, it is important to provide instruction on diet as part of total care that is tailored to a patient's medical condition, nutritional status, and social condition.

3.11 Exercise Therapy

The important points for the prevention of PEW, sarcopenia, and frailty are nutrition and muscle strength. Maintaining or improving muscle mass and strength is important. RCTs and observational studies on patients with CKD showed that exercise leads to increase in muscle mass and strength, weight loss, improvement of ADL, and decrease in the risks of death and ESKD [93–98]. A systematic review of CKD patients shows improvement of muscular strength and motor function by exercise [99].

In interventional studies of CKD patients taking low-protein diet (0.6 g/kg/day), the effect of 12-week resistance training on physical function was evaluated [93, 94, 98]. An increase in intramuscular mitochondrial DNA was observed in the training group [93, 94]. In addition, serum CRP and IL-6 levels, which are related to inflammation, decrease with the improvement of patients' nutritional status [98]. These results suggest that PEW may be improved by exercise therapy.

In a systematic review of hemodialysis patients, it has been reported that their physical function is improved by exercise [99]. A study showed that protein anabolism is enhanced by resistance training before hemodialysis and nutrition intake during dialysis [100]. Another systematic review has shown that resistance training conducted during hemodialysis improves Kt/V, increases the maximum oxygen intake, and improves physical function [101].

An RCT of hemodialysis patients for 6 months, in which a group with resistance training before dialysis and nutritional supplementation during dialysis was compared with the group given only nutritional supplements, showed that the group with resistance training and nutritional supplementation showed weight gain [102].

Another RCT showed that the distance after 6-min walking was increased by combining an ergometer during dialysis with nutritional supplementation [103]. Considering these results, it is expected that physical function can be improved by exercise therapy and nutritional supplementation. The combination of exercise and nutritional supplementation is effective for the prevention and improvement of PEW in CKD patients.

It has been reported that in CKD patients, muscular strength and ambulatory ability are improved by periodic exercise [99]. Regarding aerobic training both are recommended for these patients. For dialysis patients, the same physical function improvement effect was observed for cycling exercises using an ergometer during dialysis and walking at home [104].

Moreover, in CKD patients, muscle training as a resistance training three times a week increases muscle mass [93, 94]. However, cycling exercises and muscle training during dialysis are often difficult in practice. In such a case, they can perform training to improve muscle strength by pulling a tube lightly or squatting lightly by bending the knees. Older people often have problems such as pain in their shoulders, knees, and waist. Therefore, when teaching exercise, it is necessary to observe the patients' state and decide their training program. Moreover, in order to prevent falls and fractures in elderly patients, it would be better to watch over and assist them during their exercise.

3.12 Summary

In CKD patients, not only problems associated with aging but also various complications are often present, which affect their nutritional status. Their malnutrition causes a decrease in muscle strength and ADL. Falls and fractures may occur owing to the decrease in muscle strength, which leads to a decrease in social activity, and an increase in care problems. These problems also lead to loss of appetite and PEW. Because PEW involves nutritional status, muscular strength, ADL, and social life, the combined effect of various problems exacerbates PEW and affects life prognosis of CKD patients and dialysis patients. Taking these factors into consideration, it can be understood that not only nutritional therapy but also exercise therapy to maintain physical function are necessary to stop the vicious cycle related to PEW and the decline of ADL. It is necessary to develop a social support system that enables patients to continue their treatments.

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Benefit and Risk of Exercise Training in Chronic Kidney Disease Patients

4

Masahiro Kohzuki, Toshimi Sato, Chaeyoon Cho, and Naoki Yoshida

Abstract

Chronic kidney disease (CKD) is a worldwide public health problem. In CKD patients, exercise endurance is lowered, and this phenomenon becomes more distinct as the renal dysfunction advances. This is due to the combined effects of uremic acidosis, protein-energy wasting, and inflammatory cachexia, which lead to and are further aggravated by a sedentary lifestyle. Together, these factors result in a progressive downward spiral of deconditioning. This review focuses on the benefits and risks of exercise training in CKD patients. In Japan, we have established the Japanese Society of Renal Rehabilitation in 2011 to evaluate and promote renal rehabilitation (RR). We use a comprehensive approach to RR including physical exercise and psychological, vocational, and dietary counseling. RR is a feasible, effective, and safe secondary prevention strategy following CKD and offers a promising model for new field of rehabilitation. Urgent efforts should be made to increase the implementation rate of the RR.

Keywords

Chronic kidney disease · Rehabilitation · Exercise · Cardio-renal syndrome · Renal protection

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4.1 Introduction

Chronic kidney disease (CKD) is a worldwide public health problem. The numbers of patients of hemodialysis (HD) in Japan are more than 340,000, which correspond to 1 in 370 of the total population. Furthermore, the numbers of patients of CKD in Japan are more than 11% of the total population.

In CKD patients, exercise endurance is lowered, and this phenomenon becomes more distinct as the renal dysfunction advances. This is due to the combined effects of uremic acidosis, protein-energy wasting (PEW), and inflammatory cachexia, which lead to and are further aggravated by a sedentary lifestyle. Together, these factors result in a progressive downward spiral of deconditioning.

CKD patients undergoing dialysis have very high mortality with cardiovascular diseases such as chronic heart failure, and yet higher mortality risk has been reported for sedentary CKD patients undergoing dialysis [1]. As well as being a strong cardiovascular risk factor, physical inactivity (PI) is associated with increased risk of rapid kidney function decline in CKD patients [2]. This review focuses on the benefits and risks of exercise training in CKD patients.

4.2 CKD and Physical Inactivity

PI is well recognized as a major health issue in today's society. Regular exercise is important in maintaining health and preventing chronic disease. Moreover, the association between PI and poor outcomes is well established for CKD patients [3–5]. CKD patients typically engage in a lower level of PA than do the general population, which can induce a catabolic state including reduced neuromuscular functioning, reduced exercise tolerance, and reduced cardiorespiratory fitness.

Results from an international study of CKD patients undergoing dialysis indicate that regular exercise is associated with better outcomes, and that patients at facilities offering exercise programs have higher odds of exercising. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), overall, 47.4% of participants were categorized as regular exercisers. The odds of regular exercise were 38% higher for patients from facilities offering exercise programs ($P = 0.03$) [4].

In addition to PI, cardiorespiratory fitness is an important consideration, as it is a strong predictor of mortality [6, 7]; low cardiorespiratory fitness presents a particularly high risk of death compared to other common risk factors, such as diabetes, high cholesterol, or hypertension [8]. Cardiorespiratory fitness is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity (PA) and is usually expressed as maximal oxygen uptake (VO_2 max) or peak oxygen uptake (peak VO_2) during exercise stress testing [9]. VO_2 max is expressed either as an absolute rate in, for example, liters of oxygen per minute (L/min) or as a relative rate in, for example, milliliters of oxygen per kilogram of body mass per minute (e.g., mL/[kg min]). Figure 4.1 shows gas transport mechanisms for coupling cellular (internal) to pulmonary (external) respiration [10]. The gears represent the functional interdependence of the physiological components of the system.

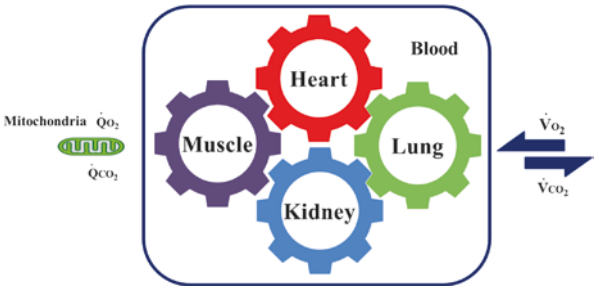

Fig. 4.1 Gas transport mechanisms for coupling cellular to pulmonary respiration: five major determinants for peak VO_2. (Used with permission from Kohzuki [10])

Cardiac output, pulmonary diffusion capacity, oxygen carrying capacity, renal function, and other peripheral limitations like muscle diffusion capacity, mitochondrial enzymes, and capillary density are all examples of VO_2 max determinants.

The large increase in O_2 utilization by the muscles (QO_2) is achieved by increased extraction of O_2 from the blood perfusing the muscles, the dilatation of selected peripheral vascular beds, an increase in cardiac output (stroke volume and heart rate), an increase in pulmonary blood flow by recruitment and vasodilatation of pulmonary blood vessels, and finally, an increase in ventilation. O_2 is taken up (VO_2) from the alveoli in proportion to the pulmonary blood flow and degree of O_2 desaturation of hemoglobin in the pulmonary capillary blood. Metabolic acidosis in CKD patients promotes muscle protein wasting and PEW by increasing protein degradation [11] and reducing protein synthesis [12]. As a result, maintenance of muscle mass is impaired in CKD patients with altered protein turnover rates [13]. Adding to sarcopenia, metabolic acidosis, PEW, angiotensin II, myostatin overexpression in uremia contribute to the etiology in muscle wasting in CKD [14]. Moreover, the drug erythropoietin (EPO) can boost VO_2 max by a significant amount in both humans and other mammals [15].

4.3 Effects of Exercise Training in CKD Patients

1. *The effect of exercise training in chronic kidney disease patients undergoing dialysis*.

   In DOPPS study, regular exercisers in CKD patients undergoing dialysis had higher health-related quality of life (HR-QL), physical functioning, and sleep quality scores; reported fewer limitations in physical activities; and were less bothered by bodily pain or lack of appetite [4]. Regular exercise was also correlated with more positive patient affect and fewer depressive symptoms [4]. In models extensively adjusted for demographics, comorbidities, and socioeconomic indicators, mortality risk was lower among regular exercisers (hazard ratio = 0.73 [0.69–0.78]; $P < 0.0001$) and at facilities with more regular exercisers (0.92 [0.89–0.94]; $P < 0.0001$ per 10% more regular exercisers) [4].

   A systematic review and meta-analysis controlled trials were reported about regular exercise training for at least 3–10 months in CKD patients undergoing dialysis demonstrated that baseline, peak VO_2 values were 70% of age-predicted

values, exercise intervention patients improved post-training peak VO_2 to 88% predicted [5]. In CKD patients undergoing dialysis, exercise training produced 26% improvements in eight studies that reported peak VO_2. Equivocal results for change in short-form 36 health questionnaire scores were reported post-training [5]. Significant improvements in lean body mass, quadriceps muscle area, knee extension, hip abduction, and flexion strength were also reported [5]. They did not find any deaths directly associated with exercise in 28,400 patient-hours and no differences in withdrawal rates between exercise and control participants. Exercise training for 6 months or more conveyed larger improvements in peak VO_2 than shorter programs. Therefore, exercise training is safe and imparts large improvements in peak VO_2 and heart rate variability in CKD patients undergoing dialysis [5].

Moreover, a growing evidence suggests that exercise training in CKD patients undergoing dialysis improves VO_2 max, left ventricular function, cardiac sympathetic and parasympathetic disharmony, PEW, anemia, sleep quality, anxiety, HR-QL, activities of daily living, shunt size, Kt/V, and mortality [3, 16].

2. *The effect of exercise training in pre-dialysis CKD animal models*.

There is increasing evidence of the benefit of regular physical exercise in a number of long-term conditions including CKD. It is also necessary to consider the influence of exercise on renal functions because acute exercise causes proteinuria and subsequent reductions in both the renal blood flow and glomerular filtration rate (GFR). It has also been demonstrated clinically that sudden exercise decreases renal function. There are few reports on the influence of chronic exercise on renal function, and there is little information about the effect of exercise on pre-dialysis CKD patients. The optimal intensity and duration of exercise for pre-dialysis CKD patients have not yet been formulated.

We have published several papers in this field. We assessed the renal effects of moderate chronic treadmill exercise in several CKD rat models and reported that exercise does not worsen renal function and has renal-protective effects in some models of rats such as a remnant kidney model of spontaneously hypertensive rats with 5/6 nephrectomy, [17] 5/6-nephrectomized Wistar–Kyoto rats, [18] a rat model of diabetic nephropathy (Goto–Kakizaki rats), [19] and Zucker diabetic rats [20].

3. *The effect of regular exercise training in pre-dialysis chronic kidney disease patients*.

Relatively few studies have included patients with stage 1–4 CKD, which limits the generalization of findings to pre-dialysis CKD patients. Sedentary pre-dialysis CKD men (eGFRcreat 27.5 ± 11.6 mL/min) were randomly assigned to a center-based exercise group, home-based exercise group, or control group. In exercise groups, the aerobic training was performed three times per week during 12 weeks. eGFRcreat increased 3.6 ± 4.6 mL/min ($P = 0.03$) in the center-based group. The parameter remained unchanged in the control group [21].

Greenwood et al. examined the effect of moderate-intensity exercise training on kidney function and indexes of cardiovascular risk in patients with progres-

sive stages 3–4 CKD. Single-blind randomized controlled studies showed that a significant mean difference in rate of change in eGFRcreat was observed between the rehabilitation and usual care groups, with the rehabilitation group demonstrating a slower decline [22].

Chen et al. investigated the association of walking with overall mortality and renal replacement therapy (RRT) such as hemodialysis, peritoneal dialysis, or kidney transplantation in patients with stages 3–5 CKD. A total of 6363 patients (average age, 70 years) were analyzed. There were 1341 (21.1%) patients who reported walking as their most common form of exercise training. The incidence density rate of overall mortality was 2.7 per 100 person-years for walking patients and 5.4 for non-walking ones. The incidence density rate of RRT was 22 per 100 person-years for walking patients and 32.9 for non-walking ones. Walking, independent of patients' age, renal function, and comorbidity, was linked to lower overall mortality and lower RRT risk in the multivariate competing-risks regression. The adjusted subdistribution hazard ratio (SHR) of walking was 0.67 (95% confidence interval [95% CI], 0.53–0.84; $P < 0.001$) for overall mortality and 0.79 (95% CI, 0.73–0.85; $P < 0.001$) for the risk of RRT. The SHRs of overall mortality were 0.83, 0.72, 0.42, and 0.41 for patients walking 1–2, 3–4, 5–6, and 7 times per week, and the SHRs of RRT were 0.81, 0.73, 0.57, and 0.56, respectively. Walking is the most popular form of exercise training in CKD patients and is associated with lower risks of overall mortality and RRT. The benefit of walking is independent of patients' age, renal function, and comorbidity [23].

4. *The effect of regular exercise training in pre-dialysis chronic kidney disease patients with acute myocardial infarction.*

Combined renal dysfunction worsens the subsequent prognosis in patients after acute myocardial infarction (AMI). We elucidated the association between PA level and changes in renal function in patients after AMI [24]. Renal function was evaluated based on cystatin C based-estimated glomerular filtration rate (eGFRcys) which is independent of skeletal muscle mass. Patients were stratified into low (2335 ± 1219 steps/day) and high groups (7102 ± 2365 steps/day). eGFRcys significantly increased from baseline to after 3 months in the high group (76.5 ± 13.8 to 83.2 ± 16.0 mL/min/1.73m^2), whereas no significant change was observed in the low group (65.1 ± 15.9 to 62.2 ± 20.2 mL/min/1.73m^2). Changes in eGFRcys was −2.9 mL/min/1.73m^2 among low group versus +6.7 mL/min/1.73 m^2 among high group [24]. PA level was positively associated with changes in renal function, demonstrating that high PA may suppress renal function decline in patients after AMI. Figure 4.2 shows the associations between the number of steps and ΔeGFRcys or ΔeGFRcreat in all patients [24]. The results of Pearson's correlation analysis showed significant correlations between the number of steps and both parameters. Furthermore, the correlation coefficient between ΔeGFRcreat and the number of steps ($r = 0.38$, $p = 0.015$) was lower compared to the correlation coefficient between ΔeGFRcys ($r = 0.55$, $p < 0.001$) and the number of steps. As previously pointed out, changes in the serum creatinine level through movement of the skeletal muscles is one of

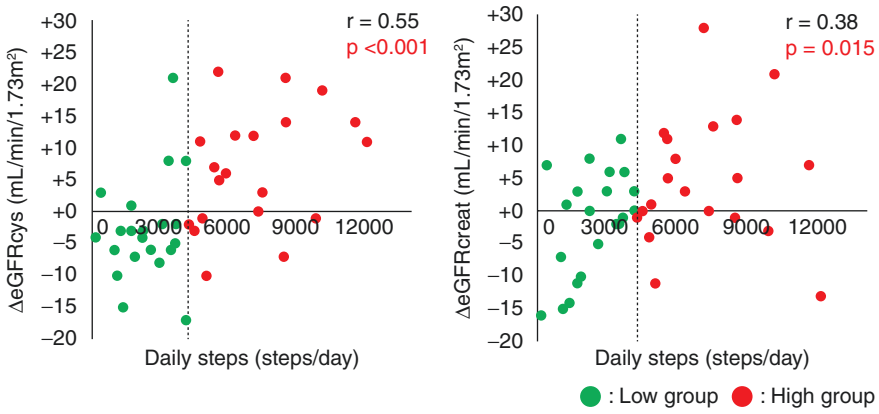

Fig. 4.2 Association between the number of steps and ΔeGFRcys or ΔeGFRcreat. (Used with permission from Sato et al. [24])

the causes, and the significance of using eGFRcys as an indicator for renal function in this study was confirmed [25, 26].

In recent years, a prior prospective study verified the association between PA level and renal function in CKD patients [27]. The results of this study are similar to our present findings and indicate that maintaining a high level of PA in daily life leads to suppression of renal function deterioration. The present study is the first to show the association between PA level and changes in renal function after the onset of AMI using an accelerometer and eGFRcys. High PA was suggested to suppress renal function decline in patients with AMI. Our findings support the importance of interventions to maintain high PA as a strategy for renal protection in AMI patients. Future research should verify the long-term effect of PA level on renal function among AMI patients.

4.4 Indications and Contraindications of Exercise Stress Test and Exercise Training in CKD Patients

4.4.1 Medical Checkups

Prior to beginning exercise training programs, candidates should be assessed for clinical status and undergo examinations at rest and exercise stress tests to determine the appropriateness of exercise training for individual participants and to establish the appropriate exercise prescription. Clinical status should be assessed through medical interviews about subjective symptoms, medical history, family history, and lifestyle. Medical checkups should include measurement of blood pressure, pulse rate, and electrocardiographic activity. Levels of blood glucose, total cholesterol, triglycerides, hepatic enzymes, and body mass index should also be evaluated [28].

4.4.2 Exercise Stress Test

Those who have not participated in regular exercise training in the previous 3 months should be referred for medical clearance prior to beginning exercise training. Because cardiovascular disease (CVD) is the major cause of death in CKD patients, when symptoms are present or CVD is diagnosed, exercise stress test may be indicated as part of the medical clearance process prior to beginning an exercise program of moderate to vigorous intensity. In CKD patients undergoing dialysis, exercise stress test should be scheduled for non-dialysis days, and blood pressure should be monitored in the arm that does not contain the arteriovenous fistula. For comfort purposes, patients receiving continuous ambulatory peritoneal dialysis should be tested with little dialysate fluid in their abdomen [29].

However, some suggest that exercise test for CKD patients, as well as those who are frail, is not warranted because their performance may be affected by muscle fatigue, and such testing may act as an unnecessary barrier to their participation in an exercise program. If performed, exercise stress test of CKD patients should use standard test termination criteria and test termination methods [28].

Absolute contraindications for exercise stress test are acute myocardial infarction developed within 2 days, unstable angina not controlled with medical treatment, uncontrolled arrhythmia that causes symptoms or hemodynamic compromise, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure, acute pulmonary embolism or pulmonary infarction, acute myocarditis or pericarditis, acute aortic dissection, and mental disorders associated with communication difficulties [28].

Relative contraindications for exercise stress test are left main coronary artery stenosis, moderate stenotic valvular heart disease, electrolyte abnormality, severe hypertension (systolic blood pressure of >200 mmHg and/or a diastolic blood pressure of >110 mmHg,), tachyarrhythmia or bradyarrhythmia, hypertrophic cardiomyopathy or other outflow tract obstruction, mental or physical impairment leading to inability to exercise adequately, and advanced atrioventricular block [28].

Criteria for terminating exercise stress test are as follows: (1) Symptoms—anginal pain, dyspnea, syncope, dizziness, light-headed feeling, and leg pain (claudication); (2) signs—cyanosis, facial pallor, cold sweat, and ataxia; (3) blood pressure—insufficient increase or progressive decrease in systolic blood pressure during exercise, or abnormal increase in blood pressure (≥225 mmHg); (4) ECG—apparent ischemic ST-T changes, cardiac rhythm disorder (e.g., severe tachycardia or bradycardia, ventricular tachycardia, frequent arrhythmias, atrial fibrillation, R on T, and premature ventricular contractions), and second or third degree atrioventricular block [28].

4.4.3 Exercise Training

All CKD patients must be assessed carefully to determine whether exercise training is indicated.

Absolute contraindications for exercise training in CKD patients are as follows: (1) Exacerbation of heart failure symptoms (e.g., dyspnea, easy fatigability) during the last week, (2) unstable angina or low-threshold myocardial ischemia that is induced by slow walking on a flat surface (2 METs), (3) severe valvular heart disease indicated for surgery, especially aortic stenosis, (4) severe left ventricular outflow tract obstruction (hypertrophic obstructive cardiomyopathy), (5) untreated severe exercise-induced arrhythmia (ventricular fibrillation, sustained ventricular tachycardia), (6) active myocarditis, (7) acute systemic disease or fever, and (8) other diseases in which exercise is contraindicated (moderate or severe aortic aneurysm, severe hypertension, thrombophlebitis, embolism that developed in the last 2 weeks, and serious organ diseases) [28].

Relative contraindications for exercise training in CKD patients are as follows: (1) NYHA classification of Class IV heart failure or heart failure requiring intravenous cardiotonics, (2) heart failure with an increase in body weight by ≥2 kg during the last week, (3) exercise-induced decrease in systolic blood pressure, (4) moderate left ventricular outflow tract obstruction, (5) exercise-induced moderate arrhythmia (e.g., non-sustained ventricular tachycardia, tachycardiac atrial fibrillation), (6) advanced atrioventricular block, (7) exacerbation of exercise-induced symptoms (e.g., fatigue, dizziness, excessive sweating, dyspnea) [28].

Moreover, CKD patients are likely to be on multiple medications including those that are commonly used in the treatment of hypertension, dyslipidemia, and diabetes mellitus. If they have such diseases, they should follow indications and contraindications for exercise training in lifestyle-related diseases too. Indications are shown as follows: Hypertension—BP of 140–159/90–94 mmHg; diabetes—fasting blood glucose level of 110–139 mg/dL; dyslipidemia—TC of 220–249 mg/dL or TG of 150–299 mg/dL; and obesity—BMI of 24.0–29.9 [28].

Conditional indications are shown as follows: Hypertension—BP of 160–179/95–99 mmHg, ongoing antihypertensive treatment with BP less than the contraindicated level, men over 40 years and women over 50 years should undergo exercise stress tests whenever possible. If exercise stress tests are not feasible, prescribe walking or other light exercise. Diabetes—fasting blood glucose level of 140–249 mg/dL; ongoing antidiabetic treatment with glucose levels less than the contraindicated level; men over 40 years and women over 50 years should undergo exercise stress tests whenever possible. If exercise stress tests are not feasible, prescribe walking or other light exercise. Dyslipidemia—TC of ≥250 mg/dL or TG of ≥300 mg/dL, ongoing lipid management; men over 40 years and women over 50 years should undergo exercise stress tests whenever possible. If exercise stress tests are not feasible, prescribe walking or other light exercise. Obesity—BMI of 24.0–29.9, detailed assessment for leg joint disorder; limitation of exercise [28].

Contraindications are shown as follows: Hypertension—BP of ≥180/100 mmHg; chest X-ray findings with a CTR of ≥55%; ECG indicating severe arrhythmia or ischemic changes (excluding those with favorable results of exercise stress tests); hypertensive changes (IIb or higher) on funduscopy; urinary protein of ≥100 mg/dL. Diabetes—Fasting blood glucose level of ≥250 mg/dL; positive urinary ketones; diabetic retinopathy; and obesity—BMI ≥30.0 [28].

4.5 Barriers to Exercise Participation Among CKD Patients

Unfortunately, the role of PA in CKD has been largely overlooked. The supply of exercise advice and rehabilitation programs for CKD patients are lagging behind that of cardiology and pulmonary services.

The Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines on management of cardiovascular disease state that, "all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of PA" [30].

In multivariate analysis, a greater number of reported barriers were associated with lower levels of PA. Lack of motivation was associated with less PA. Endorsement of too many medical problems and not having enough time on dialysis days were also associated with less activity in adjusted analysis [31].

Delgado et al. administered a 30-item survey regarding exercise counseling to nephrologists attending the American Society of Nephrology meeting in 2007 [32]. In multivariate analysis, older nephrologists (odds ratio; 95% CI) (3.3; 1.2–9.0) and those more physically active (5.5; 2.0–14) were more likely to ask and counsel patients about PA [32]. Opinions associated with less counseling behavior included lack of confidence in ability to discuss PA. They also reported that CKD patients undergoing dialysis were interested in PA [31]. They reported that 92% of participants reported at least one barrier to PA. The most commonly reported barriers were fatigue on dialysis days and non-dialysis days and shortness of breath. In multivariate analysis, a greater number of reported barriers were associated with lower levels of PA. Lack of motivation was associated with less PA. Endorsement of too many medical problems and not having enough time on dialysis days were also associated with less activity in adjusted analysis [31].

The location of the exercise training is also an important factor influencing adherence. In CKD patients undergoing dialysis, intra-dialysis programs have been found to achieve higher adherence rates compared to home exercise programs or supervised programs on non-dialysis days [33].

4.6 Renal Rehabilitation

Several international initiatives and working groups have been established to tackle the specific contribution of physical inactivity to the burden of disease in CKD patients [34–37]. In line with recommendations for the general population, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that patients with CKD undertake moderate PA for at least 30 min five times per week [38].

In Japan, we established the Japanese Society of Renal Rehabilitation (JSRR) in 2011 to evaluate and promote renal rehabilitation (RR). We define RR as, "RR is coordinated, multifaceted interventions designed to optimize a renal patient's physical, psychological, and social functioning, in addition to stabilizing, slowing,

or even reversing the progression of renal deterioration, thereby reducing morbidity and mortality. RR includes five major components: such as exercise training, diet and fluid management, medication and medical surveillance, education, psychological and vocational counseling" [3, 16]. We use a comprehensive approach to RR including physical exercise and psychological, vocational, and dietary counseling. We first published the book titled *Renal Rehabilitation* [3, 16]. In recent years, the concept of RR has become widely known among nephrology specialists, dialysis specialists, kidney transplantation specialists, rehabilitation specialists, nutrition specialists, guideline specialists, nurses, physiotherapists, and representatives of patients. In order to make clear the methods and effectiveness of renal rehabilitation in Japan, we launched Renal Rehabilitation Guideline Preparation Committee in 2016 as a part of works in the JSRR and created a guideline in accordance with the "Minds Handbook for Clinical Practice Guideline Development 2014" [39, 40]. Six recommendations for the condition of each kidney disorder, groups addressing nephritis/nephrosis, chronic kidney diseases, dialysis therapy, and kidney transplantation were created. All the recommendation grades were determined by a consensus conference participated in by representatives of patients and various professionals.

Moreover, to our knowledge, health-care systems in most countries offer no or limited reimbursement for exercise training for CKD patients. In contrast, such infrastructure and reimbursement systems do exist in many countries for rehabilitation after cardiac diseases. Therefore, CKD patients are largely unsupported in overcoming barriers to exercise and in finding suitable exercise facilities [41]. To our knowledge, Japan is the only country to offer exercise training for patients with diabetes and pre-dialysis CKD stage 3B–5 that is covered by the national health insurance system [42, 43].

4.7 Adding Life to Years and Years to Life

As super-aged society has come, the number of persons with multimorbidity and multiple disabilities and their needs of rehabilitation have increased rapidly more than we had expected [44]. Medical science basically aims to "Adding Years to Life" by increasing life expectancy. Rehabilitation generally aims to "Adding Life to Years" by helping patients with impairment achieve, and use, their full physical, mental, and social potential. However, recent growing evidence suggests that rehabilitation for patients with visceral impairment such as renal, cardiac, and pulmonary impairment can not only improve exercise performance and HR-QL but also increases survival (Fig. 4.3) [45]. Therefore, modern comprehensive rehabilitation for CKD patients does not simply aim to "Adding Life to Years" but "Adding Life to Years and Years to Life," which is a new rehabilitation concept [45].

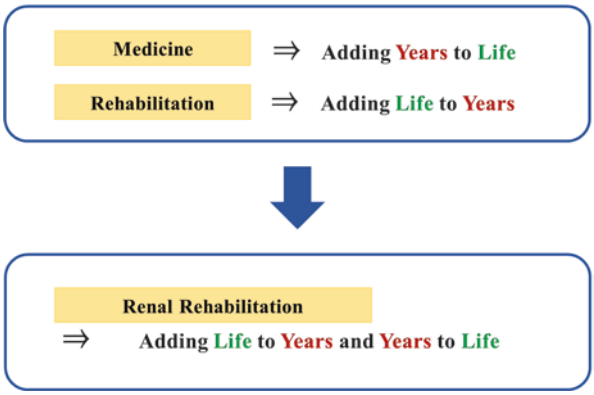

Fig. 4.3 Renal rehabilitation is a new paradigm of rehabilitation. (Used with permission from Kohzuki et al. [45])

4.8 Conclusion

In RR, we should improve not only HR-QL but also biological lifespan in CKD patients. RR is a feasible, effective, and safe secondary prevention strategy following CKD and offers a promising model for new field of rehabilitation. Future larger randomized controlled trials should focus more on the effects of exercise training and rehabilitation programs as these subjects and exercise types have not been studied as much as cardiovascular exercise. Moreover, urgent efforts should be made to increase the implementation rate of the RR.

Conflict of Interest The author declares no conflict of interest.

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5 Frailty in Patients with Pre-dialysis Chronic Kidney Disease: Toward Successful Aging of the Elderly Patients Transitioning to Dialysis in Japan

Yugo Shibagaki

Abstract

Japan has been recognized as having best prognosis of dialysis patients in the world; however, the early mortality of elderly incident dialysis patients is the same as or even worse compared to that in the developed countries in the Western world. One leading reason of this is rapidly growing number of frail aging population among incident dialysis patients.

Frailty in elderly incident dialysis patients was prevalent and severe in degree, and frailty develops in the continuous process. We investigated in pre-dialysis patients of ours to find that physical functional decline is prevalent and develops in early stages in chronic kidney disease (CKD), and mild cognitive impairment is also prevalent in CKD and is associated with physical functioning decline. We demonstrated that even the home-based exercise may improve physical activity and function in elderly CKD patients.

We also pay attention to our routine medical practice if it really helps our patients achieve successful aging. Although recommended in the clinical practice guidelines, protein restriction and intensive blood pressure control, especially in frail elderly with CKD, may not be so effective as in younger counterparts and even be harmful to them. We also need to check how patients face with their reality with illness and how much hope they have.

We just need to pause, look back, and reconsider what we usually do and try our best to think what we can do our best to achieve the successful aging of our elderly patients with CKD.

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Keywords

Frailty · Physical function · Cognitive function · Elderly · Pre-dialysis · Chronic kidney disease · Protein restriction · Target blood pressure · Hope · Successful ageing

5.1 Introduction

Japan has been recognized to enjoy the highest cumulative survival of hemodialysis patients compared to Europe and United States [1, 2]. For example, the cumulative 5-year survival of incident dialysis patients as of 2005 was 59.6% in Japan [3] compared to 35% in United States [4]. I experienced clinical practice in Nephrology both in United States (1999–2002) and in Japan (since 1995) and still cannot feel that Japanese dialysis patients are much happier than those of other countries where survival rate is much lower. Then, what is the problem?

Aging in chronic kidney disease (CKD) and dialysis population has been a common problem worldwide, especially in Japan [5, 6]. Moreover, CKD has been associated with unsuccessful aging [7]. Rowe and Kahn once defined "successful aging" as being multidimensional, encompassing the avoidance of disease and disability, the maintenance of high physical and cognitive function, and sustained engagement in social and productive activities [8]. Successful aging in patients with dialysis means they are not only free from disease and disability other than kidney disease but also maintain high physical and cognitive function and continue to engage in social/productive activity. But, are we physicians trying our best to achieve all these elements of successful aging instead of just taking care of diseases?

5.2 Current Status of Dialysis in Japan

As mentioned above, we believed that Japanese dialysis patients enjoy one of the best survival rates in the world. In addition, quality control of dialysis in Japan is superb by rapid technological development and improvement; endotoxin-free dialysate was used in almost all the facilities, and hemodiafiltration (HDF) is offered in more than 10% of all facilities with average single-pool Kt/V of 1.4 in male and 1.6 in female [3]. However, in spite of these improvements in technical quality control in dialysis, annual crude death rate remains flat around just <10% (9.7% in 1992 and 9.8% in 2013) [3]. One of the biggest reasons why crude death rate is not improving is of course rapid aging in dialysis population in Japan. As of end of 2013, age 60 or older accounted for 76.0% and age 75 or older for 30.2% of all prevalent dialysis population (Data from current status of chronic dialysis therapy as of the end of year 2013 by The Japanese Society for Dialysis Therapy), and this

number is projected to increase surprisingly and rapidly in year of 2025 with age 60 or older accounting for more than 90% and age 75 or older for 40% of all prevalent dialysis population [9].

Thus, this surprisingly high burden of elderly population seems to be one of the plausible reasons why survival is not improving longitudinally although the survival is still better than those of other countries. However, recently, we doubt that prognosis of elderly incident dialysis patients in Japan is good since many of those patients we took care of died early after initiation of dialysis therapy. So, we investigated the early mortality in incident dialysis patients using large Japanese national registry data in 2007 and surprisingly found that 1-year and 3-month mortality was as much as 30.2% and 15.8% in those aged 80 or more, respectively [10] (Fig. 5.1), which is not superior to or even inferior to other developed countries [11, 12]. Thus, Japanese dialysis patients are not superior in terms of early mortality after dialysis initiation although survival in those who survived a year after dialysis initiation may be better. We then investigated the risk factors of early mortality in Japanese dialysis population and found that functional status was among the most influential factors tightly associated with early mortality with risk ratio of early mortality at 3 months being 3.43 [95% confidence interval (CI) 2.09–5.63] in severe and 2.26 (95%CI 1.37–3.74) in moderate functional impairments compared to mild or no functional impairment [10] (Fig. 5.2).

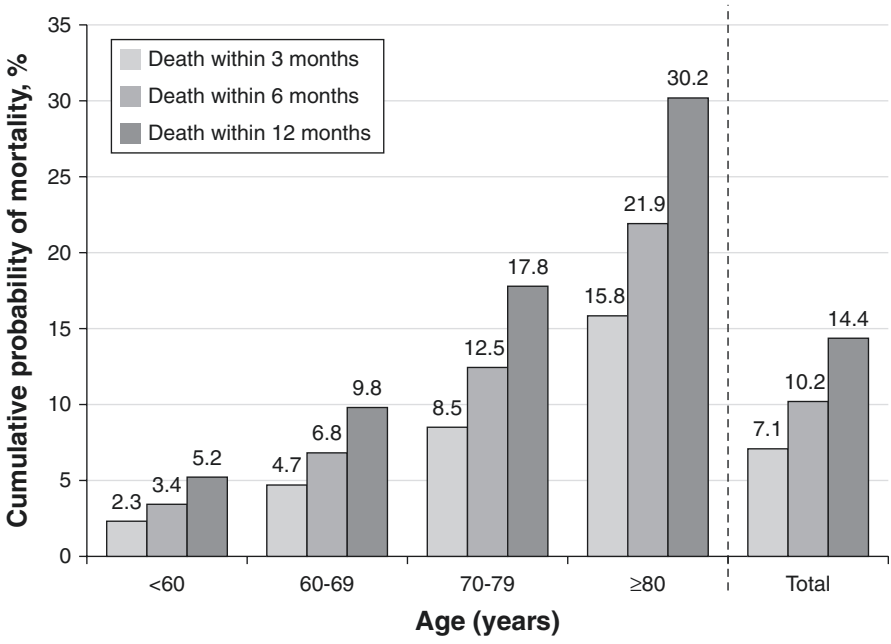

Fig. 5.1 Cumulative probability of early mortality after dialysis initiation by age (n = 33.281). (PMID: 2727061)

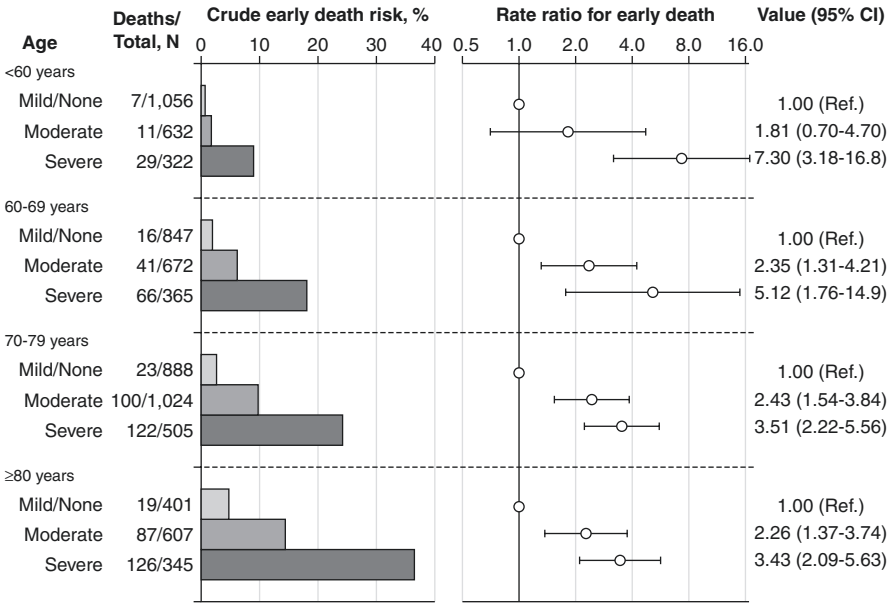

Fig. 5.2 Early mortality risk and the association with functional status at dialysis initiation by age (n = 7.664). (PMID: 27270615)

5.3 Frailty in CKD and Incident Dialysis Patients

Frailty is a physiologic state of increased vulnerability to stressors from decreased physiologic reserves or dysregulation of multiple physiologic systems and is operationally defined by physical and cognitive functional declines, which is associated with poor outcomes [13]. Frailty is very prevalent in CKD and dialysis population, and the prevalence of frailty has been reported to be > 60% in dialysis-dependent CKD patients compared to around 10% in general elderly population and is tightly associated with poor prognosis such as all-cause mortality and morbidities [14].

Thus, many elderly patients who initiated dialysis are frail. As mentioned above, one of the most plausible reasons why early mortality is high in Japanese elderly incident dialysis patients is functional impairment or frailty but why do we Japanese nephrologists initiate dialysis in these population with poor prognosis? One of the biggest reasons is that we tend to ascribe functional impairments to uremia. In fact, we elucidated that Japanese nephrologists consider functional status important in terms of indication to initiate dialysis [15], since we assume that uremia is reversible by dialysis and that is the case with uremic frailty. However, we now know that it is not the case especially in patients with baseline low functional status. Kurella Tamura et al. investigated the trajectory of functional status before and after initiation of dialysis among nursing home residents and found that immediately before initiation, functional status rapidly declined, which seems likely caused by uremia,

but the functional decline did not improve but even got worse after initiation and mortality increased [16], indicating that the frailty at initiation of dialysis is more dependent on non-uremic factors than uremia [17].

5.4 Physical Functional Decline in CKD and Incident Dialysis Patients

What are the non-uremic factors leading to sustained decline in functional status after dialysis initiation? One such factor is definitely sarcopenia [17]. We demonstrated that the prevalence of sarcopenia in the dialysis patients taken care of by our facilities (average age of 70.5) by European Working Group on Sarcopenia in Older People [18] was 42.4%, which is much higher than prevalence of 22% in Japanese general elderly population (age 65–89) [19]. Furthermore, the problem in physical functional decline in elderly dialysis patients is that in this population, effectiveness in exercise training is seen in younger population but is inconclusive in the elderly because of lack of trial in this specific population [20]. Regarding why there are few trials addressing this important issue, my impression with elderly dialysis patients is that they are too frail to do the exercise. In fact, our study demonstrated the prevalence of low muscle mass in dialysis patients was 75% [19]. Since physical functional impairment is a continuous process, we hypothesized that even in pre-dialysis, CKD patients have high prevalence of physical functional decline and demonstrated that all indices of physical function decreased according to the progression of CKD with each physical function index significantly lower in CKD stage 4 or 5 patients than CKD stage 2 or 3 patients, and that in multiple regression analysis, kidney function was estimated by glomerular filtration rate (eGFR) and urinary protein, as well as age, female sex, and body mass index were significantly correlated with indices of physical function [21] (Table 5.1). Thus, we must pay more attention to physical function in even early stages of CKD as well as end-stage kidney disease.

Table 5.1 Physical functional parameters by CKD stage. (PMID: 22911116)

Functional measures	CKD G stage				One-way ANOVA	
	2	3	4	5	*F*	*P*
Grip strength (kgf)	35.2 ± 8.7	30.8 ± 10.3	24.0 ± 9.5[a,b]	22.4 ± 7.9[a,b]	8.9	<0.01
Knee extensor strength (kgf/kg)	0.66 ± 0.11	0.60 ± 0.13	0.51 ± 0.15[a,b]	0.47 ± 0.16[a,b]	9.6	<0.01
Single-leg stance time (s)	58.2 ± 7.2	50.6 ± 16.7	31.9 ± 25.1[a,b]	32.2 ± 24.2[a,b]	10.9	<0.01
Maximum gait speed (m/s)	2.2 ± 0.2	2.1 ± 0.4	1.7 ± 0.5[a,b]	1.7 ± 0.4[a,b]	9.6	<0.01

[a]Significantly different compared with the stage 2 group
[b]Significantly different compared with the stage 3 group

5.5 Cognitive Functional Decline in CKD and Dialysis

More recently, CKD and dialysis have also been identified as risk factors for declining cognitive function and dementia, even at moderate stages of CKD [22–24]. Etgen et al. demonstrated in a 2-year follow-up cohort study that odds ratio of developing new cognitive impairment by 6-Item Cognitive Impairment Test was 2.14 in those with moderate-to-severe renal impairment (creatinine clearance <45 mL/min/1.73 m^2) [25]. Poor cognitive function has been linked to poor health literacy, poor medication adherence, worse physical and mental health, greater morbidity and mortality, and may affect healthcare decision-making [22–24]. Therefore, we believe this problem warrants significant attention.

Although moderate to severe, cognitive impairment to the extent with apparent decline in Mini Mental State Examination is often irreversible, but mild cognitive impairment (MCI) is potentially reversible [26], and MCI is also suggested to be prevalent in patients with early CKD [23]. We also demonstrated in elderly CKD patients in our CKD clinic that as much as 62.5% of the elderly (age 65 or older) with pre-dialysis CKD who walk in to our clinic by themselves had MCI and that only physical function (gait speed) was significantly associated with cognitive impairment by multivariate analysis [27]. We further demonstrated that in a 2-year follow-up of our CKD clinic cohort low physical function in addition to low eGFR was associated with lower cognitive function 2 years later (Table 5.2) [28]. These results indicated that cognitive functional decline is highly prevalent in CKD, is tightly associated with physical function, and possibly physical function is the upstream of later cognitive decline.

Table 5.2 Logistic regression models of the impact of the combination of kidney and physical function on cognitive decline over 2 years in older adults with pre-dialysis chronic kidney disease. (PMID 30734184)

			Crude			Adjusted		
	N	*N* with Cognitive decline (%)	OR	95% CI	*P* value	OR	95% CI	*P* value
Group 1	34	7 (20.6)	1	Ref		1	Ref	
Group 2	11	2 (18.2)	0.86	0.15–4.90	0.86	0.56	0.07–4.57	0.58
Group 3	24	7 (29.2)	1.59	0.47–5.33	0.45	1.85	0.49–8.54	0.43
Group 4	15	9 (60.0)	5.79	1.54–21.79	0.009	5.73	1.01–32.52	0.049

Adjusted model is adjusted for age, hemoglobin, proteinuria, and MoCA-J at baseline
Patients with cognitive decline during the 2-year follow-up were defined by %MoCA-J as being in the lowest quartile of all patients
Group 1 = mild-to-moderate impairment in kidney function and high physical function group
Group 2 = mild-to-moderate impairment in kidney function and low physical function group
Group 3 = severe impairment in kidney function and high physical function group
Group 4 = severe impairment in kidney function and low physical function group
OR odds ratio, *95% CI* 95% confidence interval

5.6 Effectiveness and Feasibility of Exercise Training in Elderly Patients with Pre-dialysis CKD

As mentioned earlier, although the effectiveness of exercise in elderly patients with dialysis patients has been inconclusive, since the physical functional impairment in pre-dialysis patients is significantly less prevalent and less in degree, it is possible that exercise training in this population may be effective. However, there are very few trials examining effectiveness of exercise in pre-dialysis CKD, and there are some problems associated with this kind of study. Most of the exercise interventions were conducted center-based, which are not feasible in terms of its cost, availability, broader applicability, and sustainability [29].

Thus, we conducted a randomized controlled pilot and feasibility trial to test the effectiveness of home-based exercise training in 28 patients with CKD stage G3–4 and with average age of 68.7 ± 6.8 years [30]. The exercise group performed home-based aerobic and resistance training exercises without supervision for a period of 1 year after they were instructed how to do it at first visit in the study period. We demonstrated that physical activity by daily steps measured by pedometer significantly increased, and muscle strength (both handgrip and knee extension) was significantly improved only in the intervention group (Table 5.3).

5.7 Does Guideline-Based "Usual Care" Help Elderly CKD Patients to Lead Successful Aging?

Both global and Japanese guidelines in the management of CKD recommend protein restriction and tight blood pressure (BP) control, especially with renin-angiotensin system inhibitors (RASi) in patients with CKD irrespective of age [31, 32]. However, there us few evidences if any to support these recommendations in frail elderly patients with CKD.

Table 5.3 Changes in eGFR, urinary protein, handgrip strength, knee extensor muscle strength after the 12-month period of intervention (vs. control). (PMID 28623895)

	Exercise		Control		
	Baseline	12-month	Baseline	12-month	*P* value
eGFR (mL/min/1.73 m^2)	37.0 ± 10.9	35.1 ± 11.4	41.1 ± 12.2	39.5 ± 12.9	0.93
Urinary protein (g/gCr)	0.9 ± 1.0	1.2 ± 1.7	0.9 ± 1.4	0.9 ± 1.1	0.52
Handgrip strength (kgf)	31.7 ± 7.4	36.4 ± 6.4	35.5 ± 8.8	36.5 ± 9.2	0.01
Change (%)		17.0 ± 16.1		3.4 ± 11.2	0.02
Knee extensor muscle strength (kgf/kg)	0.65 ± 0.17	0.70 ± 0.17	0.66 ± 0.15	0.62 ± 0.13	<0.01
Change (%)		8.2 ± 10.9		−6.0 ± 7.6	<0.01

Values are the mean ± SD unless otherwise noted

Protein restriction has been proved to be renoprotective by metaanalysis [33]. However, its size effect of renoprotection is very small. Moreover, in this meta-analysis, protein restriction was not significantly renoprotective in the elderly [33]. Moreover, is renoprotection the only goal for the very old patients with CKD? Protein restriction is also recognized "safe" as long as adequate calorie (and essential amino acid supplementation) is guaranteed [34]. However, in the real-world setting, many elderly patients with CKD as well as general elderly population living alone or with house-holdwife suffering from functional decline could not adhere to this because of cost and social problems. Their socioeconomic status is often low. In these patients, it is a luxury to prepare low protein diet but with adequate calorie because they cannot cook by themselves or buy the healthy ingredients separately. Actually, it has been shown that caloric intake in elderly patients with CKD was far less than recommended in those who undergo protein restriction (30–35 kcal/kg body weight/day) [35]. Thus, if we advise them to restrict protein in addition to salt intake, they tend to decrease whole amount of foods instead of maintaining calorie intake, leading to protein energy malnutrition with poor prognosis [34]. In addition, in patients with advanced CKD, we showed that muscle strength was positively correlated with protein intake (Fig. 5.3) [36]. Since this observation could not prove causative association, we conducted prospective observational study to elucidate the relation between baseline protein intake and future prognosis (risk of ESKD and mortality) [37]. Surprisingly, those who consume low protein diet, which is recommended in patients with CKD, had significantly worse mortality risk, especially when they are old (Fig. 5.4). Recently, Levine et al. reported in the journal *Cell*

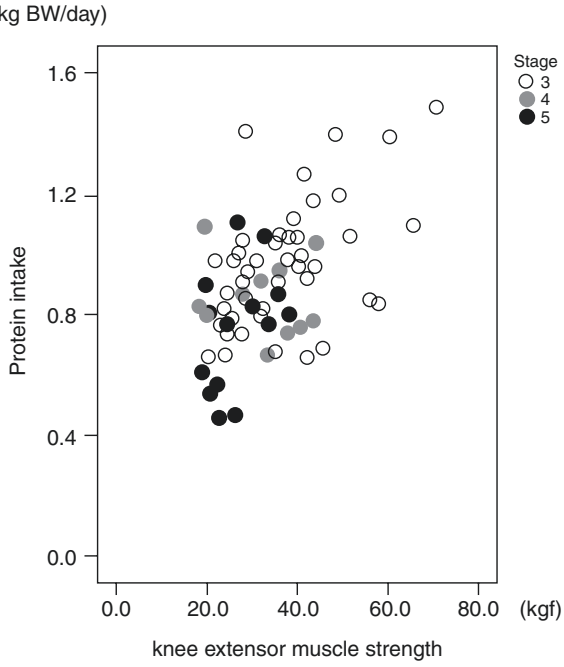

Fig. 5.3 Relation between protein intake and muscle strength in patients with CKD. (PMID: 28258495)

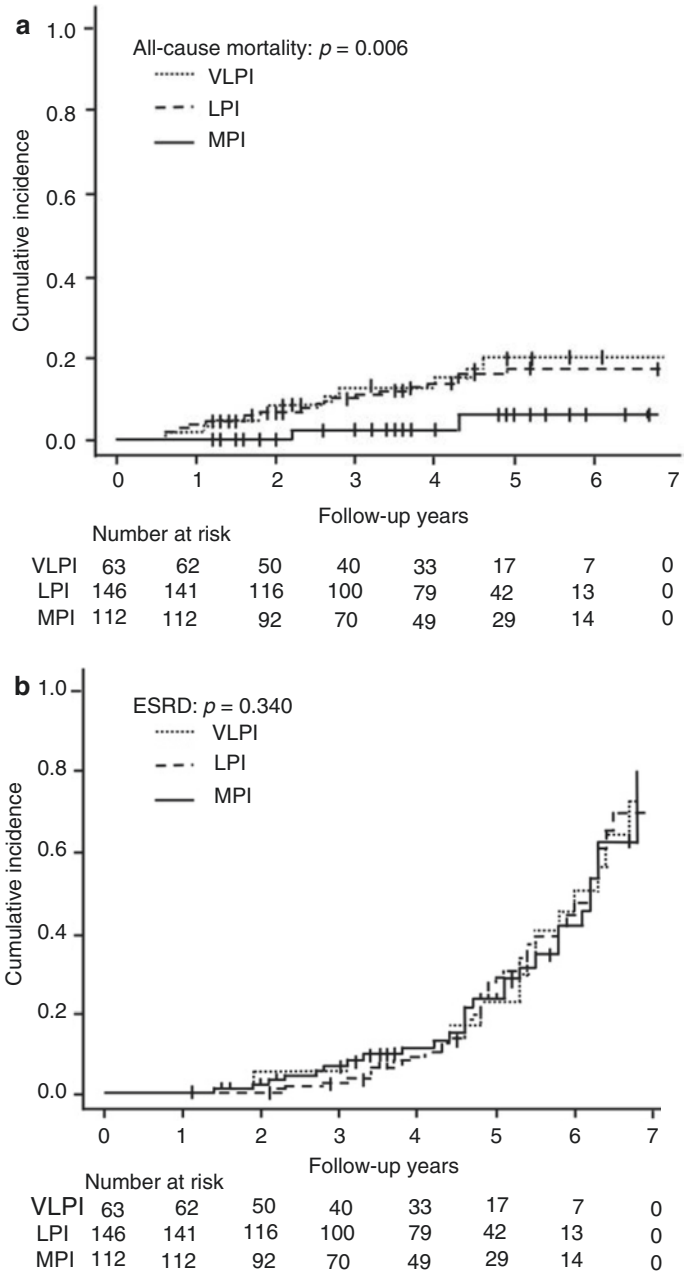

Fig. 5.4 Cumulative incidences (95% confidence interval) of (**a**) mortality and (**b**) end-stage renal disease (ESRD) in the very low protein intake (VLPI), low protein intake (LPI), and moderate protein intake (MPI) groups. (PMID: 30428524)

Metabolism that low protein intake is associated with higher mortality in older population [38]. They investigated the mechanism of this phenomena and speculated by mice experiment that older people cannot maintain anabolism with low protein due to inadequate growth hormone. We found in our patients with CKD that protein intake is significantly and positively associated with muscle strength [36]. Of course, this study is cross-sectional and does not prove the causal relationship between the two factors; however, since the study population is ambulating outpatients walking in to our CKD clinic, it is not plausible to assume they are too physically impaired to eat adequately. So, we assume that low protein intake will lead to lesser muscle strength.

How about strict BP control? Recently, The Systolic Blood Pressure Intervention Trial (SPRINT) reported reduced cardiovascular events by intensive BP control even in the elderly population [39]. However, our feeling of safety of strict BP control in the elderly population does not necessarily get along with the conclusion of SPRINT. In fact, Obi recently reported in a post hoc analysis of SPRINT [40] that intensive BP control did not reduce the cardiovascular outcome but even increased acute kidney injury events in subpopulation with low eGFR (<45 mL/min/1.73 m^2). Several other studies of patients with moderate-to-advanced CKD or coronary artery disease have reported J- or U-shaped relationship, in which low-to-normal BP is associated with higher mortality or morbidities [41–43]. This is especially relevant in elderly with frailty. Odden et al. demonstrated using data from the National Health and Nutrition Examination Survey that elevated but not reduced BP was strongly and independently associated with lower risk of death in patients with slower walking speed [44]. Sink et al. showed in a randomized controlled trial comparing target systolic BP <120 mmHg versus <140 mmHg that risk for syncope, hypotension, and falls are significantly higher in participants with CKD or frailty, especially in the elderly [45].

Interpretation of randomized clinical trials should be cautioned when we apply the results to real-world elderly patients with CKD. O'Hare et al. conducted a simulation study in a retrospective cohort of Veterans Affairs medical centers with more than 370,000 elderly patients aged 70 or older with CKD. She demonstrated that the number needed to treat (NNT) to prevent 1 case of end-stage renal disease (ESRD) ranged from 16 in patients with the highest baseline risk to 2500 for those with the lowest baseline risk and most patients belonged to groups with an NNT of more than 100, even when the exposure time was extended over 10 years and in all sensitivity analyses, indicating we need to use RASi with discretion in patients with short life expectancy considering the risks of RASi such as acute kidney injury and hyperkalemia requiring hospitalizations [46].

In the first place, guidelines may never perfectly address complex patients because this usually requires judgment along with extrapolation of evidence from less complex and often younger populations. Since frail elderly patients with CKD were among the most complex patients with multimorbidities and functional problems, it is hard to apply guidelines since most of them did not discuss the applicability of their recommendations for older patients with multiple comorbidities, nor commented on burden, short- and long-term goals, and

the quality of the underlying scientific evidence, nor gave guidance for incorporating patient preferences into treatment plans [47].

5.8 Toward Successful Aging of the Elderly Patients Transitioning to Dialysis

Now, we need to pause, look back, and rethink of what we usually do to our elderly patients with CKD. I understand that most of the conscientious physicians are trying their best to maintain health of their patients. According to the evidence-based guidelines, we often try to put them on food restrictions and lower the BP strictly, and of course with cautions. However, we often miss the fact that successful aging, especially in those with limited life expectancy as in elderly CKD, is not ever achievable without maintaining the rest of the constructs of successful aging, namely maintenance of physical and cognitive function, and keeping social engagement. Intensive treatment tends to interfere with these two important constructs of successful aging even if we are successful in achieving avoidance of progression of disease/disability status. We must not simply add years to life but add life to years.

The approach I have been exploring to achieve successful aging in my patients is to maintain their physical/cognitive function as much as possible to intervene by exercise training at the early stages of CKD. Since the intervention does not need expensive drugs or devices, it is ideal for the coming era of economic downturn in Japan. We also checked the quality of their muscle (physical function) as well as quantity (muscle mass) and if they are not physically fit, we avoid putting them on protein restriction and advise them to do home-based exercise training. I believe that if they improve their physical function, they will maintain cognition and can engage in productive social activities.

The challenge we have now is how we can involve patients with low adherence to these activities. We tend to ascribe their nonadherent behavior to their own characters, but I am sure it is not true. I think they do not have "hope."

Jerome Groopman once stated, hope, unlike optimism, is rooted in unalloyed reality and is the elevating feeling we experience when we see in the mind's eye a path to a better future, which needs to be kept alive in the face of illness [48]. Fukuhara, Kurita, Wakita, and I have been trying to develop the scale of hope in patients with chronic disease, and preliminary results showed that patients with dialysis with higher hope scale felt less burden with adherence to the treatment [49].

5.9 Conclusion

In this era of super-aging society full of frail elderly, we need to pause, look back, and reconsider the way we manage the elderly patients with CKD just by following the guidelines to protect their organs or prolong the life and try our best to achieve the successful aging and maintain their dignity and autonomy.

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Exercise Interventions in Dialysis Patients

6

Atsuhiko Matsunaga

Abstract

Approximately 70% of patients receiving dialysis in Japan at the end of 2016 were over 65 years of age. Based on the survey the author and colleagues conducted, approximately 70% of Japanese elderly hemodialysis patients were in a state of frailty or prefrailty, and physical functions (muscle strength, walking speed, standing balance and flexibility) of elderly patients attending the dialysis clinic for outpatient care decreased to approximately 60–70% of those of healthy persons, respectively, and physical activity level (steps) was under 50%. This subsequent follow-up study revealed that a clear decline in physical functions and physical activity level could be a significant and independent risk factor that worsens prognosis. The authors also developed the questionnaire on perceived mobility difficulty to accurately grasp limitations in activities of daily living (ADL) and revealed that the ADL difficulty evaluation is a simple alternative method to assess the functional status and to predict subsequent prognosis in elderly hemodialysis patients. Moreover, the author and colleagues have introduced a disease management system consisting of periodic assessment and exercise therapy in a period of roughly 10 years, and clarified that the high attendance group (attended >75% of all available sessions in the management program) had significantly better survival and lower incidence of cardiovascular disease than the low attendance group. These findings suggest that periodic physical function assessment and encouragement for participation in physical activity should be part of disease management for frail hemodialysis patients.

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Keywords

Frailty · Physical function · Physical activity · Activities of daily living · Disease management · Exercise therapy · Rehabilitation · Hemodialysis · Chronic kidney disease

6.1 Introduction

With increasing rates of population aging and lifestyle diseases, the rate of occurrence of chronic kidney disease (CKD) requiring renal replacement therapy is increasing worldwide [1]. According to a study conducted by the Japanese Society for Dialysis Therapy (JSDT), there were approximately 330,000 patients, with an average age of 67.9 years, receiving dialysis in Japan at the end of 2016, and 70% of these patients were over 65 years of age [2]. Japan's proportion of 65 years-and-over dialysis patients is nearly double that of the US and Europe, and it has been pointed out that the rate of annual increase of this segment of the population has also been extremely high over the past 20 years [3]. In this way, population aging is a striking feature in terms of the epidemiological background of Japan's hemodialysis patients, and along with aging, more patients are showing physical frailty.

Physical frailty is the state of heightened vulnerability to external stresses, due to the weakening of various physical residual functions caused by aging [4, 5]. Not only does it make the body unable to maintain physiological systems and life functions in the event of incidents like infections or short-term hospitalizations, but it is also known for causing vulnerability to adverse outcomes including mortality, institutionalization, and falls [6–8]. Many factors are related and unified into a cycle of frailty associated with declining energetics and reserve. There is a broad international consensus that markers of frailty include age-associated weight (lean body mass) loss; chronic undernutrition; loss of muscle mass (sarcopenia); and declines in endurance, walking ability (walking speed), and physical activity (Fig. 6.1) [5]. In brief, frailty is independent of the illness conditions and disabilities a patient may have and may determine medical treatment progress after the illness [9]. However, frailty is essentially a reversible condition and may be reversed toward normal by appropriate intervention [9, 10]. Therefore, the diagnosis of physical frailty is of major significance [10].

6.2 The Prevalence of Physical Frailty in Hemodialysis Patients

Based on the concept and evaluation standards of physical frailty defined by Fried et al. [5], the author and colleagues evaluated 252 hemodialysis patients (average age 67 years) capable of independent mobility who were visiting hospitals for outpatient care and found that 19.4% of men and 23.3% of women, or roughly one-fifth

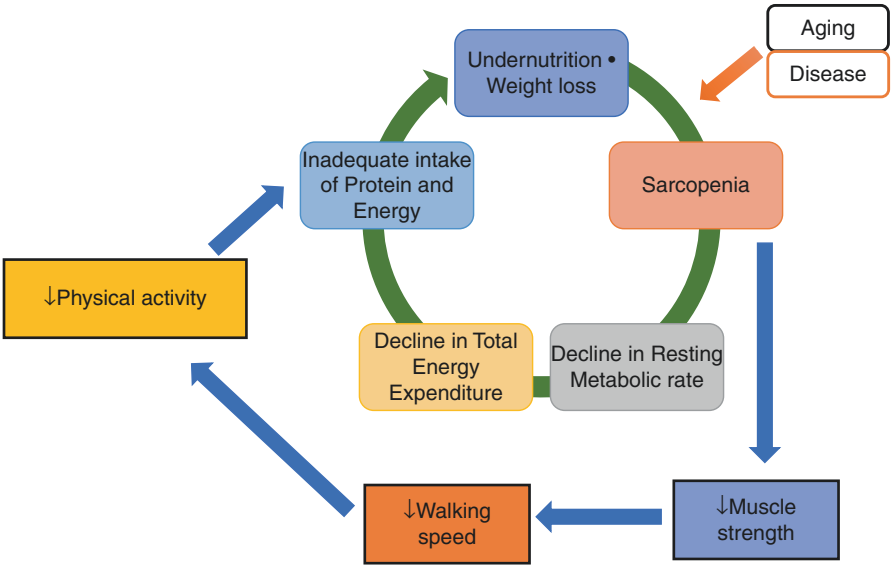


Fig. 6.1 Cycle of frailty

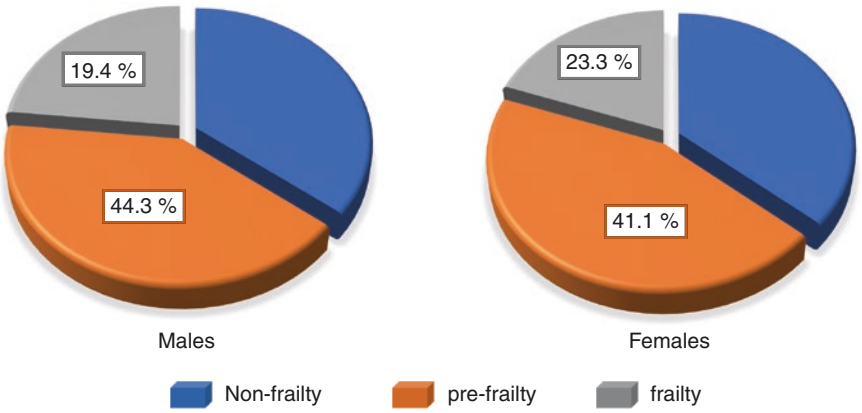


Fig. 6.2 Prevalence of frailty in ambulatory patients on hemodialysis. The mean age of patients enrolled in the study, who were able to ambulate without any assistance, was 67.4 years

of the patients, were in a state of frailty (Fig. 6.2). Considering that the frequency of frailty among the elderly aged 65–69 years without kidney disease living in the region is <1.9% [11], the prevalence of frailty among hemodialysis patients is approximately 10 times that among average seniors. Unfortunately, the rate of physical frailty is not the most important point. When McAdams-DeMarco et al. [12] studied the mortality rate of three groups of frail, intermediately frail, and non-frail

hemodialysis patients over a period of 3 years, they reported that, although there was a significantly higher rate of mortality among the frail and intermediately frail groups compared to that in the non-frail group, there was no difference in the mortality rates of the frail and intermediately frail groups. This showed that it is not only necessary to pay attention to frail patient groups but to also identify and develop appropriate exercise-based approaches for those in a pre-frail condition [13].

6.3 Positioning Exercise Therapy for Hemodialysis Patients: Exercise Therapy for Disease Management

There are still no guidelines that have earned an international (broad) consensus regarding exercise therapies and exercise instructions for CKD patients, but the Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines that were published in 2005 have become a foundation for exercise guidance carried out as a part of lifestyle guidance [14]. The K/DOQI first indicated diabetes, hypertension, and dyslipidemia as basic risk factors for cardiovascular disease, noted the importance of appropriately managing anemia and metabolic abnormalities as the characteristic risk factors of kidney failure, and provided information to rectify lifestyle-related risks such as smoking and physical inactivity. Additionally, while it lists guidelines for exercise instructions for dialysis patients and recommends physical activity, it also specifies the consideration of the effects of complications and implementation based on an evaluation of physical functions. With regard to these physical function evaluations in particular, it states that they should be regularly conducted every 6 months, and that they should not only merely assess the level of physical functions, but be implemented as a part of disease management. There were no major developments regarding exercise instruction guidelines in the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline published in 2012 [15], but the guidelines published in 2016 by the European Renal Association and European Dialysis and Transplant Association (ERA-EDTA) included considerations focused on patients aged 65 years and over with CKD severity at Stage 3b (estimated glomerular filtration rate < 45 mL/min/1.73 m^3) [16]. These guidelines contain many reviews about evaluation items for physical functions and exercise therapy effects and many points that should be referenced when implementing therapeutic exercise for Japanese dialysis patients, based on the fact that the average age of Japanese dialysis patients is over 65 years.

6.4 Physical Functions and Physical Activity Levels of Hemodialysis Patients

The abovementioned ERA-EDTA (2016) guidelines indicate that regular physical function evaluations should be carried out as a part of disease management [16]. For these evaluations, the guidelines recommend using simple evaluation indicators, that is, “field tests” that can be used in actual clinical settings, rather than test tools

that use expensive special equipment. They specifically list the sit-to-stand test as an indicator of leg muscle strength, walking speed, and 6-min walk test [17–23]. As will be mentioned later, walking speed is a strong indicator that predicts the deterioration of physical functions as well as prognoses.

6.4.1 Status of Physical Functions and Physical Activity Levels

The radar chart in Fig. 6.3 shows the relative values of leg muscle strength (knee extensor strength), walking speed, standing balance (one-leg standing time), flexibility (range of joint motion), and physical activity levels of hemodialysis patients attending the dialysis clinic for outpatient care to which the author and colleagues belong, with the value of 100 being the average value for age- and sex-matched healthy individuals. The average age of the 252 hemodialysis patients participating in this study was 67.2 years, with an average dialysis history of 9.7 years; as such, they are approximately in line with the 2016 study results shown by the JSDT [2]. Therefore, it is thought that these results showed the characteristics of the physical functions and physical activity levels of dialysis patients in Japan. Supposing that the difference was equivalent to the degree of decline when compared to healthy persons, leg muscle strength, walking speed, standing balance, and range of joint motion decreased to approximately 60–70% of those of healthy persons, respectively, and physical activity level was under 50%. Furthermore, physical functions and physical activity levels decreased with age, but longer periods (years) of hemodialysis contributed greatly to the degree of decline in both functions and levels

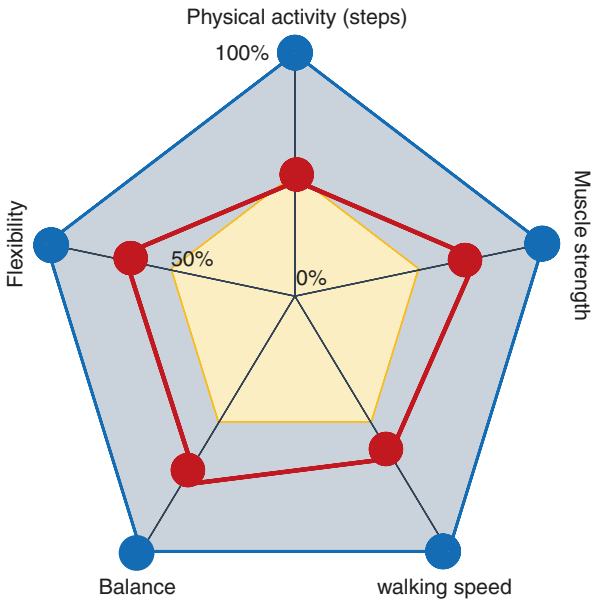


Fig. 6.3 Physical functions and physical activity levels in ambulatory patients on hemodialysis. Physical function (muscle strength, walking speed, balance, flexibility) and physical activity level (steps) for ambulatory hemodialysis patients are expressed as a percentage of the mean value for the normal subjects matched by age and sex. The mean age of hemodialysis patients enrolled in the study, who were able to ambulate without any assistance, was 67.2 years

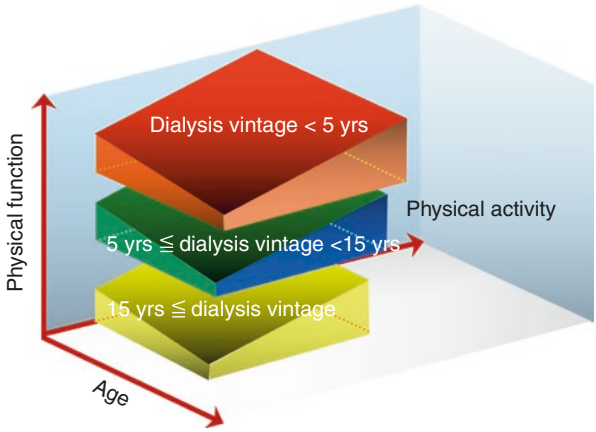


Fig. 6.4 Relationship between age, physical function, and physical activity by dialysis vintage. Dialysis vintage, time (years) on hemodialysis; *yrs* years

(Fig. 6.4) [24]. The results showed that when the period of dialysis was >15 years, there was a striking negative effect on these indicators.

6.4.2 Prognoses with Relation to Physical Functions and Physical Activity Levels

Figures 6.5, 6.6, 6.7, 6.8, 6.9, and 6.10 show the relationship between leg muscle strength, walking speed, and physical activity levels (the number of steps) of hemodialysis patients attending the dialysis clinic for outpatient care to which the author and colleagues belong and their prognoses (mortality rate and cardiovascular events). The average age for each was approximately 67 years; data that reflects the current aging of hemodialysis patients in Japan.

The frequency distribution in Fig. 6.5 shows the results of muscle strength values taken when patients extended their leg at maximum strength in the extension direction from a 90-degree stance in a seated position, measured with a handheld dynamometer. The measurement unit is body weight ratio (%), to adjust the difference in physical constitution among patients [25, 26]. It has been shown in previous reports that a body weight ratio under 40% would not satisfy the muscle strength level necessary to walk without difficulty [27]. The results showed that when comparing dialysis patients with leg strength under this body weight ratio of 40% with others (those with a leg strength body weight ratio of 40% and over), there was a distinctly higher ensuing mortality rate for the former group [28] (Fig. 6.6). Further analysis using a Cox proportional hazards regression model clarified that patients with severely decreased leg strength (<40%) had a 2.7-fold higher risk of death than those with high leg muscle strength [28]. That is, a clear decline in leg muscle strength not only interferes with the activities of daily living (ADL), but it is also an independent risk factor that worsens prognoses.

The distribution in Fig. 6.7 shows the results of measuring the walking speed (maximum walking speed) when patients were asked to walk as quickly as possible,

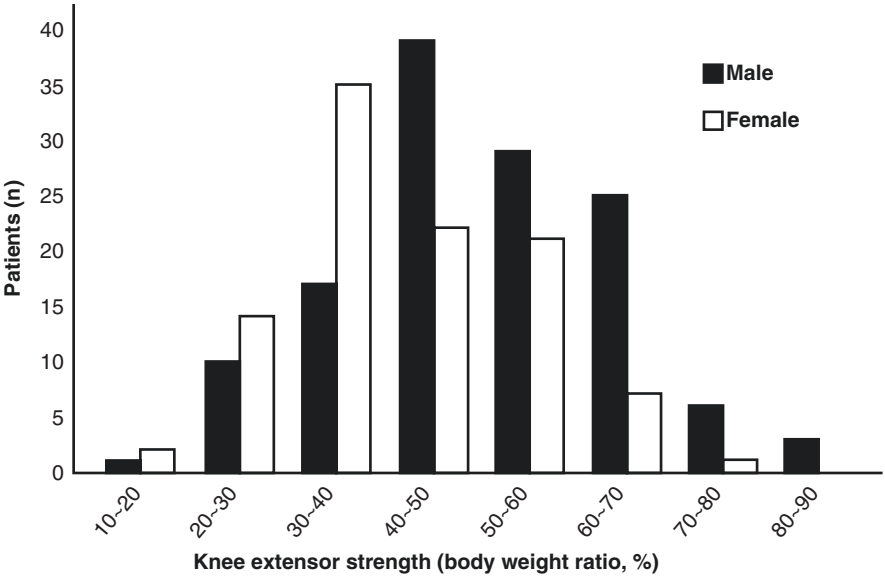
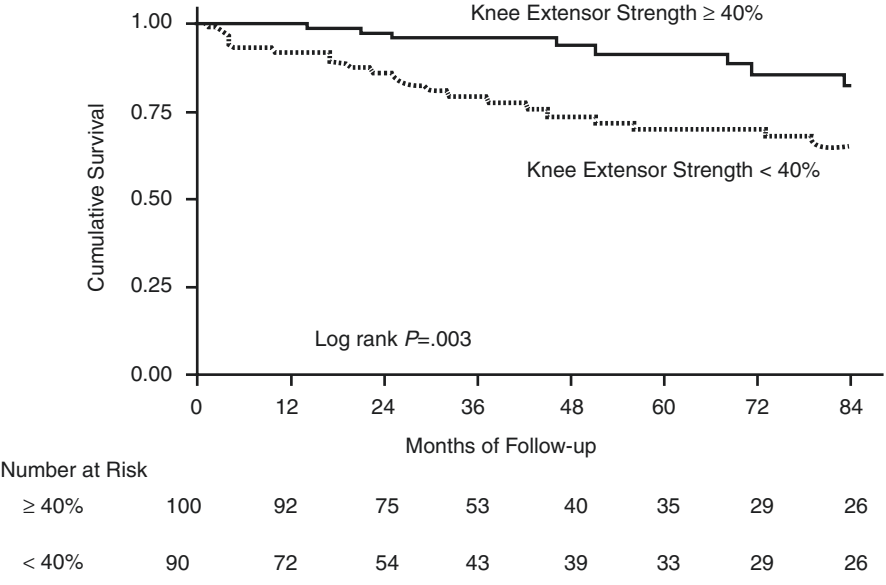


Fig. 6.5 Histogram of lower extremity muscle strength in male and female hemodialysis patients



Number at Risk

≥ 40%	100	92	75	53	40	35	29	26
< 40%	90	72	54	43	39	33	29	26

Fig. 6.6 Lower extremity muscle strength and subsequent mortality in hemodialysis patients. Kaplan–Meier analysis of survival for 202 hemodialysis patients. Participants with knee extensor strength above the median value of 40% at baseline had significantly better survival than those with a lower value ($P < 0.003$ by log-rank test)

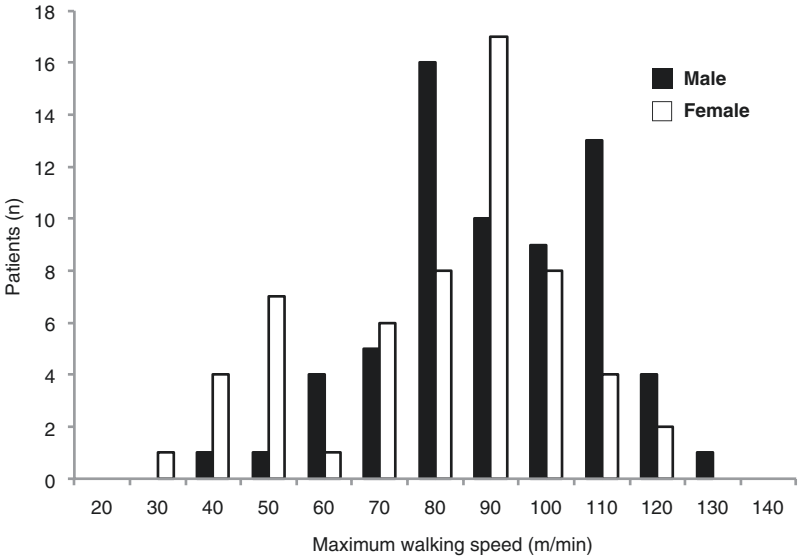


Fig. 6.7 Histogram of maximum walking speed in male and female hemodialysis patients

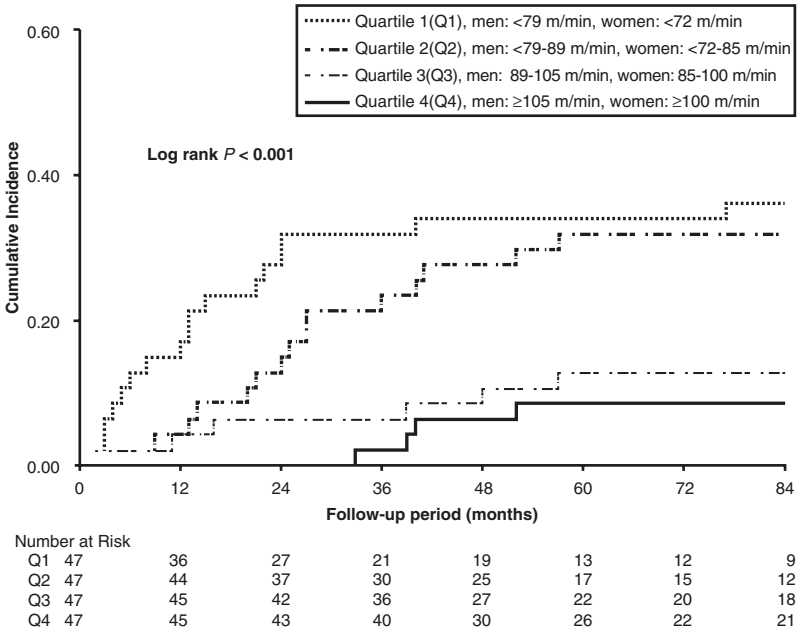


Fig. 6.8 Maximum walking speed and subsequent cardio-cerebrovascular events in hemodialysis patients. Kaplan–Meier analysis of incidence rates of cardio-cerebrovascular events according to maximum waking speed quartiles for 188 hemodialysis patients. Participants with maximum walking speed above the value of 89 m/min for men, 85 m/min for women at baseline had a significantly lower cumulative incidence of cardio-cerebrovascular events compared to other patients during the follow-up period (P <0.001 by Log-rank test)

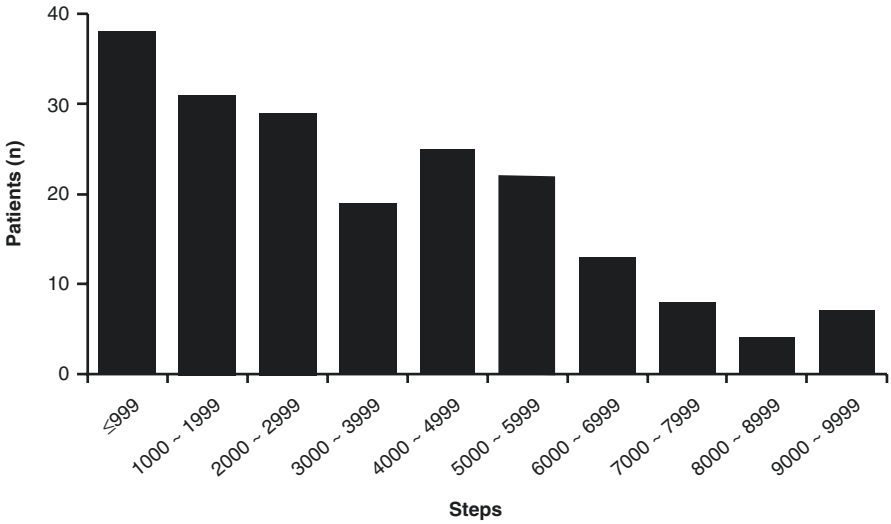
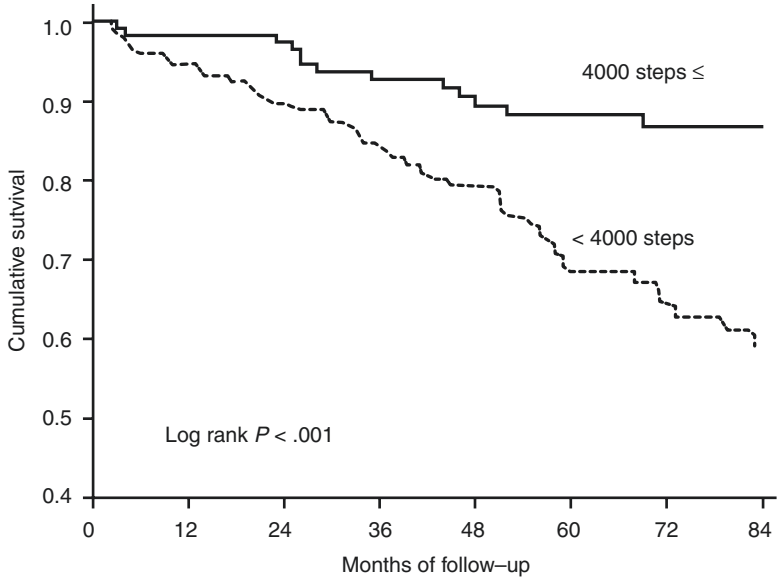


Fig. 6.9 Histogram of physical activity (steps) in hemodialysis patients



4000 steps ≤	129	112	105	93	80	73	58	49
< 4000 steps	153	136	124	94	79	59	45	30

Fig. 6.10 Physical activity (steps) and subsequent mortality in hemodialysis patients. Kaplan–Meier analysis of survival for 282 hemodialysis patients. Patients with physical activity above the 4000 steps per a non-dialysis day at baseline had significantly better survival than those with lower values ($P < 0.001$ by log-rank test)

without running, along a 10-m corridor [29]. When reviewing later cardiovascular events by the four quartiles of those walking speed results (Q1–Q4), as shown in Fig. 6.8, it was observed that the group of patients with the slower walking speeds (Q1 and Q2) had distinctly higher rates of cardiovascular events than the other patient groups (Q3 and Q4). That is, patients who had a maximum walking speed above the value of 89 m/min for men and 85 m/min for women at baseline had a significantly lower cumulative incidence of cardio-cerebrovascular events compared to other patients during the follow-up period. Further analysis using a Cox proportional hazards regression model showed that the hazard ratio for clinical events per 10 m/min increase in maximum walking speed was 0.77 [29]. Based on our subsequent analysis, if the lowest values for Q3 walking speed (men: 89 m/min, women: 85 m/min) are exchanged for a comfortable walking speed, they align with those used for diagnostic criteria for frailty (1.0 m/s) or sarcopenia (0.8 m/s) [19, 30–32], which shows that walking speed can be an important marker predicting frailty diagnoses and prognoses of hemodialysis patients.

The distribution in Fig. 6.9 shows the results of patients walking steps measured on the 4 days that patients were not receiving dialysis. Surprisingly, the greatest number of patients (mode) were in the group that walked an average of under 1000 steps per day, despite these being non-dialysis days that were not limited by the time constraints of dialysis treatment. Furthermore, when reviewing the relationship between this physical activity level (number of steps) and prognoses, there was a clear and significantly greater ensuing mortality rate for patients with an average of <4000 steps per day on non-dialysis days than those who had a greater average number of steps (Fig. 6.10) [33]. Viewing the relationship between prognoses and changes in physical activity levels over time, it was clear that there was a major difference in ensuing mortality rates when comparing those whose activity levels decreased by 30% and those whose activity levels increased by 30%, relative to each patient's activity level (number of steps) from 1 year prior [34]. Furthermore, when reviewing the relationship between the increase or decrease in physical activity levels (number of steps) (positive or negative, with the boundary of 0) and mortality risk (hazard ratio), it was shown that mortality risks increased sharply when the number of steps declined (Fig. 6.11) [34]. In this way, because physical activity levels are strongly influenced by physical functions such as leg muscle strength and walking speed, these could be useful disease management indicators that keenly reflect physical conditions and subsequent outcomes [35, 36].

6.5 Activities of Daily Living of Hemodialysis Patients

As with the aforementioned physical activity levels, an accurate grasp of the ADL is important for surmising a target person's condition, as well as their physical and even mental aspects [19, 20, 37]. If a physical function impairment should occur, such as a bone fracture due to a fall, or a cerebral stroke, a person can quickly change from being independent in their ADL to being dependent in their ADL (Fig. 6.12) Thus, it is easy to grasp the reasons or causal relationships for a decline

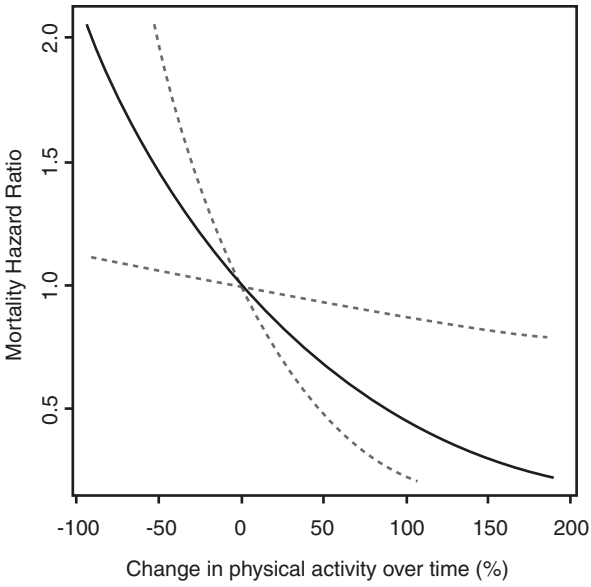


Fig. 6.11 Change in physical activity (steps) and mortality hazard ratio in hemodialysis patients. The cubic spline survival analyses exhibit the association between change in physical activity and mortality, after adjusted by age, sex, time on hemodialysis, body mass index, primary kidney disease, comorbidity index, serum albumin, and baseline physical activity

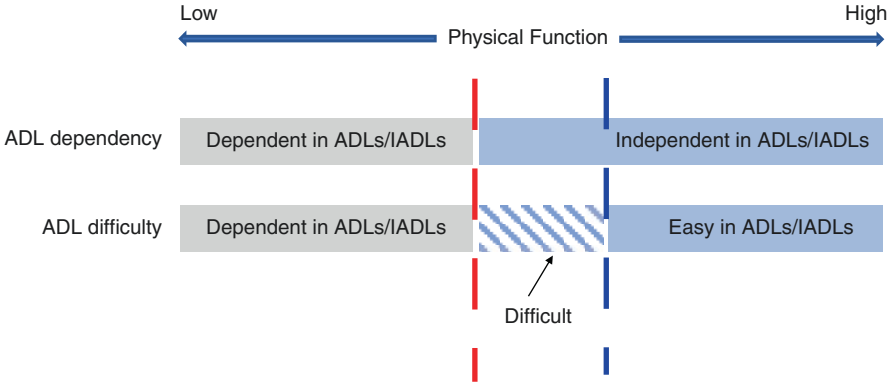


Fig. 6.12 ADL dependency and difficulty evaluations. *ADL* activities of daily living, *IADL* instrumental ADL

in ADL [38, 39]. However, for patients with CKD requiring dialysis treatment, it is often difficult to grasp the causal relationship merely based on their having a chronic illness. In particular, ADL limitations have already begun to occur before the initiation of dialysis in CKD patients [40]. For the above acute diseases, the decline in physical activity level or ADL is the result of the occurrence of a physical dysfunction, but for chronic illnesses, it is sometimes the case that a decline in physical activity level or ADL leads to further decline in physical functions. That is, for hemodialysis patients, the decline of physical functions, physical activity level, and ADL may all influence one another and create a vicious cycle that has adverse effects on quality of life (QOL) and prognoses (Fig. 6.13) [26, 41]. Therefore, it is

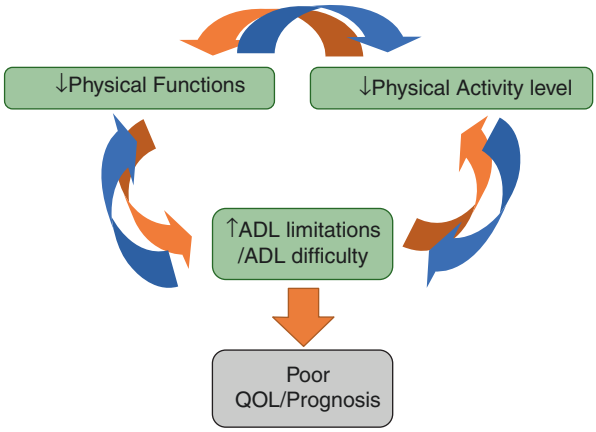


Fig. 6.13 A cycle of decline in physical functions, physical activity level, and ADL. *ADL* activities of daily living

necessary to regularly conduct ADL evaluations in addition to physical functions and physical activity levels previously mentioned in Sect. 6.4 [42].

6.5.1 ADL Dependency Evaluations

Figure 6.14 shows the relationship between mortality risk and ADL dependency scores using 5 basic ADLs and 8 instrumental ADLs, for a total of 13 ADLs (functional status score), with a study target of 7000 dialysis patients from Japan (n = 1700) and overseas [43]. In this large-scale study, scores were determined by assigning 1 point for every ADL that a patient can conduct independently (dependent score: 0), with scores of <8 out of 13 determined to be indicators of a severe level of ADL decline. As shown in Fig. 6.14, patients with a score of <8 have a higher mortality risk than those with higher scores, and this effect increases with age: for patients over 65 years of age, those with scores <8 have nearly three times the mortality risk of those with a perfect score of 13. Therefore, maintaining ADL independence for senior dialysis patients is an extremely important therapeutic strategy for keeping their prognoses from worsening [20].

6.5.2 ADL Difficulty Evaluations

Generally, when evaluating ADLs in clinical setting, each assessment is rated on a two-point scale (independent and dependent) (Fig. 6.12). In the previous section (see Sect. 6.4.1), hemodialysis patients were evaluated in two groups, independent and dependent. However, most of clinically stable patients who receive outpatient dialysis services can perform basic ADL and instrument ADL tasks without assistance [44, 45]. On the other hand, even though these outpatient patients are able to travel and move independently, few are actually able to accomplish these tasks “comfortably” and many have a sense of hardship.

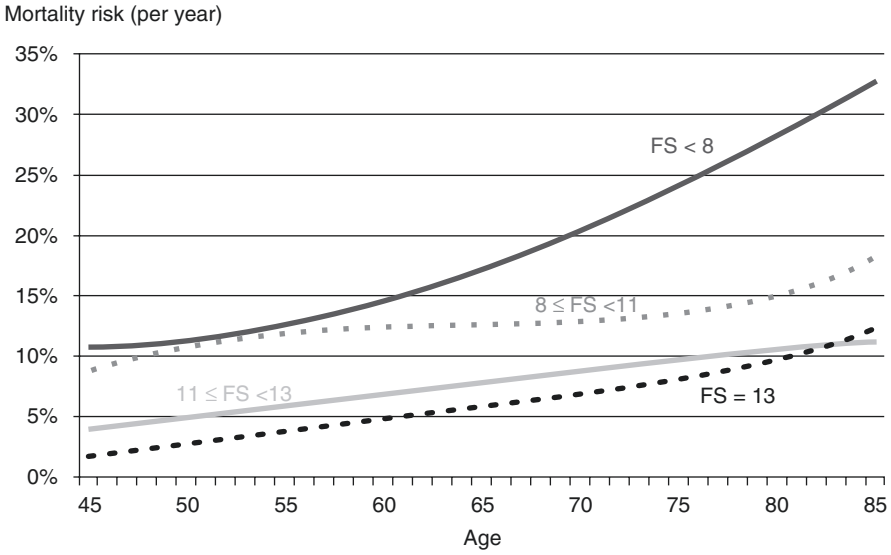


Fig. 6.14 Mortality risk (per year) by age and ADL (functional status score). The functional status (FS) score has a total of 13 ADL items consisting of 5 basic ADLs (eating, getting dressed, bathing, using the toilet, transferring from bed to chair) and 8 instrumental ADLs (using the telephone, getting places beyond walking distance, grocery shopping, preparing meals, doing housework or handyman work, doing laundry, taking medications, managing money)

Thus, it is often impossible to grasp ADL issues using the above-mentioned two-valued standard (Fig. 6.12). We developed the questionnaire on perceived mobility difficulty using a 5-point scale based on difficulty (1, not possible; 2, severe difficulty; 3, moderate difficulty; 4, mild difficulty; and 5, ease) for hemodialysis patients [45] (Fig. 6.15). This questionnaire comprises 12 items divided into the following three categories, which were obtained by a factor analysis: "basic ADL," "ambulation," and "walking up or down stairs. With a target group of 216 hemodialysis patients (average age of 67 years), Fig. 6.16a shows the frequency distribution results on the scale of dependency using the Functional Independence Measure, and Fig. 6.16b shows the result distribution using the difficulty scale we developed, for the same group of patients. As these results show, the results of the dependency evaluation indicated that nearly all subjects had independent mobility, and thus there was a concentration of perfect scores. Meanwhile, when the evaluation scale is based on difficulty, there was a wide variety of scores. Furthermore, Fig. 6.17 shows the distribution (percentage) of scores 1–5 for each of the 12 items [45]. Since the study subjects were patients capable of visiting the clinic, roughly <10% were a score of impossible (dependent). On the other hand, if we consider those who had difficulty (3 or below) even while being capable (independent) as having limited ADL, nearly 50% of patients were ADL-limited with regard to "walking 600 m," which would influence their activities in the periphery of their home, such as shopping. When

Category and item			Not possible	Severe difficulty	Moderate difficulty	Mild difficulty	Ease
	Basic ADL	Rising from a chair	1	2	3	4	5
		Rising from the floor	1	2	3	4	5
		Sitting down on the floor	1	2	3	4	5
	Ambulation	Walking 100 m	1	2	3	4	5
		Walking 300 m	1	2	3	4	5
		Walking 600 m	1	2	3	4	5
		Walking 1 km	1	2	3	4	5
		Walking 20 m quickly	1	2	3	4	5
	Walking up or down	Walking up one flight of stairs	1	2	3	4	5
		Walking up two flights of stairs	1	2	3	4	5
		Walking down one flight of stairs	1	2	3	4	5
		Walking down two flights of stairs	1	2	3	4	5

Fig. 6.15 The questionnaire on perceived mobility difficulty. This questionnaire on perceived mobility difficulty for hemodialysis patients comprises 12 items divided into the following three categories, which were obtained by a factor analysis: "basic ADL," "ambulation," and "walking up or down stairs." *ADL* activities of daily living

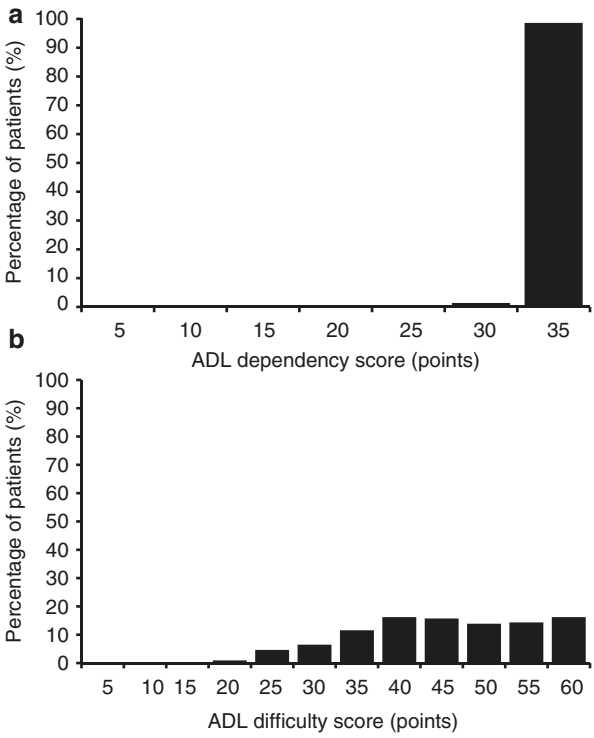


Fig. 6.16 Histogram of ADL dependency and ADL difficulty scores in hemodialysis patients. (**a**) ADL dependency was assessed by the Functional Independence Measure. (**b**) ADL difficulty was assessed by the questionnaire on perceived mobility difficulty. *ADL* activities of daily living

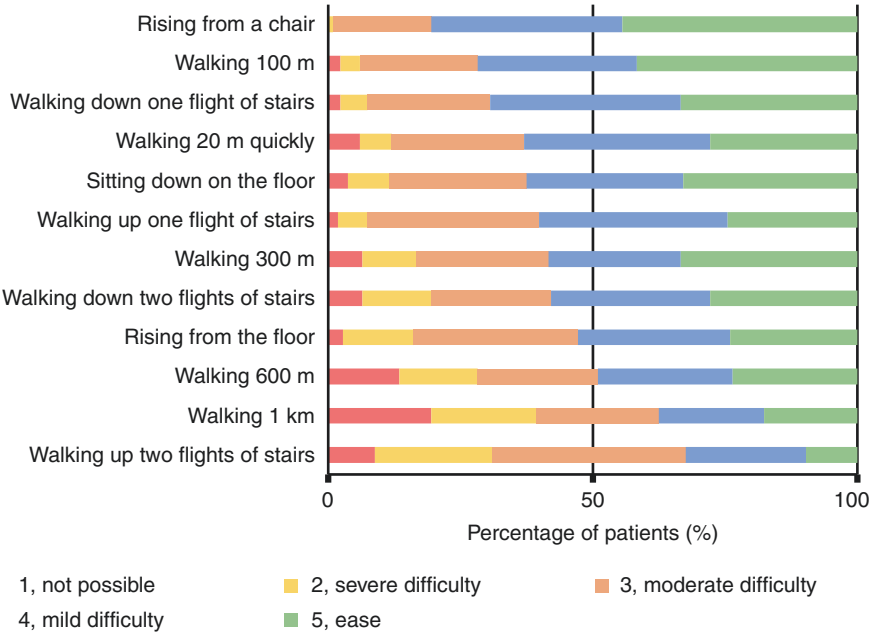


Fig. 6.17 Distribution of 12 items of the questionnaire on perceived mobility difficulty in hemodialysis patients. The distribution indicates the ADL difficulty levels when sorted by level of difficulty based on the percentage of the ADL limitation (3 or under) for 216 hemodialysis patients

sorted by level of difficulty based on the percentage of the ADL limitation, the highest item was "climbing stairs (to the third floor)" at 70%, followed by "walking one kilometer" at 60% [45].

Additionally, as a follow-up survey, we reviewed the prognoses according to the tertiles of the ADL difficulty scores that we had developed above and found that the group with the greatest level of difficulty had a mortality risk nearly four times that of the group with the least difficulty. In this way, ADL difficulty evaluation is a simple alternative method to assess the functional status and to predict subsequent prognoses in hemodialysis patients [19].

6.6 The Practice of Exercise Therapy as Disease Management

6.6.1 Protocol of Exercise Therapy (Flow Chart)

Figure 6.18 shows a therapeutic exercise flowchart developed by the authors and colleagues. The criteria (patient conditions) for implementation of this protocol include: those who have not been hospitalized in the past 3 months, those who are undergoing stable dialysis treatment, and those recognized as clinically stable by their attending physician. In practice, this exercise flowchart begins with classifying

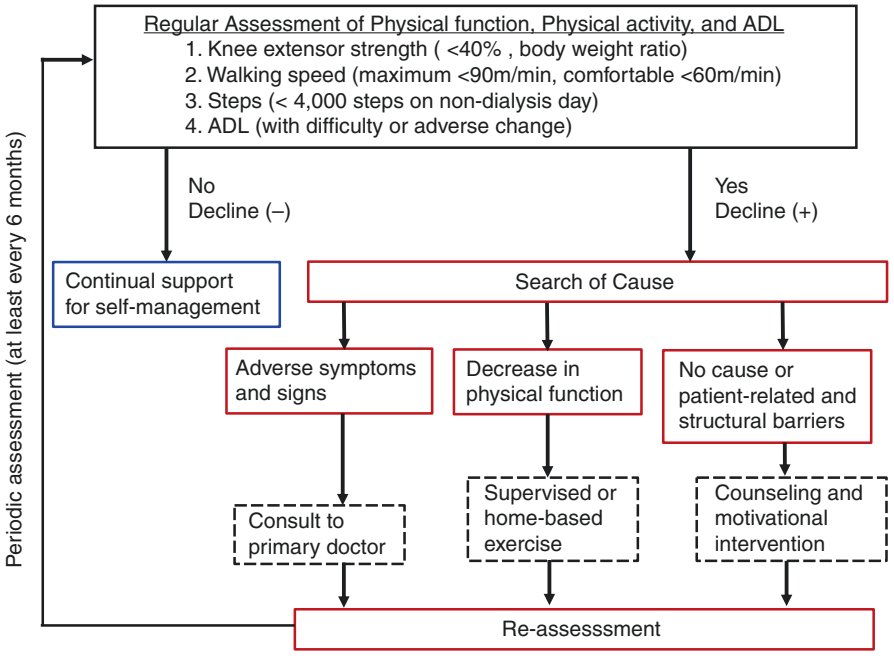


Fig. 6.18 Therapeutic exercise flowchart for hemodialysis patients. *ADL* activities of daily living

Table. 6.1 Physical performance tests and cutoff points for discriminating poor performance in patients with chronic kidney disease

Tests	Cutoffs
Comfortable walking speed	<48 m/min (0.8 m/s), <60 m/min (1.0 m/s)
Maximum walking speed	Male: <89 m/min (1.48 m/s) Female: <85 m/min (1.42 m/s)
Short physical performance battery	<10 points, <12 points
Timed up and go test	≥12 s
Knee extensor muscle strength	<40% body (dry) weight
Five sit to stand test	>14.5 s
Handgrip strength	Male: <26 kg Female: <18 kg
One leg standing time	<5 s
6-min walk distance	<300 m

patients who should do exercise therapy based on periodic assessment data for their physical functions, physical activity levels, and ADLs. In this first classification (as discussed in Sects. 6.4 and 6.5), patients are sorted by those whose indicators are not declining: leg muscle (knee extensor) strength and walking speed for physical function, number of steps for physical activity level, and difficulty in ADLs. The cutoff points for this categorization are as follows: 40% of body weight for leg strength [28]; maximum walking speeds of 90 m/min (1.5 m/s) [29] or comfortable walking speeds of 60 m/min (1.0 m/s) [32], or 48 m/min [31] for walking speeds; 4000 steps on non-dialysis day [33]; and no increase (no adverse change) in the ADL difficulty level. Other physical performance tests and cutoff points are listed in Table 6.1 [30, 36, 46–49].

As a result of the above categorization, those not determined to have a decline in any of the above items (indicators) are instructed to continue their current self-management without adding any specific exercise therapy. However, those who have a decline in any of the items are asked to undergo an exploration of the causes after a detailed examination of the changes in their symptoms, complications, and treatment content, in addition to periodic diagnostic assessments by their doctor. When causes are determined, medical treatment is justifiably given priority, but in many other cases, there are no clear reasons, with many seeing a gradual decline after a short-term hospitalization (up to 1 week) or activity limitations due to shunt issues or infections. In these cases, patients are asked to gradually progress in exercise therapies while monitoring in detail any changes in symptoms.

The most important points, as mentioned in a statement in the K/DOQI Clinical Practice Guidelines (2005) [14], are to periodically conduct physical function, activity level, and ADL assessments every 6 months, as well as showing the results of these periodic assessments to each patient individually, having the patient understand their own situation, and allowing patients to manage their own progression [50]. This process then leads to improved adherence to the exercise therapy program.

6.6.2 The Therapeutic Exercise Program in Practice

As shown in the therapeutic exercise flowchart of Fig. 6.18, exercise training program is prescribed for those patients who are determined as having a functional decline if it is necessary and safe for them to engage in exercises. Moreover, exercise training prescriptions should be individualized to the patient's physical function with an emphasis placed on regular engagement and evaluation of progress. There are primarily two options: unsupervised exercise (instructing the patient to do the exercises at home on non-dialysis days) or supervised exercise (conducting the exercises under the supervision of medical staff such as a physical therapist). The authors take full advantage of the physical conditions of having patients come for hemodialysis outpatient treatment three times per week for implementation of therapeutic exercise. In principle, individual therapeutic exercise sessions are performed under the supervision of a physical therapist by using short periods of 10 or 15 min before the start of the patients' hemodialysis treatments at dialysis day. Earlier, many studies reported that the adherence to exercise, that is, the rate of continuation of exercise implementation, is poor under unsupervised condition than under supervision [51, 52]. It has been also suggested that the amount of exercise plays a significant role in attaining health-related benefits, namely, using the time before treatment on dialysis day means that they would have a minimum frequency of three times per week for conducting therapeutic exercises. This makes it possible to attain the target level of physical function relatively early, as well as the levels of everyday physical activity and ADLs. Figure 6.19 shows a scene in which an outpatient is performing individualized exercise programs before the start of hemodialysis treatment on a dialysis day.

Exercise recommendations for patients with end-stage renal disease are suggested based on the FITT principle: frequency, intensity, time, and type [50, 53, 54]. To summarize, patients should exercise 2–3 times per week at the beginning of the training; the frequency can then be increased to 3–5 times per week. Intensity should be tailored according to patient tolerance to exercise and should be gradually increased. The duration of exercise should be progressively increased depending on the physiological and physical condition. The types of exercises should include aerobic, resistance, flexibility, and balance exercises.

However, frail elderly hemodialysis patients encounter patient-related and structural barriers in exercising, including time restriction associated with continuous dialysis treatment, limited physical capacity, low adherence to conventional exercise programs, and lack of social interaction and support, and challenges in the physical environment [50, 55, 56]. In recent years, therapeutic exercise has been developed within hemodialysis treatment times (after treatment begins), and its safety and results have been verified [51, 57]. This can be a useful option for patients who do not have time before the start of hemodialysis treatment, or in cases where vital signs such as blood pressure are not stable (Fig. 6.20). Moreover, recent studies

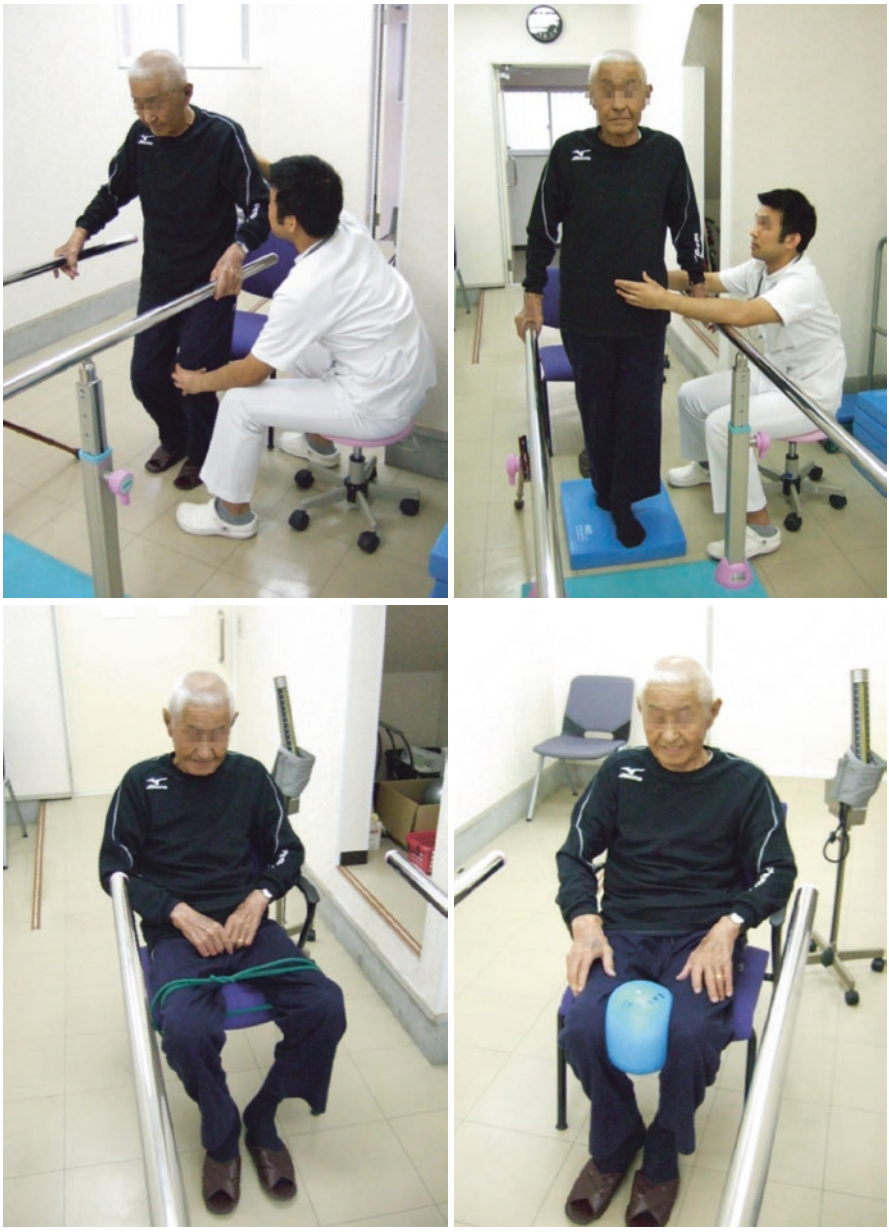


Fig. 6.19 Supervised exercise programs aimed at improving leg muscle strength and balance. This patient performs individualized exercise programs before the start of hemodialysis treatment on a dialysis day

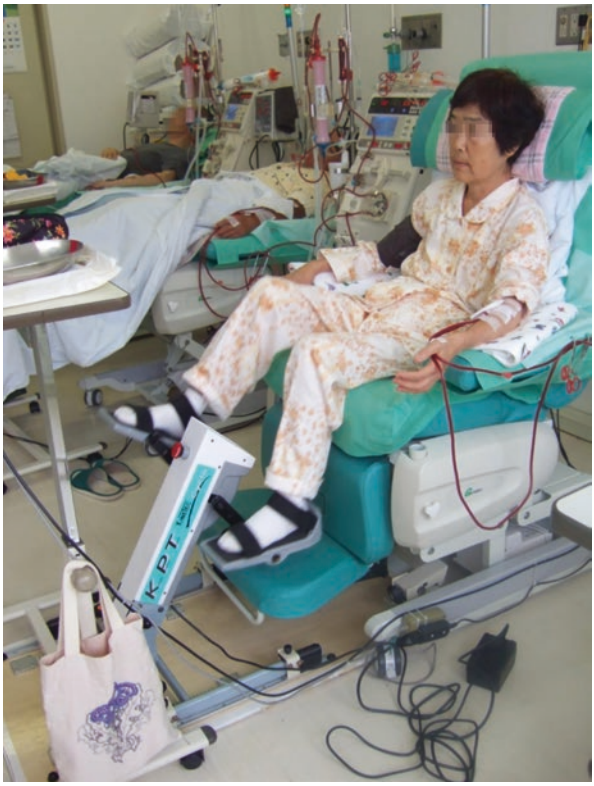


Fig. 6.20 Intradialytic exercise. This patient performs aerobic training using a cycle ergometer during her hemodialysis treatment

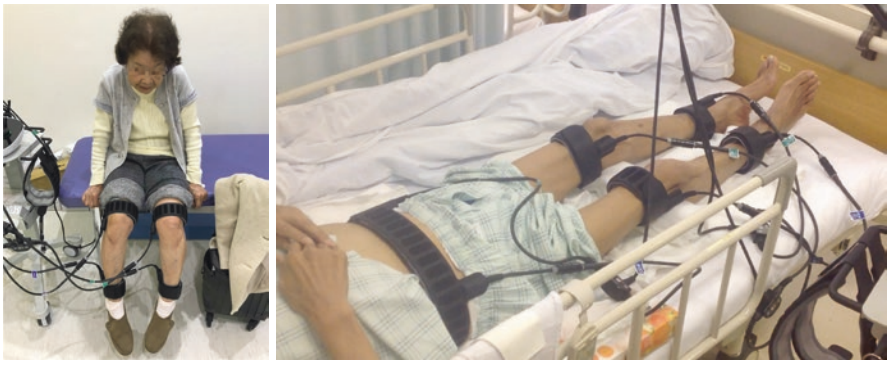


Fig. 6.21 Muscle strengthening exercise using electrical muscle stimulation. The right photograph shows a scene performing an intradialytic exercise using electrical muscle stimulation

reported that intradialytic electrical muscle stimulation can improve muscle strength, exercise capacity, and quality of life (QOL) in hemodialysis patients [58–60]. Electrical muscle stimulation is a new method for exercise therapy that can be used by patients while lying down; this method has no time restriction, requires no volitional effort, and places no hemodynamic stress on the patient (Fig. 6.21).

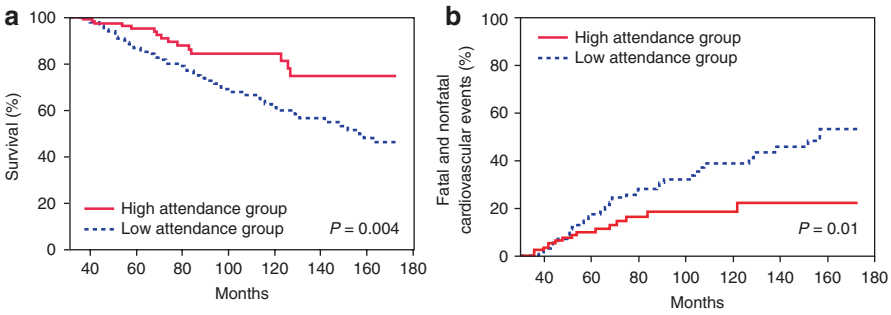


Fig. 6.22 The prognoses after introducing a disease management system (see Fig. 6.19) for hemodialysis patients. Kaplan–Meier analysis of survival (**a**) and cardiovascular events (**b**) in 266 patients undergoing hemodialysis. The high attendance group (attended >75% of all available sessions in the management program) had significantly better survival and lower incidence of cardiovascular disease than the low attendance group (≤75% attendance)

6.6.3 Long-Term Effect of Introducing a Disease Management System

The K/DOQI Clinical Practice Guidelines (2005) [14] include a statement that periodic physical function assessment and encouragement for participation in physical activity should be part of disease management for dialysis patients, but there have been very few reports verifying the outcomes of introducing these systems in practice. The author and colleagues introduced the flowchart shown in Fig. 6.18 over a period of roughly 10 years and verified the prognoses in hemodialysis patients who have been in this system for 3 years retrospectively [61]. Those results showed that high attendance (>75% attended) group had significantly lower mortality rates and rates of cardiovascular events compared to low attendance (≤75% attended) group (Fig. 6.22). In this way, it was shown that a system of periodically conducting physical function evaluations as a part of disease management protocols and intervening individually based on that data brings about effective outcomes in terms of long-term prognoses.

6.7 Future Topics

Over the course of the past 10 years, many systematic reviews have been published that focus on CKD patients who have started dialysis treatment [57, 62–65]. However, they all have a relatively young average age of <60 years, and in which there have been very few trials actually evaluating the impact of exercise on frailty regarding elder frail patients with end-stage renal disease treated with hemodialysis [66, 67]. Furthermore, there have been few reports using prospective, randomized, and controlled trials or exercise therapy. The EXerCise Introduction to Enhance performance in dialysis patient trial (EXCITE) demonstrated the effectiveness of a 6-month personalized, home-based walking exercise program to improve walking

capacity and muscle strength compared to "usual care" [64, 68]. However, this multicenter randomized, controlled trial in the dialysis population revealed that during the 6 months of training, 31% of participants withdrew from the exercise group compared with 15% from the placebo, and 47% of those who completed the study were designated as having low adherence to the protocol (<60% of sessions). Therefore, further study is needed to develop an effective strategy for promoting adherence rates to exercise therapy in frail elderly hemodialysis population, namely, there are many issues that remain unclear for senior dialysis patients.

In recent years, the age of patients starting hemodialysis treatment is gradually increasing. The content of this chapter (exercise therapy as disease management) can be summarized as frailty prevention, but developing frailty is not only attributable to physical functions but is also related to nutritional conditions, mental functions (cognitive functions), psychosocial aspects, and environmental factors. It is anticipated that these proportions of patients will increase as the population aging progresses. In summary, dialysis patients are in certain need of comprehensive care "renal rehabilitation."

6.8 Conclusion

Based on the survey the author and colleagues conducted previously, approximately 70% of Japanese elderly patients with hemodialysis are in a state of frailty or prefrailty, and physical functions and physical activity level of Japanese elderly patients attending the dialysis clinic for outpatient care decrease to approximately 50–70% of those of healthy persons. Moreover, a clear decline in physical functions and physical activity level is a significant and independent risk factor that worsens prognosis. The authors and colleagues developed the questionnaire on perceived mobility difficulty to accurately grasp limitations in ADL and revealed that the ADL difficulty evaluation is a simple alternative method to assess the functional status and to predict subsequent prognosis in elderly hemodialysis patients. The authors also have introduced a disease management system consisting of periodic assessment and exercise therapy and clarified that the high attendance group in the management program had significantly better survival and lower incidence of cardiovascular disease than the low attendance group. Therefore, periodic physical function assessment and encouragement for participation in physical activity should be part of disease management for frail hemodialysis patients.

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7 Exercise Intervention for Kidney Transplant Recipients: Recent Progress and Remaining Issues

Hideyo Oguchi and Ken Sakai

Abstract

Renal transplantation is a type of renal replacement therapy, and many patients' desire to undergo transplantation is primary aim for improving their quality of life and life prognosis. Exercise intervention is expected to improve the transplant recipients' exercise tolerance, which in turn improves their quality of life by increasing their daily activities. Exercise interventions have been reported in numerous articles. In recent years, several systematic reviews and meta-analyses have been published. These papers show that exercise improves the quality of life, exercise tolerability, and muscle performance of kidney transplant patients. However, whether the results of these randomized controlled trials and meta-analyses can be applied to daily clinical practice remains unknown. Recommendation of the strength and type of exercise for Japanese transplant patients remains unclear. A tailor-made exercise prescription for the individual recipients is required.

Keywords

Exercise intervention · Kidney transplant recipients · Rehabilitation

7.1 Introduction

Renal transplantation is one type of renal replacement therapies, and many transplant recipients' wish is to improve their quality of life (QOL) and life prognosis. Exercise therapy is expected to maintain the transplant recipients' exercise

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tolerance and improve their QOL as stated by guideline for renal rehabilitation in Japan. According to the guidelines for internal and pediatric complications after kidney transplantation [1], metabolic syndrome after kidney transplantation is a risk factor for chronic transplant renal dysfunction, and the therapeutic intervention is diet and lifestyle improvement by exercise. A previous study showed that weight gain 1 year after kidney transplantation reduces allograft survival [2]. Another study showed that weight increase within 1 year after kidney transplantation was about 10%, and that this weight increase may be important regarding change in morbidity of cardiovascular disease [3]. Exercise intervention for transplant recipients is also expected to prevent cardiovascular disease by improving obesity [4]. About 22% of living kidney transplantation in Japan are over 60 years old according to the Annual Progress Report from the Japanese Renal Transplant Registry. A recent systematic review pointed out that prevention of flail and sarcopenia is also an important issue [4]. Recently, some evidence on exercise therapy after kidney transplantation has been reported. In this review, we describe recent advances and remaining issues of exercise therapy after kidney transplantation and also describe various benefits of exercise intervention.

7.2 Systematic Review and Meta-Analysis About Exercise Intervention for Transplant Recipients

Exercise interventions, either aerobic training, resistance training, or both, have been reported in numerous articles. Aerobic exercise includes, for example, treadmill; resistance exercise includes weight training [5]. Several systematic reviews and meta-analyses on this topic have been performed in recent years. One paper discussed randomized controlled trials (RCTs) of exercise interventions in patients who underwent solid organ transplantation, but a meta-analysis was not performed [6]. Two systematic reviews and meta-analyses regarding exercise treatment for kidney transplant recipients were recently performed. One paper concluded that exercise intervention significantly improved transplant recipients' exercise tolerability and QOL, but a significant improvement in allograft kidney function was not observed [4]. The other paper revealed that exercise intervention improved transplant recipients' aerobic capacity, their muscle performance and QOL [7]. The exercise intervention periods in all of the RCTs included in these systematic reviews and meta-analyses were too short.

7.3 Expectations of Exercise Therapy for Transplant Recipients

Recent RCTs have pointed out some beneficial effects of exercise therapy for transplant recipients. The details of these effects of exercise therapy are described below.

7.3.1 Exercise Tolerance

The peak VO_2 was used to assess exercise tolerance in many reports. Painter et al. [8] performed an RCT involving 95 kidney transplant recipients in whom exercise intervention (home-based exercise and cardiovascular exercise of walking or cycling) improved the peak VO_2. Kouidi et al. [9] performed an RCT of 23 kidney transplant recipients in whom the peak VO_2 increased by 15.8% during an exercise training program consisting of four 60- to 90-min weekly sessions in a municipal gym. Riess et al. [10] also performed 31 kidney transplant recipients in whom 12 weeks of supervised endurance and strength training caused increase in the peak exercise cardiac output and peak VO_2.

7.3.2 Quality of Life

Some RCTs have been performed to assess the efficacy of exercise treatment for QOL, and improvements in QOL with exercise therapy have been reported in several of these RCTs. Riess et al. [10] reported that 12 weeks exercise treatment caused improvement of QOL using the 36-Item Short Form Health Survey (SF-36). Another report was published by Painter et al. using SF-36 [8]. Karelis et al. [11] suggested that resistance training seemed to improve QOL using a well-being score. Pooranfar et al. [12] reported that exercise intervention of 10 weeks improved quality and quantity of life regarding sleep in kidney transplant recipients.

7.3.3 Metabolic Syndrome and Muscle Strength

Juskowa et al. [13] reported muscle strength correlates improvement of allograft function in the exercise intervention versus the standard care groups. Pooranfar et al. [12] reported that 10 weeks of exercise intervention might improve the lipid profile in kidney transplant recipients. Painter et al. [14] reported that only exercise intervention did not decrease the coronary heart disease risk within one year after transplantation. O'Connor et al. [15] reported that significant between-group differences in pulse wave velocity existed when comparing resistance exercise training with usual care. It was reported that longer-term observation is required to fully assess the effect of exercise therapy on improving metabolic syndrome [4].

7.3.4 Graft Function

With respect to native kidney function as measured by the estimated glomerular filtration rate, one study involving 12 months of exercise therapy for patients with CKD showed a significant mean difference in the rate of change between the rehabilitation and usual care groups [16]. However, the authors concluded that the effect

of 1 year of exercise was not evident because of the small sample size in their study [16]. They suggested that the improvement in renal function could be explained by reductions in waist circumference and was probably related to central adiposity [16]. Another study showed that aerobic or resistance training had no significant improvement regarding the estimated glomerular filtration rate in kidney transplant recipients [5]. Tzvetanov et al. [17] showed that physical rehabilitation (resistance-based body weight training) improved allograft function, although the study population was small. Graft function improvement with exercise therapy in transplant recipients is still controversial. The muscle mass increase associated with exercise therapy should also take into consideration of a poor estimate of kidney function by creatinine production [4].

7.4 Remaining Issues and Future of Exercise Therapy for Transplant Recipients

Whether the findings of RCTs and subsequent meta-analyses regarding exercise intervention for kidney transplant recipients can be applied to daily clinical practice remains unknown. Recommendation of most appropriate exercise method and duration of exercise are unclear [4]. For example, what kind of exercise is appropriate for a transplant patient whose altitude obesity and lower limb muscular strength are declining? When considering the opinions of experts in exercise rehabilitation, it is necessary to also comprehensively consider the timing of transplantation, age, activities of daily living, and degree of obesity when choosing the most appropriate exercise intervention. Studies evaluating the adverse events due to exercise therapy are never according to recent systematic review [4], and comprehensive studies on this topic are necessary.

High-quality research on exercise interventions for transplant patients from Japan is needed. An appropriate tailor-made exercise prescription for the individual patient is required.

7.5 Conclusion

Recent advances in clinical research are expected to make exercise therapy useful in transplant recipients. However, recommendation of the strength and type of exercise for Japanese transplant patients remains unclear. A tailor-made exercise prescription for the individual transplant recipients is required.

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8 Role of Nutrition and Rehabilitation in the Prevention and Management of Sarcopenia and Frailty

Hidetaka Wakabayashi

Abstract

A concept of rehabilitation nutrition is recommended for preventing and treating sarcopenia, frailty, and malnutrition in chronic kidney disease (CKD) patients. Rehabilitation nutrition elicits the highest body functions, activities, participants, and quality of life (QOL) by improving nutritional status, sarcopenia, and frailty. Iatrogenic sarcopenia and iatrogenic frailty are defined as sarcopenia and frailty caused by the activities of medical staff including doctors, nurses, or other health-care professionals in health-care facilities. Prevention and treatment of iatrogenic sarcopenia and iatrogenic frailty are particularly important in acute phase hospitals. Sarcopenic dysphagia is defined as dysphagia due to sarcopenia in both generalized skeletal muscles and swallowing-related muscles. Presbyphagia is characterized by age-related changes in the swallowing mechanism. Sarcopenic dysphagia and presbyphagia are common in older CKD patients with sarcopenia, frailty, and malnutrition. High-quality rehabilitation nutrition for preventing and treating sarcopenia, frailty, sarcopenic dysphagia, and presbyphagia in CKD patients can be implemented by using the rehabilitation nutrition care process. Rehabilitation nutrition care process includes five steps such as rehabilitation nutrition assessment and diagnostic reasoning, rehabilitation nutrition diagnosis, rehabilitation nutrition goal setting, rehabilitation nutrition intervention, and rehabilitation nutrition monitoring. Further studies on rehabilitation nutrition are important, where the number of CKD patients with sarcopenia and frailty is expected to increase.

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Keywords

Clinical practice guideline · Iatrogenic frailty · Iatrogenic sarcopenia · Sarcopenic dysphagia · Presbyphagia · Rehabilitation nutrition · Rehabilitation nutrition care process

8.1 Introduction

Sarcopenia, frailty, and malnutrition are common and associated with poor rehabilitation outcome in older chronic kidney disease (CKD) patients. Our retrospective cohort study in patients with end-stage renal disease on maintenance hemodialysis who had undergone rehabilitation showed 87.7% were identified as having a nutritional risk assessed by the Geriatric Nutritional Risk Index [1]. Moreover, nutritional risk was associated independently with functional recovery [1]. Another retrospective cohort study in maintenance hemodialysis patients showed 55.6% were diagnosed with pre-sarcopenia [2]. Furthermore, the Geriatric Nutritional Risk Index was correlated with walking ability, and a Geriatric Nutritional Risk Index of 87 might be the target for maintaining walking ability [2]. Therefore, nutritional management is very important in CKD patients who require rehabilitation.

A concept of rehabilitation nutrition is recommended for preventing and treating sarcopenia, frailty, and malnutrition. Rehabilitation nutrition is defined as that which (1) evaluates holistically by the International Classification of Functioning, Disability and Health (ICF), and the presence and cause of nutritional disorders, sarcopenia, and excess or deficiency of nutritional intake; (2) conducts rehabilitation nutrition diagnosis and rehabilitation nutrition goal setting; and (3) elicits the highest body functions, activities, participants, and quality of life (QOL) by improving nutritional status, sarcopenia, and frailty using "nutrition care management in consideration of rehabilitation" and "rehabilitation in consideration of nutrition" in people with a disability and frail older people [3]. The prevalence of sarcopenia and malnutrition are approximately 50% in rehabilitation settings [4–6]. Moreover, sarcopenia is associated with worse recovery of activities of daily living (ADL) and dysphagia, and a lower rate of home discharge in hospitalized patients undergoing convalescent rehabilitation [7]. In this review, I address the clinical practice guidelines of sarcopenia, iatrogenic sarcopenia, sarcopenic dysphagia, the clinical practice guideline of frailty, iatrogenic frailty, presbyphagia, rehabilitation nutrition, the clinical practice guidelines of rehabilitation nutrition, and rehabilitation nutrition care process for sarcopenia and frailty.

8.2 Sarcopenia

8.2.1 The Clinical Practice Guideline of Sarcopenia

The clinical practice guideline of sarcopenia 2017 edition was created by the Japanese Society of Sarcopenia and Frailty and National Center for Geriatrics and

Gerontology in 2017 [8–11]. Sarcopenia is generally defined as a decrease in skeletal muscle mass and muscle strength or physical function, such as gait speed, observed in elderly individuals [8]. Proper nutrition and exercise are strongly recommended for prevention of sarcopenia as follows:

> Proper nutritional intake, especially protein intake of ≥1.0 g/kg of bodyweight per day (assuming appropriate bodyweight), might be effective for preventing the development of sarcopenia, and is therefore recommended (evidence level: low; recommendation level: strong) [10].

> Regular exercise and increased physical activity might prevent the onset of sarcopenia. Therefore, regular exercise and an active lifestyle are recommended (evidence level: low; recommendation level: strong) [10].

For treatment of sarcopenia, exercise intervention, nutritional intervention, and combined interventions are weakly recommended as follows:

> Exercise interventions can be effective for increasing appendicular skeletal muscle mass, knee extension muscle strength, normal gait speed and maximum gait speed in patients with sarcopenia, and therefore are recommended (evidence level: very low; recommendation level: weak) [11].

> Nutritional interventions focused on the intake of essential amino acids might improve knee extension muscle strength in patients with sarcopenia and are therefore recommended. However, the ability of this treatment approach to improve long-term outcomes is not yet clear (evidence level: very low; recommendation level: weak) [11].

> Compared with singular interventions, combined interventions, including comprehensive exercise-based treatment interventions, such as resistance training and nutritional intervention, are effective for improving sarcopenia and are recommended. However, the ability of this approach to improve long-term outcomes is not yet clear (evidence level: very low; recommendation level: weak) [11].

In 2018, international clinical practice guidelines for sarcopenia was created by the task force of the International Conference on Sarcopenia and Frailty Research [12]. Physical activity (resistance-based training) for treatment of sarcopenia is strongly recommended as follows:

> In patients with sarcopenia, prescription of resistance based training can be effective to improve muscle strength, skeletal muscle mass and physical function (Grade: strong recommendation, moderate certainty of evidence) [12].

Protein supplementation, adequate calorie and protein intake, and combined interventions are conditionally recommended as follows:

> We recommend that clinicians consider protein supplementation/a protein-rich diet for older adults with sarcopenia (Grade: conditional recommendation; low certainty of evidence) [12].

> Clinicians may also consider discussing with patients the importance of adequate calorie and protein intake (Grade: conditional recommendation; very low certainty of evidence) [12].

> Nutritional (protein) intervention should be combined with a physical activity intervention (Grade: conditional recommendation, low certainty of evidence) [12].

In contrast, there is no recommendation for Vitamin D supplementation:

> Insufficient evidence exists to determine whether a Vitamin D supplementation regime by itself is effective in older adults with sarcopenia (Grade: no recommendation; very low certainty of evidence) [12].

Effectiveness of nutrition and exercise intervention for sarcopenia depends on causes of sarcopenia. These clinical practice guidelines for sarcopenia indicate importance of nutrition and exercise intervention in the prevention and treatment of primary sarcopenia (age-related sarcopenia). However, intervention of nutrition alone or exercise alone for secondary sarcopenia, such as activity-related, nutrition-related, and disease-related sarcopenia, may get worse sarcopenia. For example, nutrition-alone intervention seems not to be effective for activity-related sarcopenia, and exercise-alone intervention is not effective for nutrition-related sarcopenia. Therefore, it is important to utilize the clinical practice guidelines for sarcopenia after considering the causes of sarcopenia.

8.2.2 Iatrogenic Sarcopenia

Iatrogenic sarcopenia is defined as sarcopenia caused by the activities of medical staff including doctors, nurses, or other health-care professionals in health-care facilities [3, 13]. Iatrogenic sarcopenia is categorized into the following three categories according to causes of sarcopenia: (1) activity-related iatrogenic sarcopenia caused by unnecessary inactivity or unnecessary no oral intake, (2) nutrition-related iatrogenic sarcopenia caused by inappropriate nutritional care management, and (3) disease-related iatrogenic sarcopenia by iatrogenic diseases (Table 8.1). Iatrogenic sarcopenia is likely to occur in acute phase hospitals, because of focus on the treatment of diseases with less attention to activity and nutrition. Appropriate nutritional

Table 8.1 Classification of iatrogenic sarcopenia and no iatrogenic sarcopenia

Causes of sarcopenia	Iatrogenic sarcopenia	No iatrogenic sarcopenia
Age-related sarcopenia	Absence	All age-related sarcopenia
Activity-related sarcopenia	Unnecessary bed rest and no oral intake in hospitals and facilities	Sedentary lifestyle Necessary bed rest and no oral intake for disease treatment
Nutrition-related sarcopenia	Inappropriate nutritional care management in hospitals and facilities Anorexia due to adverse drug event	Inadequate dietary intake malabsorption Gastrointestinal disorders Anorexia due to diseases
Disease-related sarcopenia	Iatrogenic diseases Adverse drug event	No iatrogenic diseases Required surgery

care management and rehabilitation immediately after hospitalization is important for prevention of iatrogenic sarcopenia.

Activity-related iatrogenic sarcopenia is mainly caused by unnecessary bed rest and immobilization. Leg lean mass was reduced by 1.4% and 3.1%, and leg strength was decreased by 9.0% and 22.9%, following 5 and 14 days of immobilization in healthy young male [14]. During 10 days of bed rest, lean body mass in the lower limbs reduced by 6% and lower limbs strength decreased 16% in healthy older adults [15]. Furthermore, the incidence of sarcopenia during hospitalization was significantly associated with the number of days spent in bed [16]. Patients who developed sarcopenia during hospitalization spent an average of 5.1 days in bed compared with 3.2 days for those with no sarcopenia at discharge [16]. Therefore, early mobilization after admission should be promoted to prevent activity-related iatrogenic sarcopenia.

Nutrition-related iatrogenic sarcopenia is caused by inappropriate nutritional care management in hospitals and facilities, and anorexia due to adverse drug event. None of the inpatients with hospital-associated deconditioning had a normal nutritional status, and 44% of those inpatients had starvation [17]. Median energy intake was 1159 kcal in inpatients who require dysphagia rehabilitation [18]. Moreover, 25 percentile of energy intake in this study was 648 kcal [18]. Indeed, patients undergoing rehabilitation often consume less energy and protein than they need [19]. Inappropriate nutritional care management is often performed in hospitals who require rehabilitation. Moreover, patients who consumed approximately <22 kcal/kg/day during the acute period showed significantly poorer recovery from dysphagia and poorer outcomes compared to those who consumed approximately >22 kcal/kg/day [20]. Therefore, prevention of nutrition-related iatrogenic sarcopenia and appropriate nutritional care management are important.

Disease-related iatrogenic sarcopenia develops following iatrogenic diseases and adverse drug event. Iatrogenic disease is a disease or symptoms induced in patients by the treatment or instructions of doctors, which results in harmful consequences for the patients' health. Prevalence of possibly and definitely iatrogenic admissions to the Departments of Medicine/Cardiology/Pulmonology were 29% and 19%, respectively [21]. Risk factors of iatrogenic diseases in older people are drug-induced iatrogenic diseases, multiple chronic diseases, multiple physicians, hospitalization, and medical or surgical procedures [22]. Moreover, polypharmacy is associated with sarcopenia in older adults [23, 24]. Needless to say, iatrogenic diseases and adverse drug events should be prevented.

8.2.3 Sarcopenic Dysphagia

Sarcopenic dysphagia is defined as dysphagia due to sarcopenia in both generalized skeletal muscles and swallowing-related muscles and was excluded if whole-body sarcopenia was absent [25–27]. Whole-body sarcopenia was positively associated with dysphagia in a systematic review and meta-analysis (odds ratio: 4.06) [28]. Hemodialysis patient with protein-energy wasting and whole-body sarcopenia may exhibit sarcopenic dysphagia [29]. Tongue pressure was associated with

malnutrition and sarcopenia in older patients with peritoneal dialysis [30]. Penetration and tracheal aspiration, which requires oral intake changes may be common in chronic renal failure [31]. Sarcopenic dysphagia can occur in patients with CKD, cardiovascular diseases, respiratory diseases, and orthopedic diseases such as hip fracture, cancer, and hospital-associated deconditioning.

Recently, the position paper of sarcopenia and dysphagia was published by the Japanese Society of Dysphagia Rehabilitation, the Japanese Association of Rehabilitation Nutrition, the Japanese Association on Sarcopenia and Frailty, and the Society of Swallowing and Dysphagia of Japan to consolidate the currently available evidence on the topics of sarcopenia and dysphagia [32]. The position paper elaborated the following five main issues by using scientific evidence obtained from medical journals: (1) the relationship between sarcopenia and swallowing muscles; (2) the definition of dysphagia due to sarcopenia; (3) the evaluation and diagnosis of dysphagia due to sarcopenia; (4) treatment and rehabilitation for dysphagia due to sarcopenia; and (5) the current status of dysphagia in relation to sarcopenia, related issues, and perspectives [32].

Sarcopenic dysphagia is diagnosed using a reliable and validated five-step algorithm for the condition (Fig. 8.1) [27, 32]. The diagnostic algorithm divides participants into

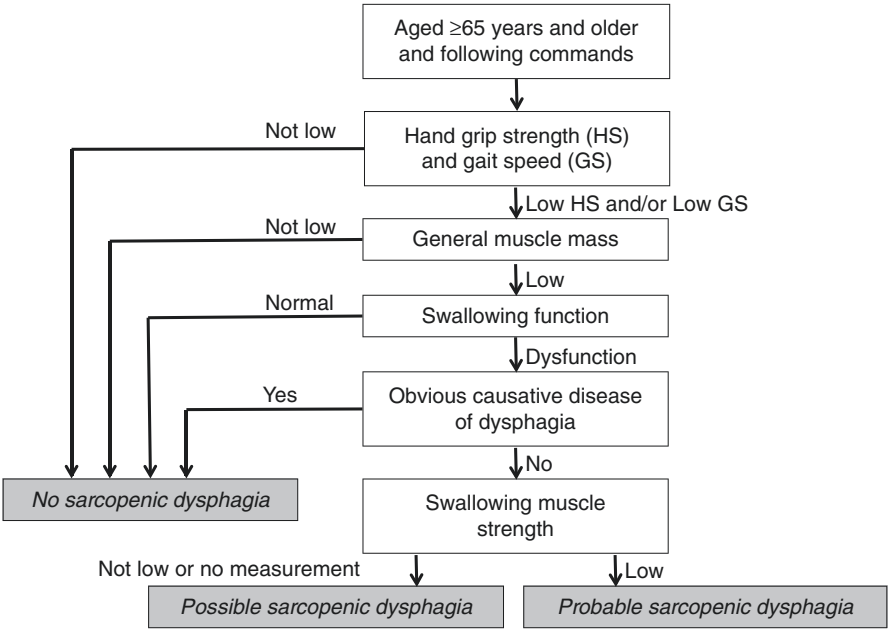

Fig. 8.1 Diagnostic algorithm for sarcopenic dysphagia. The diagnostic algorithm is consisted of five steps: (1) Whole-body sarcopenia (skeletal muscle strength and physical function). (2) Whole-body sarcopenia (skeletal muscle mass). (3) The presence of dysphagia. (4) The causes of dysphagia. Patients who had a disease that was the obvious cause of dysphagia were excluded from the study. However, patients with stroke, brain injury, neuromuscular disease, head and neck cancer, or connective tissue disease in whom the main cause of dysphagia was considered to be age-, activity-, nutrition-, invasion-, or cachexia-related sarcopenia were included. (5) Swallowing muscle strength. Cut-off value: 20 kPa tongue pressure

three categories: probable sarcopenic dysphagia, possible sarcopenic dysphagia, and no sarcopenic dysphagia. The diagnostic algorithm consisted of five steps:

1. Whole-body sarcopenia (skeletal muscle strength and physical function).
2. Whole-body sarcopenia (skeletal muscle mass).
3. The presence of dysphagia.
4. The causes of dysphagia. Patients who had a disease that was the obvious cause of dysphagia were excluded. However, patients with stroke, brain injury, neuromuscular disease, head and neck cancer, or connective tissue disease in whom the main cause of dysphagia was considered to be age-, activity-, nutrition-, invasion-, or cachexia-related sarcopenia were included [27, 32]. For example, in stroke patients aged 65 years or older receiving enteral nutrition, the risk of severe malnutrition independently predicts the achievement of full oral intake, indicating the presence of sarcopenic dysphagia in stroke patients [33]. Moreover, dysphagia was independently associated with sarcopenia in convalescent rehabilitation ward inpatients with stroke, musculoskeletal diseases, and hospital-associated deconditioning [34].
5. Swallowing muscle strength assessed by tongue pressure measurement. People with low swallowing muscle strength (<20 kPa tongue pressure) are judged as being at probable risk for sarcopenic dysphagia. People with normal swallowing muscle strength and people who cannot measure tongue pressure are judged as being at a possible risk for sarcopenic dysphagia

Assessment of swallowing muscle mass is not included in the diagnostic algorithm for sarcopenic dysphagia because it is difficult to measure swallowing muscle mass in clinical practice. However, ultrasound examination can be used for assessing swallowing muscle mass and muscle quality. The area of the tongue muscle and its area of brightness examined by ultrasound were independent risk factors for sarcopenic dysphagia in older patients who had been recommended to undergo dysphagia assessment and/or rehabilitation [35].

Sarcopenic dysphagia seems to be common in older patients with dysphagia. The prevalence of sarcopenic dysphagia in patients who require dysphagia rehabilitation in acute care hospital was 32% [18]. In this study, sarcopenic dysphagia was independently associated with poor swallowing function at discharge [18]. The prevalence of sarcopenic dysphagia in pneumonia patients over 65 years who could follow commands in acute care hospital was 81% (152/187) [36]. Another study investigating the incidence of dysphagia after hospitalization among older inpatients who did not have dysphagia before admission, but were maintained on a nil per os (NPO) regimen for >2 days showed that 26% of patients exhibited dysphagia 60 days after admission [37]. All patients who developed dysphagia after NPO had whole-body sarcopenia, and causes of dysphagia were mainly considered sarcopenic dysphagia [37]. Furthermore, skeletal muscle index, activities of daily living, and body mass index (BMI) were independent predictors of dysphagia [37]. Therefore, improvement of skeletal muscle index, activities of daily living, and body mass index may prevent the occurrence of sarcopenic dysphagia.

8.3 Frailty

8.3.1 The Clinical Practice Guideline of Frailty

The Asia-Pacific clinical practice guidelines for the management of frailty was created by a clinical expert panel comprised of multidisciplinary experts on frailty from various countries in 2017 [38]. In the Asia-Pacific clinical practice guideline, frailty is defined as an age-related state characterized by a reduced strength and physiologic malfunctioning that increases an individual's susceptibility to increased dependency, vulnerability, and death [38]. However, there are no globally unified definition and diagnostic criteria of frailty. Physical activity containing resistance training and addressing polypharmacy are strongly recommended as follows:

> We strongly recommend that older adults with frailty be referred to a progressive, individualized physical activity program that contains a resistance training component. [38]

> We strongly recommend that polypharmacy be addressed by reducing or deprescribing any inappropriate/superfluous medications [38].

Nutritional intervention for unintentional weight loss and vitamin D deficiency is conditionally recommended as follows:

> We conditionally recommend that older adults with frailty who exhibit unintentional weight loss should be screened for reversible causes and considered for food fortification/protein and caloric supplementation [38].

> We conditionally recommend that vitamin D be prescribed for persons found to be deficient in Vitamin D [38].

Effectiveness of nutrition and exercise intervention for frailty depends on causes of frailty. The Asia-Pacific clinical practice guidelines for the management of frailty indicate importance of nutrition and exercise intervention and addressing polypharmacy. However, intervention of nutrition alone or exercise alone for frailty may get worse frailty. For example, nutrition-alone intervention seems not to be effective for age-related sedentary lifestyle. Exercise-alone intervention is not effective for malnutrition-related frailty. Intervention of nutrition alone or exercise alone seems not to be effective for polypharmacy-related frailty. Therefore, it is important to utilize the clinical practice guidelines for frailty after considering the causes of frailty.

8.3.2 Iatrogenic Frailty

Iatrogenic frailty can be defined as frailty caused by the activities of medical staff including doctors, nurses, or other health-care professionals in health-care facilities. Major causes of frailty are decrease in physical activity, inadequate dietary intake, vitamin D deficiency, sarcopenia, polypharmacy, and diseases (Table 8.2). Iatrogenic

Table 8.2 Classification of iatrogenic frailty and no iatrogenic frailty

Causes of frailty	Iatrogenic frailty	No iatrogenic frailty
Decrease in physical activity	Unnecessary bed rest and no oral intake in hospitals and facilities	Age-related sedentary lifestyle Necessary bed rest and no oral intake for disease treatment
Inadequate dietary intake Vitamin D deficiency	Anorexia due to adverse drug event	Age-related anorexia Anorexia due to diseases
Sarcopenia	Iatrogenic sarcopenia	Age-related sarcopenia No iatrogenic sarcopenia
Polypharmacy	All drug-induced frailty Adverse drug event	Absence
Diseases	Iatrogenic diseases	Age-related diseases No iatrogenic diseases

frailty includes unnecessary bed rest and no oral intake in hospitals and facilities, anorexia due to adverse drug event, iatrogenic sarcopenia, polypharmacy, adverse drug event, and iatrogenic diseases. Frailty may occur in iatrogenic rather than age related in some people. Iatrogenic frailty is likely to occur in acute phase hospitals, because of iatrogenic sarcopenia, polypharmacy, adverse drug event, and iatrogenic diseases. Therefore, prevention of iatrogenic frailty is particularly important in acute phase hospitals.

8.3.3 Presbyphagia

Presbyphagia is characterized by age-related changes in the swallowing mechanism and is different from dysphagia [25, 39, 40]. Presbyphagia is a frailty in swallowing and may be common in patients with CKD. Approximately 40% of healthy older people have presbyphagia [41]. The difference between presbyphagia and dysphagia is the necessity for food modification. Thickened drinks and texture-modified food such as pureed, minced and moist, and soft products are necessary in dysphagia. In contrast, thickened drinks and texture-modified food are not necessary in presbyphagia. However, there may be a progression from presbyphagia to dysphagia [42]. Age-related sarcopenia of the swallowing muscles is one of the causes of presbyphagia [25].

The 10-item Eating Assessment Tool (EAT-10) is useful for screening presbyphagia and dysphagia [43]. The EAT-10 is a ten-item questionnaire as follows:

To what extent are the following scenarios problematic for you?

Each item is scored from 0 to 4 according to the severity of the problem.

0 = No problem, 4 = Severe problem

1. My swallowing problem has caused me to lose weight.
2. My swallowing problem interferes with my ability to go out for meals.
3. Swallowing liquids takes extra effort.

4. Swallowing solids takes extra effort.
5. Swallowing pills takes extra effort.
6. Swallowing is painful.
7. The pleasure of eating is affected by my swallowing.
8. When I swallow food, it sticks in my throat.
9. I cough when I eat.
10. Swallowing is stressful.

An EAT-10 score ≥ 3 is abnormal and indicates the presence of swallowing difficulties. The reliability and validity of the EAT-10 has been confirmed and translated into many languages [43–54]. There are some people who cannot answer the questionnaire because of dementia and other diseases. People who cannot respond to the EAT-10 are likely to have dysphagia [44]. People with an EAT-10 score 0 have normal swallowing function or no awareness of presbyphagia and dysphagia. People with an EAT-10 score 1 or 2 are likely to have presbyphagia, while those with an EAT-10 score ≥ 3 are likely to have dysphagia or presbyphagia.

8.4 Rehabilitation Nutrition

8.4.1 Definition of Rehabilitation Nutrition

Rehabilitation nutrition is defined as that which (1) evaluates holistically by the International Classification of Functioning, Disability and Health (ICF) and the presence and cause of nutritional disorders, sarcopenia, and excess or deficiency of nutritional intake; (2) conducts rehabilitation nutrition diagnosis and rehabilitation nutrition goal setting; and (3) elicits the highest body functions, activities, participants, and QOL by improving nutritional status, sarcopenia, and frailty using "nutrition care management in consideration of rehabilitation" and "rehabilitation in consideration of nutrition" in people with a disability and frail older people [3]. The term "rehabilitation nutrition" is quite different from that of "nutritional rehabilitation" [26]. "Nutritional rehabilitation" usually refers to nutritional improvement of malnourished children in developing countries [55–57] and malnourished patients with anorexia nervosa [58–60]. In contrast, "rehabilitation nutrition" not only refers to nutritional improvement but also to rehabilitation in people with a disability and frail older people [26, 61–64]. Therefore, both concepts of "nutritional rehabilitation" and "rehabilitation nutrition" are very important; however, both concepts are quite different.

Appropriate and aggressive nutritional care management to improve malnutrition is an important part of rehabilitation nutrition for preventing and treating sarcopenia and frailty. Patients' total daily energy expenditure was usually based on a basal energy expenditure calculated using the Harris-Benedict equation gross an activity factor and a stress factor [17]. In the case of normal nutritional status, total daily energy intake should be set equal to total daily energy expenditure to keep normal nutritional status. However, it is suggested to add to the total daily energy expenditure the amount of energy accumulation needed for weight gain in the case of malnutrition [13]. Hebuterne

et al. [65] reported that older people require 8800–22,600 kcal to gain 1 kg body weight. This suggestion is supported by several case reports of sarcopenic dysphagia in which aggressive nutrition care with an energy and protein intake of approximately 35 kcal/kg/day (ideal body weight) and 1.4 g/kg/day (ideal body weight) was implemented along with dysphagia rehabilitation [62, 66, 67]. As a result, in addition to a weight gain of approximately 10 kg, both physical and swallowing function improved.

8.4.2 The Clinical Practice Guidelines of Rehabilitation Nutrition

The clinical practice guidelines of rehabilitation nutrition 2018 edition was created by the Japanese Association of Rehabilitation Nutrition in 2018 [68–71]. Cerebrovascular disease, hip fracture, acute diseases, and cancer were included in the clinical practice guidelines of rehabilitation nutrition 2018 edition. Enhanced nutrition care is recommended in patients with cerebrovascular disease, hip fracture, and acute diseases as follows.

Cerebrovascular disease: We weakly recommend enhanced nutrition care for older patients with cerebrovascular disease undergoing rehabilitation in acute phase to reduce mortality and infection and to improve quality of life (evidence level: low; recommendation level: weak). Appropriate dose and route of nutrition care should be selected according to individual conditions such as swallowing function and intestinal function, and favorable types of enhanced nutrition care include oral nutritional supplements, protein-rich food, and other supplements [69].

Hip fracture: We weakly recommend enhanced nutrition care for older patients with hip fracture in conjunction with early rehabilitation after surgery to reduce mortality and complications and to improve activities of daily living and muscle strength (evidence level: low; recommendation level: weak). Favorable types of enhanced nutrition care include oral nutritional supplements with high energy and protein density, and nutritional counseling and nutritional support by registered dietitians [71].

Acute diseases: We weakly recommend enhanced nutrition care for patients with acute diseases undergoing rehabilitation in acute phase to reduce mortality and infection, and to improve quality of life. However, in addition to voluntary rehabilitation, it is desirable to combine an enhanced rehabilitation program (evidence level: very low; recommendation level: weak) [68].

In contrast, there is no recommendation in adult cancer patients.

Cancer: We have no uniform or constant recommendation on program combined rehabilitation and nutritional counseling for adult cancer patients undergoing adjuvant chemotherapy or radiotherapy (evidence level: very low). However, it is desirable to judge the necessity of rehabilitation and nutritional counseling individually taking into consideration the patient's and family's intentions and medical conditions. We cannot make any specific recommendation on combination effects of rehabilitation and enhanced nutrition care for adult cancer patients with malnutrition, cachexia, and ADL declines because there is no evidence currently [68–70].

Recommendations of enhanced nutrition care for patients with cerebrovascular disease, hip fracture, and acute diseases indicate the importance of specific nutrition

care undergoing rehabilitation. Intervention of nutrition alone or rehabilitation alone cannot elicit the highest body functions, activities, participants, and QOL in patients with malnutrition, frailty, sarcopenia, and cachexia. Therefore, enhanced nutrition care for CKD patients with malnutrition, frailty, sarcopenia, and cachexia undergoing rehabilitation is weakly recommended, although there is no clinical practice guideline of rehabilitation nutrition for CKD patients. Further randomized controlled trials of rehabilitation nutrition are necessary to create clinical practice guideline of rehabilitation nutrition for CKD patients.

8.4.3 Rehabilitation Nutrition Care Process

The rehabilitation nutrition care process is defined as a systematic problem-solving method for nutrition status, sarcopenia, nutrient intake, and frailty in people with a disability and frail older people [3, 13]. Rehabilitation nutrition care process includes five steps such as rehabilitation nutrition assessment and diagnostic reasoning, rehabilitation nutrition diagnosis, rehabilitation nutrition goal setting, rehabilitation nutrition intervention, and rehabilitation nutrition monitoring (Fig. 8.2). The nutrition care process developed by the Academy of Nutrition and Dietetics is used only by registered dietitians [72–74]. However, the rehabilitation nutrition care

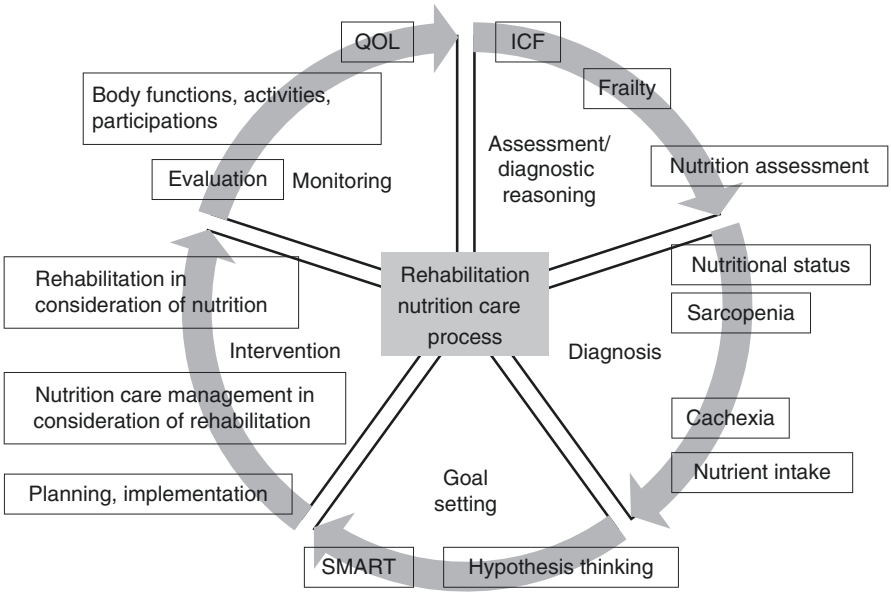

Fig. 8.2 Rehabilitation nutrition care process. Rehabilitation nutrition care process is consisted of five steps: (1) rehabilitation nutrition assessment and diagnostic reasoning, (2) rehabilitation nutrition diagnosis, (3) rehabilitation nutrition goal setting, (4) rehabilitation nutrition intervention, and (5) rehabilitation nutrition monitoring. SMART means a goal that is specific, measurable, achievable, relevant or related, and time bound

process can be used by not only registered dietitians but also many medical occupations such as doctors, nurses, physical therapists, occupational therapists, speech-language-hearing therapists, pharmacists, dentists, and dental hygienists.

8.4.3.1 Rehabilitation Nutrition Assessment and Diagnostic Reasoning

Rehabilitation nutrition assessment should include a comprehensive assessment by the ICF, clinical history, a detailed nutritional assessment including nutritional status and nutritional intake, and the presence of sarcopenia and its etiology based on appropriate criteria [13]. Rehabilitation nutritional assessment and rehabilitation nutrition diagnosis can be reciprocating. Diagnostic reasoning is considered to be the most critical skill of doctors [75]. It is useful to conduct rehabilitation nutrition diagnostic reasoning with multidisciplinary rehabilitation nutrition team. Two systems for decision-making have been proposed: System 1, heuristic and intuitive and System 2, systematic and analytical [75]. Rehabilitation nutrition diagnosis mainly depends on System 1, because of few reliable data on prevalence and specific clinical characteristics.

8.4.3.2 Rehabilitation Nutrition Diagnosis

Rehabilitation nutrition diagnosis identifies the rehabilitation nutrition-related problems. It comprises three major categories with 15 subitems: nutritional status, sarcopenia, and excess and/or insufficient nutrient intake (Table 8.3). I address nutritional status, and excess and/or insufficient nutrient intake.

The domain of nutritional status is composed of undernutrition, overnutrition, at risk of malnutrition, at risk of overnutrition, lack of nutrients, and excess of nutrients. Undernutrition can be used synonymously with malnutrition [76]. The Global Leadership Initiative on Malnutrition (GLIM) for the diagnosis of malnutrition was

Table 8.3 Rehabilitation nutrition diagnosis

Major categories	Subitems
Nutritional status	Undernutrition
	Overnutrition
	At risk of malnutrition (undernutrition, overnutrition)
	Lack of nutrients
	Excess of nutrients
	Absence
Sarcopenia	Sarcopenia
	Decreased muscle mass
	Decreased muscle strength and/or physical performance
	Absence
Excess and/or insufficient nutrient intake	Excess nutrient intake
	Insufficient nutrient intake
	Prediction of excess nutrient intake
	Prediction of insufficient nutrient intake

published in 2018 [76]. First, screening to identify "at risk of malnutrition" status by the use of any validated screening tool such as the Malnutrition Universal Screening Tool (MUST), the Nutritional Risk Screening-2002 (NRS-2002), the Mini Nutritional Assessment-Short Form (MNA-SF), and the Subjective Global Assessment (SGA). Second, assessment of three phenotypic criteria (non-volitional weight loss, low body mass index, and reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation, and inflammation or disease burden). Non-volitional weight loss means >5% within past 6 months, or >10% beyond 6 months. Low body mass index in Asian people means <18.5 if <70 years, or <20 if >70 years. Reduced muscle mass means reduced by validated body composition measuring techniques. Reduced food intake or assimilation means ≤50% of energy requirements >1 week, or any reduction for >2 weeks, or any chronic gastrointestinal condition that adversely impacts food assimilation or absorption. Inflammation means acute disease/injury or chronic disease related. For the diagnosis of malnutrition, the combination of at least one phenotypic criterion and one etiologic criterion is required [76].

Overnutrition is the excess deposition of nutrients. Overnutrition includes overweight and obesity, which are defined as abnormal or excessive fat accumulation that may impair health [77]. Obesity is defined as people with a body mass index (BMI) of 30 kg/m^2 or greater, while those with a BMI between 25 and 29.9 kg/m^2 were classified as overweight. However, people with a BMI of 25 kg/m^2 or greater are diagnosed with obesity in Japan. Body composition analysis (e.g., bio-impedance analysis, dual-energy X-ray absorptiometry, computed tomography, and magnetic resonance imaging) may help to confirm the degree and distribution of fat accumulation. Individuals at risk of overnutrition are not necessarily obese or overweight at the time. Some obese people may have sarcopenia. Sarcopenic obesity is defined as having both sarcopenia and obesity, that is associated with a higher risk for adverse outcomes including functional disability, frailty, poor quality of life, longer hospitalization, and higher mortality rates [78].

Lack and excess of nutrients indicates under- or over-accumulation of one or more nutrients in the body. Lack and excess of nutrients mean nutritional status, but not nutrient intake. These states can occur regardless of nutrient intake. Individuals with lack and excess of nutrients show various symptoms such as abnormal blood concentration and specific symptoms or signs of nutrient deficiency (e.g., iron-deficiency anemia and hyperkalemia) or toxicity (e.g., Parkinsonism by brain accumulation of manganese), respectively.

Excess or insufficient nutrient intake means that the habitual nutritional intake is too much or too little compared with the appropriate reference, such as the dietary reference intake in each country [79]. Excess or insufficient nutrient intake does not mean nutritional status. These states can occur regardless of nutritional status. Several conditions produce a future risk of excess or insufficient nutrient intake (prediction of excess or insufficient nutrient intake). For example, if a survivor of acute myocardial infarction in an acute care hospital had an excessive intake of sweetened beverages and snacks before acute myocardial infarction and no compliance with the hospital diet, he or she may be predicted to have excess nutrient intake after discharge. Conversely, patients with cancer who is scheduled for

chemotherapy with a higher possibility of adverse effects such as nausea or oral ulcer can be predicted to have insufficient nutrient intake.

8.4.3.3 Rehabilitation Nutrition Goal Setting

Goal setting is a fundamental step for rehabilitation nutrition intervention. It should be performed in accordance with the SMART concept: Specific, Measurable, Achievable, Realistic/Relevant, and Timed/Time-bound [80]. Outcome measurements need to be Specific for the rehabilitation nutrition diagnosis. They also should be Measurable quantitative variables, rather than qualitative. An Achievable goal motivates both the clients and healthcare staff. For long-term goals, Relevant indicators for the clients would be employed instead of simple biomarkers or the results of functional tests. Because all interventions will be performed within a specific time frame, the goal should be Timed/Time-bound. For example, body weight and muscle mass are Specific, Measurable and Relevant nutritional goals. To gain 1 kg body weight within 1 month is Achievable and Time-bound nutritional goal. In contrast, nutrition improvement is not a SMART goal.

8.4.3.4 Rehabilitation Nutrition Intervention

There are two aspects to the methods of rehabilitation nutrition intervention. Namely, "nutrition care management in consideration of rehabilitation" and "rehabilitation in consideration of nutrition."

"Nutrition care management in consideration of rehabilitation" means nutrition care management for maximizing functions, activities, participation, and QOL through improving nutritional status and/or sarcopenia in light of the ICF and ongoing rehabilitation program. Several studies reported that higher energy intake or improvement of nutritional status significantly is associated with higher functional capacity in the rehabilitation patients [81–83]. Some randomized controlled trials showed that rehabilitation patients with decreased muscle mass or sarcopenia receiving an oral nutritional supplement showed greater functional recovery [84–86]. Recent systematic reviews regarding rehabilitation and nutrition intervention for older adults with disability or sarcopenia is effective for muscle strength [87, 88], although another review reported higher mortality and hospitalization risk, probably due to selection bias of the included studies [89]. Therefore, disabled patients with malnutrition and/or sarcopenia can benefit from "nutrition care management in consideration of rehabilitation."

"Rehabilitation in consideration of nutrition" means the rehabilitation for maximizing functions, activities, participation, and QOL through improving nutritional status and/or sarcopenia in light of nutritional status, sarcopenia, the ICF, and/or ongoing nutrition care. In the tertiary-care acute general hospital, most of the older inpatients (88%) referred to the department of rehabilitation medicine for hospital-associated deconditioning were malnourished, and malnutrition was independently associated with lower independence in ADL at discharge [17]. Malnutrition itself can reduce functions, activities, participation, and QOL. Therefore, a rehabilitation program should be planned with consideration for nutritional status and the ongoing nutritional care plan as well as the ICF.

In Japan, with the emphasis on "Rehabilitation in consideration of nutrition", the Ministry of Health, Labor and Welfare revised the medical fee system in the convalescent rehabilitation hospitals in 2018. Since April 2018, the convalescent rehabilitation hospitals can claim highest medical fee, if multidisciplinary team including a registered dietitian implements nutritional care management. Moreover, assignment of a registered dietitian for each convalescent rehabilitation ward is encouraged in the highest medical fee.

8.4.3.5 Rehabilitation Nutrition Monitoring

In the rehabilitation nutrition monitoring, the following indicators are recommended: general condition, nutritional status, nutritional intake, body weight, body composition (e.g., muscle mass, fat mass), physical and mental function, ADL, social participation, and QOL. When implementing rehabilitation nutrition intervention, timing and frequency of rehabilitation nutrition monitoring should be scheduled. For example, monitoring the body weight every week by nurses should be implemented in hospitals. If the current rehabilitation nutrition intervention is not effective, the rehabilitation nutrition plan would be changed, if applicable. Monitoring frequency can be determined by patients' condition, settings, and type and severity of rehabilitation nutrition diagnosis, and specific indicators must be followed for the patients. In underweight stroke patients who undergo tube feeding, monitoring the patients' nutritional status once per week seems to be superior to once per month [90].

8.5 Conclusion

Malnutrition, sarcopenia, frailty, and dysphagia are common in older CKD patients. These conditions affect lower body functions, activities, participants, and QOL. Therefore, prevention and treatment of these conditions are very important in CKD patients. Recent clinical practice guidelines of sarcopenia, frailty, and rehabilitation nutrition recommend exercise and nutrition intervention. Therefore, rehabilitation nutrition plays a central role in the prevention and management of sarcopenia and frailty. High-quality rehabilitation nutrition can be implemented by using the rehabilitation nutrition care process. Especially, iatrogenic sarcopenia and iatrogenic frailty should be prevented and treated in CKD patients. Further studies on rehabilitation nutrition are important, where the number of CKD patients with sarcopenia and frailty is expected to increase.

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Nutritional Interventions in Elderly Pre-dialysis Patients

9

Hiroe Sato and Yoshiki Suzuki

Abstract

Dietary protein restriction is recommended in pre-dialysis patients with chronic kidney disease (CKD), and its major purpose is preventing the progression to end-stage renal disease (ESRD), which was determined based on evidence of renal prognosis and survival in mostly young and middle-aged patients. In contrast, elderly people have been recommended to consume higher protein intake to maintain and regain muscle mass and strength compared to younger people. Protein restriction to prevent CKD progression and the recommended protein intake to prevent or improve sarcopenia and/or frailty are incompatible at this time. Sufficient energy intake is needed in patients with CKD with protein restriction and sarcopenia. Here, we discuss nutritional interventions with a focus on dietary protein intake in elderly pre-dialysis patients with CKD.

Keywords

Nutritional intervention · Chronic kidney disease · Sarcopenia · Frailty · Dietary protein intake · Energy intake · End-stage renal disease · Mortality · Elderly pre-dialysis patients

9.1 Introduction

Dietary protein restriction is recommended in pre-dialysis patients with chronic kidney disease (CKD) [1–6], and its major purpose is preventing the progression to end-stage renal disease (ESRD). In contrast, elderly people have been recommended

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to consume higher protein intake to maintain and regain muscle mass and strength compared to younger people [5, 7, 8]. Sufficient energy intake is needed in patients with CKD with protein restriction [5] and sarcopenia [9]. Here, we discuss nutritional interventions with a focus on dietary protein intake in elderly pre-dialysis patients with CKD.

9.2 Recommended Protein Intake for Patients with CKD

The dietary protein intake and energy intake recommendations for patients with CKD are listed in Table 9.1. Lower dietary protein (0.8 g/kg BW/day or 0.6–0.8 g/kg BW/day) is recommended for patients with severe CKD (i.e., estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) [1–3, 5, 6], and < 1.0 g/kg BW/day [5], ≤1.0 g/kg BW/day [4, 6] or ≤ 1.3 g/kg BW/day [1] is recommended for patients with moderate CKD. The recommended dietary allowance (RDA) of protein has been determined to be 0.83 g/kg BW/day as estimated by the nitrogen balance method [10], and 0.8 g/kg BW/day nearly corresponds to the RDA. The recommended dietary protein intake was determined based on evidence of renal prognosis and survival in mostly young and middle-aged patients [11–13]. Inappropriate dietary protein restriction with insufficient energy intake causes malnutrition [14], protein-energy wasting (PEW) [15], and poor prognosis [16]. The risk of CKD progression is lower than the mortality risk in older patients [17], and the protective effects of protein restriction may differ among young, middle-aged, and elderly patients with CKD.

Some cohort studies have reported dietary protein intake and risks for renal survival and mortality in elderly patients with CKD [18, 19]. Dietary protein intake was not related to a rapid decline in renal function in 3623 older men and women (mean dietary protein intake of four quartiles, 1.0–1.63 g/kg BW/day), which was also observed in 836 patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 [18]. A cohort study including patients with CKD stage 3–5 (73.6% were >65 years old, and the median follow-up period was 4.2 years) indicated that baseline dietary protein intake >0.8 g/kg BW/day had a significantly lower risk of all-cause mortality, but a similar risk of ESRD, comparing with 0.6–0.8 g/kg BW/day [19]. However, a relatively more rapid decline in eGFR was reported in the group with baseline dietary protein intake >0.8 g/kg BW/day [19]. Based on these results, protein restriction may have less of a preventative effect against disease progression in elderly patients with CKD, but these patients should be concerned about their mortality risk.

Several studies have shown the effectiveness of dietary protein restriction in elderly patients with advanced CKD or CKD with a high risk of progression [20–22]. Dietary protein intake of 0.7 g/kg BW/day reduces the decline in renal function and proteinuria in elderly patients with CKD stage 3b-4 and type 2 diabetes mellitus (mean urinary protein >2 g/day, mean body mass index [BMI] >30 kg/m^2), compared to that of 1.1 g/kg BW/day after 3 years. BMI, serum albumin level, and fat-free mass remained unchanged for 3 years [20]. In patients with a high risk for CKD

Table 9.1 Recommendations for dietary protein and energy intake in patients with chronic kidney disease (CKD)

Guideline and recommendation	Year	CKD stage	Protein intake	Energy intake
KDIGO [1]	2012	Adults with diabetes or without diabetes and GFR <30 mL/min/1.73 m^2 (GFR categories G4-G5)	0.8 g/kg BW/day, with appropriate education	–
		Adults with CKD at risk of progression	Avoiding high protein intake (>1.3 g/kg BW/day)	–
ADA [2]	2020	People with nondialysis-dependent diabetic kidney disease	0.8 g/kg BW/day	–
KDOQI [3]	2007	People with diabetes and CKD stages 1–4	0.8 g/kg BW/day	–
KHA-CARI [4]	2013	Adults with early CKD (stage 1–3)	0.75–1.0 g/kg BW/day	Overweight/obese patients with CKD; caloric restriction under the management of an appropriately qualified dietitian
Kalantar-Zadeh et al. [5]	2017	Normal kidney function with increased CKD risk (eGFR ≥60 mL/min/1.73 m^2 without proteinuria)	<1.0 g/kg BW/day	30–35 kcal/kg BW/day; adjust to target weight reduction if BMI >30 kg/m^2
		Mild-to-moderate CKD (eGFR 30–60 mL/min/1.73 m^2, UP <0.3 g/day)	<1.0 g/kg BW/day (consider 0.6–0.8 if eGFR <45 mL/min/1.73m^2 or rapid progression)	30–35 kcal/kg BW/day; increase proportion with LPD
		Advanced CKD (eGFR <30 mL/min/1.73 m^2 or UP ≥0.3 g/day)	0.6–0.8 g/kg BW/day, including 50% HBV protein, or <0.6 with addition of EAA or KA	30–35 kcal/kg BW/day; increase proportion with LPD
JSN [6]	2013	Early CKD with the risk of progression	0.8–1.0 g/kg BW/day	–
		CKD stage 3b–5	0.6–0.8 g/kg BW/day	–

KDIGO Kidney Disease Improving Global Outcomes, *ADA* The American Diabetes Association, *KDOQI* National Kidney Foundation Kidney Disease Outcomes Quality Initiative, *KHA-CARI* Kidney Health Australia-Caring for Australasians with Renal Impairment, *JSN* Japan Society of Nephrology, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *UP* urinary protein, *BMI* body mass index, *HBV* high biologic value, *EAA* essential amino acid, *KA* keto acid, *LPD* low-protein diet

progression (CKD stage 4–5, CKD stage 3 with rapid decline of renal function and/or refractory nephrotic syndrome; 61% ≥65 years of age), the relative risk for mortality of the dietary protein restricted population (0.6 g/kg BW/day) was significantly lower than that of the dialysis population, and half of the patients with eGFR <15 mL/min/1.73 m^2 lived dialysis-free for at least 2 years [21]. The authors also mentioned that the protein-restricted diet reduces costs. Another study in elderly patients with advanced CKD (age ≥70 years, GFR 5–7 mL/min/1.73 m^2) showed that a supplemented very low-protein diet postponed dialysis treatment and resulted in better survival and lower hospitalization risk than dialysis [22]. These studies required careful nutritional management and/or supplements, but protein restriction was considered to protect against decline in renal function and mortality even in elderly patients with advanced CKD or CKD with a high risk for progression.

Thus, protein intake should be determined individually based on the risk of CKD progression, mortality risk due to underlying disease, comorbidities, and initiation of dialysis.

9.3 Recommended Protein Intake for Elderly People with Sarcopenia and/or Frailty

The prevalence of sarcopenia is higher in patients with CKD and has been associated with the progression of CKD [23, 24]. The International Clinical Practice Guidelines for Sarcopenia recommend that a nutritional (protein) intervention should be combined with a physical activity intervention (Grade: conditional, low certainty of evidence) [9]. Here, we discuss dietary protein intake combined with physical activity intervention.

The RDA of protein is not different between young and elderly people [25, 26]; however, postprandial muscle protein synthesis rates are lower in elderly people than in younger people [27], and a greater amount of protein is needed for muscle synthesis in the elderly than in younger people, especially in cases of sarcopenia and frailty. Table 9.2 lists recommendations for dietary protein intake in elderly people; 1.2 g/kg BW/day is recommended for people with preserved renal function, but more is needed in cases of malnutrition and/or acute or chronic disease [5, 7, 8]. Thus, the recommended protein intake is inconsistent with that for CKD. Some recommendations also mentioned that 0.8 g/kg BW/day was a critical threshold for elderly patients with CKD [7, 8], and the other was 1.2–1.4 g/kg BW/day in any CKD stage with existing or imminent PEW [5]. A nutritional intervention for patients with CKD and sarcopenia and frailty has not been well elucidated; thus, further studies are needed.

Higher protein intake in elderly people is related to cardiovascular disease (CVD) events and CVD mortality. In elderly people with a high risk for CVD, higher protein intake (1.5 g/kg BW/day) is related to higher CVD mortality risk and all-cause mortality risk than protein intake of 1.0–1.5 g/kg BW/day [28]. Higher protein intake is associated with the risk of a CVD event after adjusting for CVD risk factors in the general population [29]. CKD is a CVD risk factor, and higher protein intake in patients with CKD leads to an increased risk for CVD. Higher protein

Table 9.2 Recommendations for dietary protein and energy intake in older or malnourished patients, and patients with complications, with or without CKD

Guideline and recommendation	Year	CKD stage	Protein intake	Energy intake
ESPEN [7]	2014	Older adults with healthy kidneys or with only mild dysfunction	1.0–1.2 g/kg BW/day for healthy older people	–
			1.2–1.5 g/kg BW/day for malnourished or at risk of malnutrition because they have acute or chronic illness	–
		Older adults with severe CKD	0.6–0.8 g/kg BW/day	30 kcal/kg BW/day
PROT-AGE Study Group [8]	2013	Mild CKD, GFR > 60 mL/min/1.73 m^2	1.0–1.2 g/kg BW/day for healthy older adults	–
			1.2–1.5 g/kg BW/day for most older adults with acute or chronic disease	–
			2.0 g/kg BW/day for people with severe illness or injury or with marked malnutrition	–
		Moderate CKD, 30 < GFR < 60 mL/min/1.73 m^2	>0.8 g/kg BW/day is safe, but GFR should be monitored 2×/year	–
		Severe CKD, GFR <30 mL/min/1.73m^2	0.8 g/kg BW/day	–
Kalantar-Zadeh et al. [5]	2017	Any stage with existing or imminent PEW	1.2–1.4 g/kg BW/day; may require >1.5 if hypercatabolic state develops	30–35 kcal/kg BW/day; target higher intake if PEW present or imminent

ESPEN The European Society for Clinical Nutrition and Metabolism, *CKD* chronic kidney disease, *GFR* glomerular filtration rate, *PEW* protein-energy wasting

intake (>1.5 g/kg BW/day) should be avoided in elderly patients with CKD. Furthermore, an increase in eGFR occurs in younger people after high protein intake, but a decline in GFR was reported after short-term high protein intake (1.8 g/kg BW/day) in elderly people, even in those with preserved renal function [30]. Thus, elderly people should avoid excessive protein intake.

9.4 Actual Protein Intake in Elderly People with CKD

Actual protein intake in elderly people with CKD is lower than that in younger people and lower in advanced stages of CKD [31, 32]. Uremic toxins and inflammation associated with the progression of CKD can cause loss of appetite, which

decreases dietary intake, including protein intake [31, 32]. As consuming sufficient energy has a protein-saving effect [33], adequate total dietary intake with enough energy is important in elderly patients with CKD. Monitoring total dietary and energy intake as well as nutrition markers is needed when protein restriction is undertaken, and individual dietary instructions should be adjusted as necessary.

Differences in dietary intake among meals are another important point, and a low intake at breakfast has been reported in adults, including elderly people [34, 35]. Adequate protein intake for muscle protein synthesis is reported to be 25–30 g/meal [8, 35, 36], and consuming adequate protein at every meal should be monitored in elderly patients with CKD.

9.5 Protein Sources

Animal protein contains many branched chain amino acids, e.g., leucine, and has better absorbance than plant protein. Some studies have shown that consuming animal protein results in better muscle protein synthesis than consuming plant protein [37, 38]. Higher animal protein intake has beneficial effects on muscle mass maintenance regardless of physical activity, whereas higher plant protein intake is associated with muscle mass only in physically active adults [39]. The influence of protein source on kidney function has also been studied. Higher nondairy animal protein intake is related to a decline in kidney function and ESRD risk [12]. However, a cohort study in elderly people showed that a rapid decline in kidney function is not related to the protein source [18]. A diet with a higher proportion of protein from plant sources has been associated with lower mortality in middle-aged patients with eGFR <60 mL/min/1.73 m^2 [40]. Thus, animal protein is considered more beneficial than plant protein for muscle protein synthesis, but a possible association between animal protein and kidney function decline has been reported, and plant protein may be effective in reducing mortality in patients with CKD. Further studies on protein sources and amounts for elderly patients with CKD and sarcopenia and/or frailty are needed.

9.6 Conclusion

Protein restriction to prevent CKD progression and the recommended protein intake to prevent or improve sarcopenia and/or frailty are incompatible at this time. CKD progression and mortality risk should be considered in nutritional interventions, including protein and energy intake, but further studies are needed.

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Nutritional Interventions in Dialysis Patients

10

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Abstract

Recently, dialysis patients are often suffering from frailty, protein energy wasting, and sarcopenia. Nutritional intervention is one of the important treatments to these statuses. Japanese Society of Dialysis Therapy published the standard nutrition intake in dialysis patients, which basically indicated the minimum nutritional requirements to avoid the dialysis complication, such as calcification, atherosclerosis, hypotension during dialysis therapy. But, theoretically maximum nutritional intake is much larger than the standard intake. Indeed, 60 kg dialysis patients could take 12.6 g/day at maximum, according to the relationship between body weight increase between dialysis sessions and mortality. Moreover, recent improvement of phosphate binders and dialysis therapy itself enlarged the allowance of nutritional intake. Under these circumstances, more aggressive nutritional intervention had become available for dialysis patients. Nutritional intervention could improve not only protein energy wasting, but also sarcopenia, or frailty itself, because these three concepts measured the same condition that aged patients are fragile from another aspect. Dual intervention (nutritional intervention and exercise intervention) had reported to improve not only nutritional or physical factors, but also quality of life, which indicating that dual intervention could ameliorate frailty itself. Multiple interventions to Frailty including aggressive nutritional intervention are expected to improve the mortality of dialysis patients.

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Keywords
Frailty · Sarcopenia · Protein energy wasting · Hypercatabolism · Counseling Intradialytic

10.1 Introduction

Malnutrition in dialysis patients has been recognized recently by many medical staff. However, we do not have good procedure to improve the nutritional status in present. In theory, recommendation to increase the patients' daily diet intake especially protein and amino acid, may have some beneficial effect on the status in nutrition and physical activity. Daily diet intake is personally influenced by many factors, economy, housemate, and work-life cycle, so it is very difficult to improve the patients' dietary intake in their house. We have some medical preparation to support the patients' nutritional status, but do not have established evidence.

10.2 Concept of Frailty, Sarcopenia, Protein Energy Wasting

Generally speaking, aged population are usually fragile to diseases, such as infection, bone fractures, atherosclerosis diseases and so on, and long periods of hospitalization are often required to fix these diseases, and they are difficult to recover to full condition. But, these conditions are very difficult to measure exactly, while it is easy to recognize these conditions by intuition. To evaluate everything scientifically, it is essential to measure quantitively these things in all scientific fields. The concept and definition of Frailty, sarcopenia, and protein energy wasting had been developed, in order to measure these conditions quantitively. These conditions consisted of three major factors. One is mental or social factor. The concept of Frailty had put stress on this factor [1, 2]. Second is nutrition factor. The concept of protein energy wasting had placed importance on this factor [3]. Third is physical factor. The concept of sarcopenia had focused on this factor [4]. These three concepts had tried to measure quantitively the same condition that the aged population are fragile to diseases, therefore the definition of these three factors overlapped with each other (see Fig. 10.1). If dialysis patients become Frailty condition, they were suffering from poor prognosis [5]. Recently this effect caused by frailty had been confirmed, and this relationship could be observed even in dialysis patients with obesity [6] (see Fig. 10.2). Intervention to single factor had been reported, because the evaluation system itself had been developing. Single intervention to nutritional factor had well established, and had more enough evidences than multiple intervetions. Theoretically, intervention to multiple factors should be more effective to improve the Frailty condition. Recently, new research using multiple interventions to these conditions had been reported.

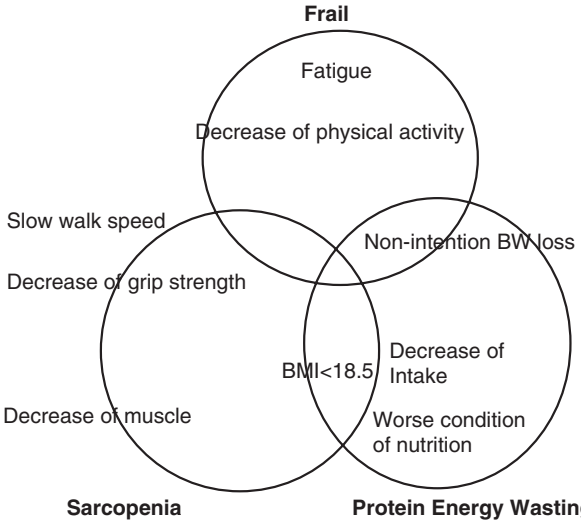

Fig. 10.1 Relationship between frailty, sarcopenia, protein energy wasting. These three concept treated fragility in old patients. These three concepts had overlapped criteria each other, because all of concepts treated same condition from another aspect, Frailty regards mental factor as important one, sarcopenia regards physical factors including muscle condition as important, and protein energy wasting regards nutritional factor as important one

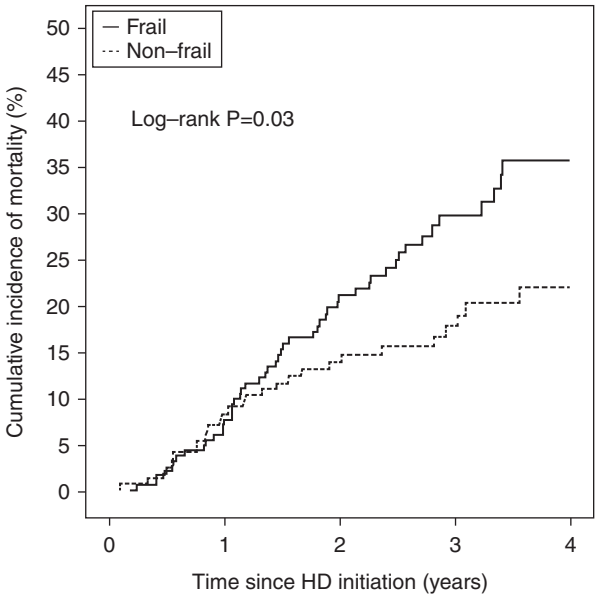

Fig. 10.2 Survival curve in dialysis patients with or without frailty. Dialysis patients with frailty had worse prognosis than those without frailty. This figure is cited from [6]

10.3 Standard Nutrition Intake in Dialysis Patients and Perspective of Dietary Counselling

In dialysis patients, obesity paradox had been well known. On the contrary to the normal subjects, dialysis patients with higher BMI always have better prognosis. This obesity paradox could be observed in dialysis patients with inflammation [7], which might indicate that dialysis patients with higher BMI could survive from many complications. Moreover, dialysis patients who lost their body weight have poor prognosis [8] (Fig. 10.3). Even in dialysis patients with BMI over 30 who gain body weight have good prognosis. On the contrary to the standard nutrition intake for diabetic patients, the aim of standard nutritional intake in dialysis patients is obviously, not to lose or keep body weight. Originally, the aim of standard nutrition intake in dialysis patients is to prevent complications, such as calcification, atherosclerosis diseases, hypotension in dialysis session, hyperparathyroidism, which were often observed only in dialysis patients.

Japanese Society of dialysis therapy published the standard nutrition intake in dialysis in 2014 [9]. This guideline provided standard intake of water, salt, protein, phosphate, potassium, total calorie (see Table 10.1). The standard intake of each component of diet based on the evidences at that points, But, basically this standard provide minimum requirement of each components, because patients usually eat more than target intakes in dietary counselling. But, more intakes should be encouraged, because aged dialysis patients had increased in Japan as well as in the world. The maximum allowance of each component of dietary intake is described in the following paragraphs.

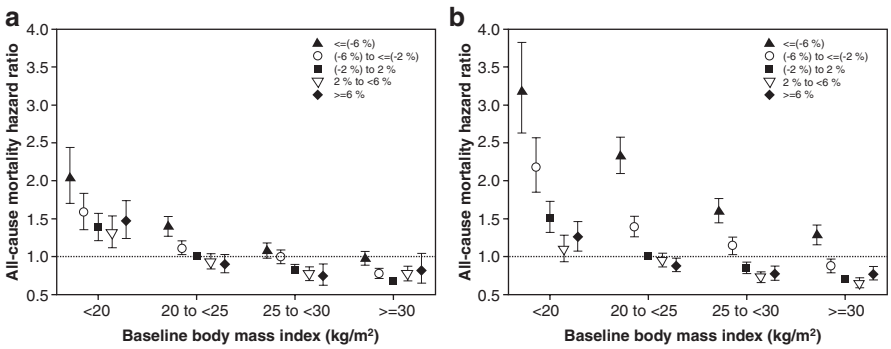

Fig. 10.3 Relationship between body weight change and all cause mortality in dialysis patients. (**a**) Relationship between body weight change between 1 and 5 months and hazard ratio of all-cause mortality Obviously, body weight loss related with worse mortality in each BMI category. Even in dialysis patients with more than 30 BMI, body weight loss related with worse morality. (**b**) Relationship between body weight change between 5 and 12 months a and hazard ratio of all-cause mortality. There were more strong relationship between body weight loss and worse all-cause mortality in each BMI category including dialysis patients even with more than 30 BMI. This figure is cited from [8]

Table 10.1 Standard nutritional intake in hemodialysis patients in Japan

Energy	30–35 kcal/kg[a,b]
Protein	0.9–1.2 g/kg[a]
Salt	<6 g[c]
Water	Minimum requirement
Potassium	<2000 mg
Phosphate	<Protein (g) × 15 mg

This recommendation was published by committee for nutritional factors in Japanese Society of Dialysis Therapy including authors. The original recommendation was written in Nakao T, Kanno Y, Nagasawa Y, Kanazawa Y, Akib T, Sanaka K, et al., Standard nutritional intake in maintained dialysis patients. Journal of Japanese Society of dialysis therapy, 2014. 47(5): p. 287–291. in Japanese language [9]

[a]Standard Body Weight (BMI = 22)

[b]Depending on sex, age, physical activity

[c]Depending on urine volume, physical activity, body weight, nutritional status, increase of body weight between HD sessions

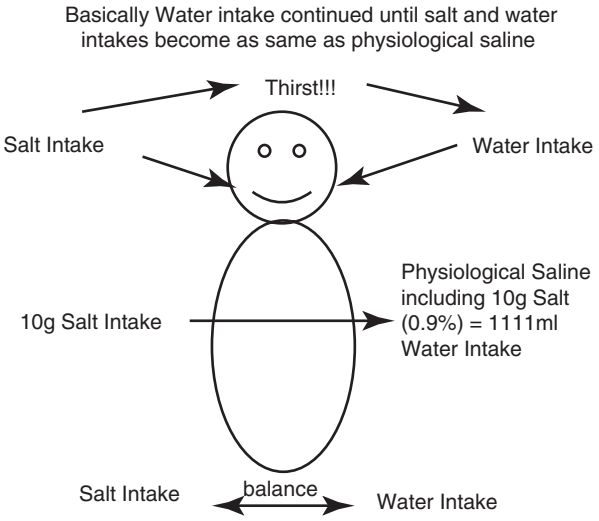

Fig. 10.4 Balance of salt intake and water intake in dialysis patients. Water intake continued until salt and water intake become as same as physiological saline. Therfore, 10 g salt intake induced 1111 mL water intake, resulting in making physiological saline in body. Salt intake should be balanced with water intake by thirst

In dialysis patients, salt intake should be balanced with water intake spontaneously (see Fig. 10.4). When dialysis patients take salt as additional taste of meals, the sodium concentration should go up. In such case, sodium concentration, tending to go up, causes strong thirst via thirst center in brain. This thirst continues until sodium concentration becomes normal, as same as, physiological saline solution (isotonic sodium chloride solution). These phenomena can be also observed in normal population. Those who takes high salt diet, usually feels thirst until the sodium concentration keeps normal. In such case, normal population can excrete the sodium via kidney. But, dialysis patient lose this function, therefore, the sodium intake

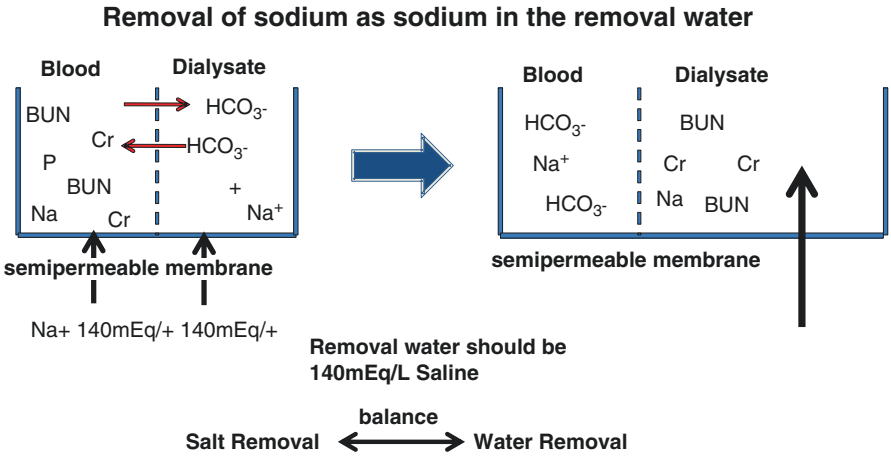

Fig. 10.5 Balance of salt removal and water removal in dialysis patients. Sodium concentration in blood is as same as that in dialysate (140 mEq/L) Therefore, sodium could not basically move through semipermeable membrane. Removal water in dialysis therapy should include sodium as same as physiological saline (140 mEq/L). Salt removal should be balanced with water removal because both water and salt are removed at the same time from body as physiological saline during dialysis therapy

should be completely balanced with water intake via thirst center. 10g sodium chloride intake requires 1111 ml water, resulting in making physiological saline (0.9% sodium chloride solution).

In dialysis patients, salt removal should be also balanced with water removal (see Fig. 10.5). The sodium concentration in dialysate is usually as same as the serum sodium concentration (140 mEq/L), which means that during dialysis sodium could not move to dialysate. During dialysis, water is usually removed. This water includes sodium, whose concentration should be equal to serum sodium concentration. Water and salt are removed at the same time during dialysis process as removal of physiological saline. Therefore, in dialysis patients intake of sodium and water is basically equal to the removal of sodium and water during dialysis session, because they lose kidney function (Fig. 10.6).

Generally speaking, the estimation of sodium intake is very difficult, because precise intake and sodium concentration of each meal are usually unknown. But, the estimation of water intake is very easy, because the volume increase during dialysis interval is equal to the water intake. We can estimate salt intake, using water intake, because salt intake is basically balanced with water intake. Reports of Japanese dialysis patient registry which are provided by Japanese Society of Dialysis Therapy had published the relationship between the increase of body weight during dialysis interval, and mortality at 1 year after. Body weight increase between dialysis interval from 3% to 7% could make good prognosis, according to the relationship between body weight increase and mortality after adjustment of fundamental

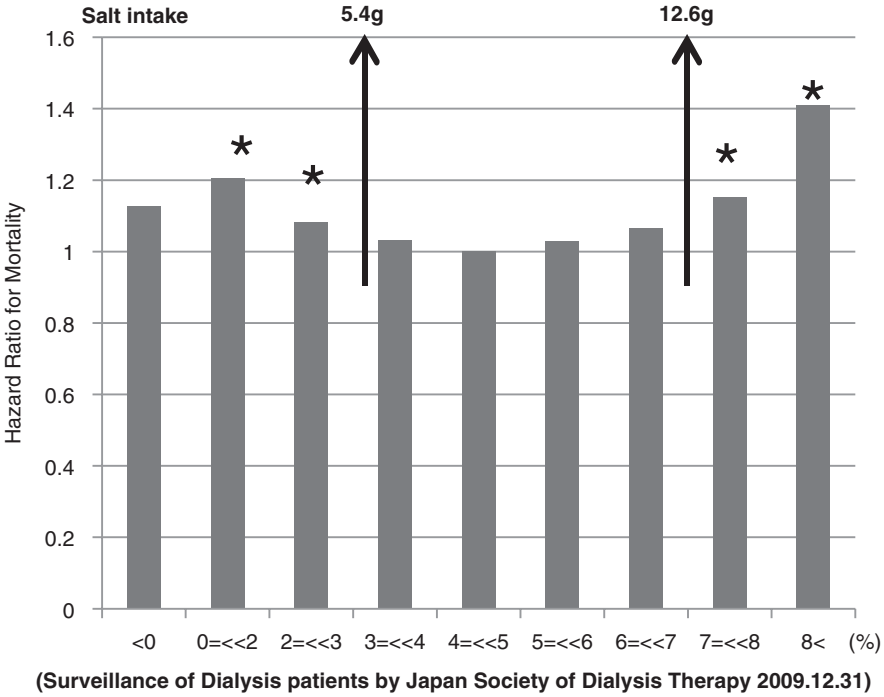

Fig. 10.6 Relationship between body weight increase (%) and mortality after adjustment of fundamental factors, amount of dialysis therapy, nutritional factors. If body weight increase is less than 3%, mortality in dialysis patients became worse. To gain 3% increase of body weight in 60 kg dialysis patient, the patient should at minimum 5.4 g salt/day. If body weight increase is more than 7%, mortality in dialysis patients became worse. To gain 7% increase of body weight in 60 kg dialysis patient, the patient should at maximum 12.6 g salt/day. This calculation can be done, based on the balance between water and salt in dialysis patients. This figure is basically original figure. But, this figure is created using the data in "An overview of regular dialysis treatment in Japan as of Dec 31, 2009" by Japan Society of Dialysis Therapy [10]

factors, amount of dialysis therapy, nutritional factors (see Fig. 10.7). If the body weight of the dialysis patient was 60 kg, 3% body weight increase means 1800 g. 1800 g divided by 3 days equals to 600 g. 600g divided by 1111 mL physiological saline including 10 g sodium chloride means 5.4 g sodium chloride. This calculation means at least around 6 g sodium chloride is essential for 60 kg dialysis patient. On the contrary, in 60 kg dialysis patient, 7% body weight increase means 4200 g. 4200 g divided by 3 days equals to 1400 g. Thousand four hundred grams divided by 1111 mL physiological saline including 10 g sodium chloride means 12.6 g sodium chloride. This calculation means 60 kg dialysis patient can take 12.6 g sodium chloride per day.

There is a pit hall in the method to determine the recommendation of salt intake. The reason why the standard salt intake can be calculated by the increase

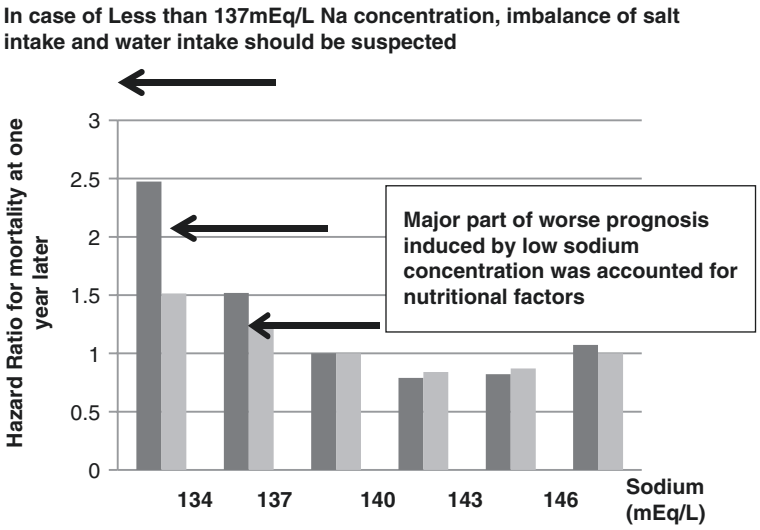

Fig. 10.7 Relationship between pre-dialysis sodium concentration and mortality after adjustment of fundamental factors, amount of dialysis therapy, nutritional factors. If pre-dialysis sodium concentration is less than 137 mEq/L, mortality in dialysis patients became worse. In this case, doctor should pay attention to over-drink rather than salt or too-strict salt restriction. This figure is basically original figure. But, this figure is created using the data in "An overview of regular dialysis treatment in Japan as of Dec 31, 2009" by Japan Society of Dialysis Therapy [10]. Black bar is hazard ratio for the mortality after adjustment using sex, age, cause of ESRD, and dose of dialysis. Light bar is the hazard ratio for mortality after adjustment using nutritional factors addition to those factors

of body weight during hemodialysis interval depends on the thirst. If people drink water without thirst, the standard salt intake recommendation could not make sense. Typical drink without thirst is alcohol drink. If a dialysis patietnt drinks a 350 g bottle of beer every day, this patients drank total 1050 g water during interval of dialysis (3 days), resulting in giving up total 9.4 g salt intake during this periods. If a patients drank two bottles of beer every day, this patients took total 3798 g water during hemodialysis intervals, resulting in giving up 11.3 g salt intake a day, which means that this patient could not eat anything except beer. If the patient really wants to drink alcohol, patient should choose the alcohol drink including high concentration of alcohol, such as whisky without water. In case of sick, patients tend to take some food including much water, such as soup, rice porridge (Okayu), oat meal. These kinds of food also made capacity of salt intake reduced.

In case of hypernatremia, strong thirst induced water drink, resulting in normalization of hypernatremia. This system can work both in normal subjects and in hemodialysis patients. On the contrary, in case of hyponatremia, activation of renin-angiotensin-aldosterone along with inhibition of vasopressin induces

upper-regulation of salt retention in the kidney without water retention, resulting in normalization of hyponatremia. This system can work in normal subjects, but in dialysis patients this system cannot work because their kidney lost its function. Moreover, salt removal in dialysis patients was done by salt in the removal of water during dialysis therapy. The balance between the removal of salt and that of water is basically constant as serum sodium concentrations, like physiological saline. Under hyponatremia condition, thirst could not correct the balance between water intake and salt intake. Therefore, dialysis patients are very easy to become hyponatremia. Japan Society of Dialysis Therapy reported that the pre-dialysis hyponatremia is associated with worse mortality after 1 year (see Fig. 10.6). Hyponatremia itself had been reported to have strong relationship with worse prognosis in several disease conditions [11–14]. If hyponatremia is found in dialysis patients, the balance between water intake and salt intake should be checked. Over-dose of water intake, or over-restriction of salt intake along with relative over-dose of water results in hyponatremia.

Protein and phosphate are usually treated at the same time, because phosphate intake mainly comes from protein. Phosphate intake is in proportion to protein intake. The standard intake of phosphate means this parameter should be automatically satisfied when the protein intake is within the standard intake [15]. In terms of protein, more protein intake until 1.4g/kg/day protein could make dialysis patients more have better prognosis [16]. Basically, limitation of protein intake had aimed for phosphate control, which had been believed to determine the calcification and long survival. Recently, several new phosphate binders had become available. These phosphate binder allow dialysis patients to take more protein than used be. Actually, some phosphate binder had reported to make better survival, which could be accounted for by amelioration of nutrition status [17].

Potassium is obviously one of most important factors which dialysis patients should pay attention for, because high potassium could cause sudden cardiac death. But, Japanese Society for Dialysis Therapy surveillance found until 6.5 mEq/L higher potassium just before dialysis is related with better mortality (see Fig. 10.8). Of course, almost all dialysis patients somehow paid attention to over-intake of diet including high potassium, such as fruits. If no dialysis patients pay attention to potassium, higher potassium before dialysis may be more directly associated with worse mortality. In the meantime, sufficient food intake which increased serum potassium levels ameliorated the dialysis mortality until 6.5 mEeq/L serum potassium before dialysis. Actually, those who ate fruits and vegetables most has reported to have best prognosis [18].

Considering recent conditions of each component of food, more aggressive intake might be encouraged. For the dialysis patients in Frailty and/or sarcopenia and/or protein energy wasting, nutritional intervention using diet including much more nutrition, which should be more attractive and appetizing, may improve the Frailty status, resulting in better prognosis.

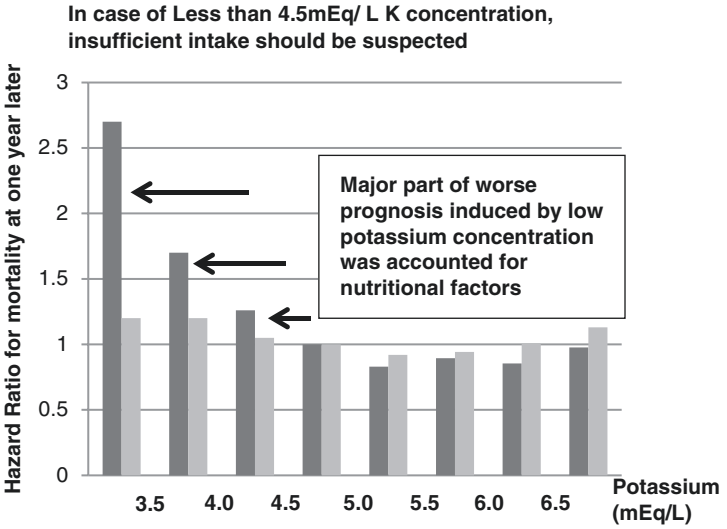

Fig. 10.8 Relationship between pre-dialysis potassium concentration and mortality after adjustment of fundamental factors, amount of dialysis therapy, nutritional factors. If pre-dialysis potassium concentration is <45 mEq/L, mortality in dialysis patients became worse, which can be explained by nutritional factor. If pre-dialysis potassium concentration is less than 5.0 mEq/L until 6.5 mEq/L, mortality in dialysis patients became better, which also can be explained by nutritional factor. This figure is basically original figure. But, this figure is created using the data in "An overview of regular dialysis treatment in Japan as of Dec. 31, 2009" by Japan Society of Dialysis Therapy [10] Black bar is hazard ratio for the mortality after adjustment using sex, age, cause of ESRD and dose of dialysis. Light bar is the hazard ratio for mortality after adjustment using nutritional factors addition to those factors

10.4 Single Interventions to Nutrition in Dialysis Patients

It is well known that dialysis patients are often suffering from protein energy wasting, or malnutrition. Pathogenesis of protein energy wasting in dialysis patient are caused multiple factors, such as reduced protein and energy intake, hypercatabolism, metabolic acidosis, reduced physical activity, reduced anabolism, many complications, and dialysis therapy itself, which may cause inflammatory reaction, loss of amino acids and protein in the dialysate, hypermetabolism related to dialysis [19]. Therefore, many interventions to nutrition in dialysis patients had been tried for a long periods.

Nutritional counseling is one of important and standard intervention to nutrition. At the initiation of dialysis therapy, dialysis patients should change their daily diet for chronic kidney disease G5 stage patients to the diet for dialysis patients. The difference of the diets are relative large, so the supports of nutritionist are essential for dialysis patients. No one doubts the necessity of this support, although it is difficult to evaluate the effect of these supports, because of individual differences and ethical problems.

Oral nutritional supplementation is recommended as the initial step of nutritional support for dialysis patients when dietary counseling is not sufficient to achieve the

enough nutritional requirements. Intradialytic oral nutrition had reported to improve protein homeostasis in dialysis patients [20]. Oral nutritional supplementation can add total calorie and protein intake over spontaneous intake. Moreover, intradialytic intake of protein-rich food or oral nutritional supplementation can be effective in mitigating the catabolism during hemodialysis therapy and in increasing of total protein intake. But, oral nutritional supplementation during dialysis session has a serious disadvantage. When some patients take oral nutritional supplementation during hemodialysis therapy, severe hypotension often occurs because the fluid volume is concentrated in gastro intestinal, resulting in abdominal pain and discontinuation of dialysis session. Diabetic dialysis patients could experience these phenomena more highly than non-diabetic dialysis patients. Therefore, supplementation cannot be often executable.

Intradialytic parenteral nutrition had been suggested by the International Society of Renal Nutrition and Metabolism [21]. It was suggested that a safe intradialytic parenteral nutrition in one dialysis session could include not more than 1 L of fluids, 1000 kcal, and total 50 g of amino acids in a 75 kg hemodialysis patient. Intradialytic parenteral nutrition cannot be considered as long-period nutritional therapy, because there was not enough evidences which support the intradialytic parenteral nutrition can improve mortality or need for hospitalization. After improvement of nutritional status, intradialytic parenteral nutrition should discontinue. If the nutritional status stays in bad condition, total parental nutrition or enteral nutrition should be considered.

Enteral nutrition and total parenteral nutrition should be selected in case of severe protein energy wasting, such as spontaneous intakes less than 20 kcal/day. Enteral nutrition should be always preferred to parenteral nutrition, as far as possible. If dialysis patients were suffering from major swallowing difficulties, nutrition support could be delivered via nasogastric, via naso-jejunal tubes, or via percutenous-endoscopic gastrostomy (PEG). When enteral nutrition support is contraindicated due to severe dysfunction of gastrointestinal tract, total parental nutrition should be applied to the dialysis patients.

There were some possible interventions to the appetite or anorexic conditions. Anorexia had been associated with low plasma concentrations of branched chain amino acids. Theoretically, supplementation of branched chain amino acids may improve nutritional condition in dialysis patients. In fact, it has reported that oral amino acids supplementation improved significantly serum albumin levels in hypoalbuminemic hemodialysis patients [22]. This study demonstrated oral amino acids supplementation improved grip strength, and mental status (SF-12), which may indicate that Frailty in hemodialysis patients was improved. Another report also supported the effect of branched chain amino acids upon serum albumin level, which might be caused by improvement of food intake [23]. More directly appetite stimulant; ghrelin administration enhanced food intake, both in patients receiving peritoneal dialysis and hemodialysis [24, 25]. Low levels of zinc is well known to be related with disorder of taste, resulting in appetite loss. Supplementation of zinc in dialysis patients increased significantly food intake, resulting in marginal significant improvement of serum albumin [26]. Salt intake is also well known to be related with taste and appetite. There is strong possibility that more salt intake than

usual in dialysis patients improved taste and appetite, resulting in improvement of nutritional conditions, which had not been demonstrated in clinical trial.

Recently, new phosphate binders have become available for dialysis patients, such as Lanthanum carbonate, Sucroferric oxyhydroxide, Ferric citrate hydrate. These new phosphate binders made phosphate control in dialysis patients easier than used to be, which might result in better mortality. In fact, Komaba et al. reported that treatment with lanthanum is associated with improved survival in hemodialysis patients, which could be accounted partially by relaxation of dietary phosphate restriction and improved nutritional status [17]. Moreover, secondary hyperparathyroidism has been thought to have relationship with Protein-Energy Wasting in end-stage renal disease, as one of uremic toxins [27]. These new phosphate binders could allow dialysis patients to take more protein intake without high phosphate level.

FrEDI randomized control study demonstrated that high-protein meal with lanthanum carbonate during hemodialysis therapy significantly improved albumin level only in 8 weeks in hypoalbuminuria dialysis patients [28]. In this study, high-protein group were administered as prepared boxes containing meals with 50–55 g of protein, 850 kcal and 0.5–1.5 g of lanthanum carbonate. Patients assigned to the low-protein hemodialysis meal group received prepared boxes containing meals with minimal protein (<1 g), <20 mg phosphorus, and low-caloric (<50 kcal) content, such as salads, during the first 60 min of each hemodialysis. There was no significant phosphate level. Serum albumin level increased significantly in high protein group only after 8 weeks intervention, while there was no albumin change in low protein group. Moreover, creatinine level also significantly increased in high protein group, which might indicate the increase of muscle volume. Serum IL-6 level in high protein group significantly decreased, while no IL-6 change was observed in control group. This study suggested that high protein with new phosphate binders might ameliorate nutritional status in dialysis patients without increase of phosphate level, maybe resulting in the increase of muscle volume and the amelioration of inflammation status.

10.5 Dual Intervention to Frailty (Nutrition Factor and Physical Factor)

Theoretically dual intervention to both nutritional factor and physical factor should be more effective, because frailty consists of nutritional, physical and mental factors. But, the evidences for supporting of efficacy of dual intervention to dialysis patients remained limited, because dual interventions to dialysis patients are more difficult than single nutritional intervention to dialysis patient. One group tried to demonstrate the effect of dual intervention to frailty [29]. In this randomized clinical trial, patients were divided into two groups: a control group that received a can of oral nutritional supplementation during their HD sessions and an intervention group that received same oral nutritional supplementation and underwent a 40-min session of resistance exercise during their HD sessions for 12 weeks. Unfortunately, there were no significant different in nutritional factors. But, some indicator of quality of life such as social function become better significantly in dual intervention group, while there was no difference in

single nutritional intervention group. This result may indicate that dual interventions to nutritional and physical factors might be useful for mental factor. Another group also tried to demonstrate the effect of dual intervention to nutritional and physical factors [30]. More interestingly, this reported demonstrated that combination of intra-dialytic exercise and nutritional supplementation in malnourished older hemodialysis patients ameliorated quality of life factors instead of nutritional factors. This randomized controlled trial investigated the feasibility and the effects of a 6 month intra-dialytic cycling programcombined to a nutritional support on PEW, physical functioning and quality of life in older HD patients (mean age 69.7 ± 14.2 years). Twenty one patients fulfilling diagnostic criteria of PEW were randomly assigned to Nutrition-Exercise group (GN-Ex, $n = 10$) or Nutrition group (GN, $n = 11$). Both groups received nutritional supplements in order to reach recommended protein and energy intake goals. In addition GN-Ex completed a cycling program. No significant difference between groups was found in factors related with PEW. On the contrary, this study found positive effects of exercise on physical function and quality of life for the GN-Ex, as evidenced by a significant improvement in the 6-min walk test, and a noteworthy increase in quality of life scores (+53%) (see Fig. 10.9). Combining intra-dialytic exercise and nutrition in

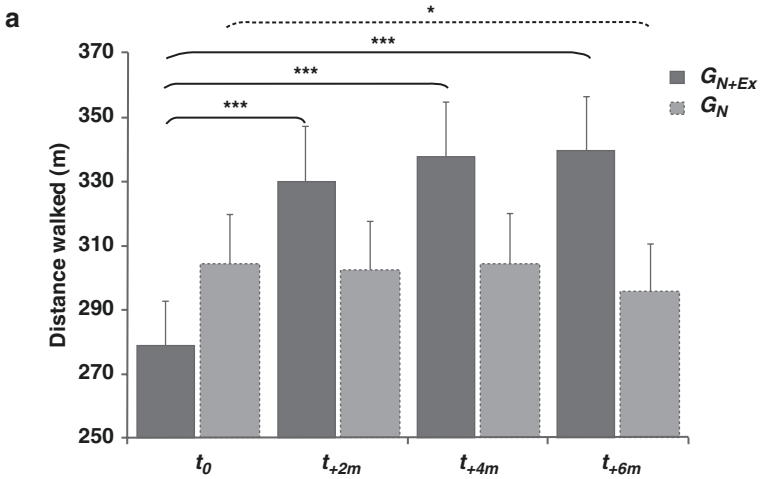

Fig. 10.9 Combination of intra-dialytic exercise and nutritional supplementation in malnourished older hemodialysis patients ameliorated quality of life factors. This randomized controlled trial investigated the feasibility and the effects of a 6 month intra-dialytic cycling program combined to a nutritional support on PEW, physical functioning and quality of life in older HD patients. Twenty one patients fulfilling diagnostic criteria of PEW were randomly assigned to Nutrition-Exercise group (GN-Ex, $n = 10$) or Nutrition group (GN, $n = 11$). Both groups received nutritional supplements in order to reach recommended protein and energy intake goals. In addition GN-Ex completed a cycling program. Improvement of nutritional factors was observed in both groups. (**a**) Evolution of the distance covered during the 6-min walk test throughout 6 months of study. (**b**) Evolution of the SF36 "physical health" score (top) and the "mental health" score (bottom) throughout 6 months of study. $^{*}P < 0.05$, $^{***}P < 0.001$. This figure is cited from [30]

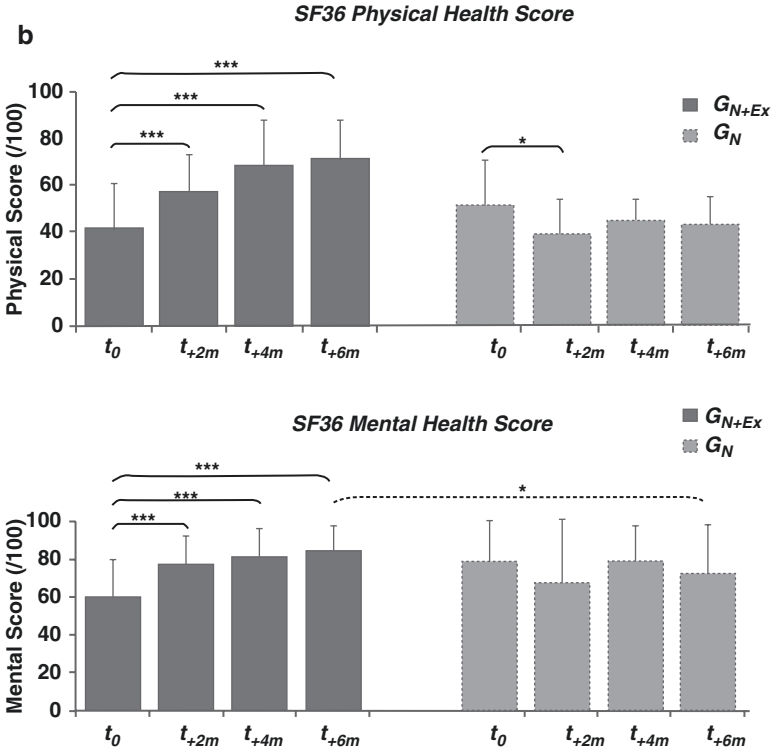

Fig. 10.9 (continued)

HD patients was feasible, and well accepted, and the combination improves physical function and quality of life. It was important that both interventions to nutritional and physical factor improved quality of life score related with mental factors. These multiple intervention might be effective for frailty in dialysis patients.

10.6 Dual Intervention to Frailty (Mental Factor and Physical Factor)

It is difficult to ameliorate mental factor by same intervention, because each person has each personality and social situation. In some countries, one religion is dominant. In this case, religious relaxation might be useful for intervention to mental factor.. Indeed, religious relaxation was reported to be useful for depressive symptoms by randomized control study [31]. Interestingly, Frih et al. reported dual interventions by religions recitation and resistance training has more effective for physical and mental factors than single intervention by resistance training [32]. In this study, 53 male haemodialysis patients were randomly assigned to an intervention group (listening to religious recitation in combination with endurance resistance training, $n = 28$) or a control group (endurance–resistance training only, $n = 25$). Functional

capacity was assessed using the Timed Up and Go test and the Six-Minute Walk Test (6MWT). Psychosocial outcomes were assessed using the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) and Hospital Anxiety and Depression Scale. All measured parameters were significantly improved over baseline in both groups, except for Kt/V in the control group). Moreover, final measurements were significantly higher in the intervention group than in the control group for all measured parameters, except for 6MWT performance and the physical component summary of the SF-36 ($p > 0.05$). In this study, nutritional parameters had not been evaluated, but the superior amelioration of Kt/V in dual intervention group than in single intervention patients might be indicate improvement of protein intake, because pre-dialysis BUN is key factor to determine Kt/V. These studies may indicate multiple interventions including mental factor might be more useful for amelioration of nutritional factor, although the intervention to mental factor is usually very difficult. Mental consulting might be useful as the intervention to mental factor.

10.7 Perspective of Intervention of Nutrition on Dialysis Patients

Recently, dialysis patients become older than used to be. Frailty including protein energy wasting had become urgent and important problem. Nutritional intervention is one of important interventions to the frailty or protein energy wasting. Recent improvement of phosphate binders enlarged protein intake in dialysis patients. Salt intake could be allowed more than many dialysis patients believed. Fruits and vegetables including high potassium also ameliorate prognosis in dialysis patents. More aggressive nutritional intervention using adequate phosphate binders along with intervention to physical and mental factors in dialysis patients might improve not only nutritional factor but also frailty itself in dialysis patients.

10.8 Conclusion

Nutritional intervention could improve not only protein energy wasting, but also sarcopenia, or frailty itself, because these three concepts measured the same condition that aged patients are fragile from another aspect. Dual intervention (nutritional intervention and exercise intervention) had reported to improve not only nutritional or physical factors, but also quality of life, which indicating that dual intervention could ameliorate frailty itself. Multiple interventions to frail including aggressive nutritional intervention are expected to improve the mortality of dialysis patients.

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11 Pharmacological Intervention for Sarcopenia in Chronic Kidney Disease

Kunihiro Sakuma and Akihiko Yamaguchi

Abstract

Sarcopenia, the age-related loss of skeletal muscle mass, is characterized by a deterioration of muscle quantity and quality, leading to a gradual slowing of movement, a decline in strength and power, increased risk of fall-related injury, and often frailty. Chronic kidney disease (CKD) is characterized by the gradual loss of renal function over a period of months to years. CKD is a catabolic state, leading to renal sarcopenia. This chapter focuses on the recent advances of pharmacological approaches for attenuating normal and CKD-induced sarcopenia. A myostatin-inhibiting antibody is the most important candidate to prevent normal sarcopenia in humans, but is needed for time to determine the effect for CKD-induced sarcopenia. Although treatment with ghrelin seems to be applicable for both types of sarcopenia in humans, further validation of this trial is necessary by increasing the sample size, varying the range of doses during treatment, and observing other outcomes. Supplementation with ursolic acid is also an intriguing candidate to combat normal and CKD-induced sarcopenia, although further systematic and fundamental research is needed for this treatment on humans.

Keywords

Sarcopenia · CKD · Myostatin · Ghrelin · Ursolic acid

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11.1 Introduction

Sarcopenia is widely accepted as causing an age-related decline of muscle mass, quality, and strength. In addition, it is often used to describe both the cellular processes (denervation, mitochondrial dysfunction, and inflammatory and hormonal changes) and the outcomes such as decreased muscle strength, mobility, and function; a greater risk of falls; and reduced energy needs. Sarcopenia can be considered "primary" (or age related) when no other cause is evident but aging itself. Primary sarcopenia is especially associated with overall reduction of the physical exercise. Secondary sarcopenia usually occurs when one or more identifiable causes coexist. This condition is a proxy of chronic or acute diseases prevalent in older persons such as diabetes, several types of cachexia (e.g., chronic obstructive pulmonary disease [COPD], cancer cachexia, chronic heart failure, and CKD), stroke, and hip fracture. Von Haeling et al. [1] estimated its prevalence at 5–13% for elderly people aged 60–70 years and 11–50% for those aged 80 years or older.

CKD is characterized by the gradual loss of renal function over a period of months to years. In addition to renal deficiency, CKD is a major risk multiplier in patients with diabetes, hypertension, heart disease, and stroke [2]. The prevalence of CKD varies between 7 and 12% in the general population worldwide and increases with age, affecting more than 30% of people over 65 years of age [3]. CKD is a catabolic state leading to renal sarcopenia, which is characterized by the loss of skeletal muscle strength and physical function [4]. To explain molecular mechanism of CKD-induced sarcopenia, there are many candidates such as the ubiquitin-proteasome system (UPS), caspase-3-mediated apoptosis, autophagy, imbalance between the anabolic insulin/IGF-I and catabolic myostatin signaling pathways, and IL-6 and TNF-a-mediated inflammatory pathways [5]. In contrast, in normal sarcopenic mammalian muscles, there is no apparent evidence for enhancement in several negative regulators such as UPS, calpain, and inflammatory pathway's downstream mediator, NF-κB (nuclear factor-kappaB) [6, 7]. In addition, many recent studies indicated an apparent functional defect of autophagy-dependent signaling in sarcopenic muscle [8–10] different to the activation of this in CKD-induced sarcopenia.

The progression of normal and CKD-induced sarcopenia is effectively prevented by the exercise, in particular, resistance training [11, 12]. Inhibiting myostatin is an important option of attenuating muscle wasting, such as cachexia, and sarcopenia [7]. More recent studies indicated the possible application of new pharmacologic agents such as ursolic acid and fibroblast growth factor 19] to prevent muscle atrophy including CKD model mice [13, 14]. In addition, new intriguing candidate for attenuating CKD has recently emerged [15, 16]. This chapter summarizes the recent strategies for inhibiting normal and CKD-induced sarcopenia.

11.2 Pharmacological Approach

11.2.1 Myostatin Inhibition

Myostatin, a novel member of the transforming growth factor-β superfamily, regulates negative muscle growth [17]. Mutations of myostatin in mice can lead to marked hypertrophy and/or hyperplasia in developmental stage. In addition, mouse skeletal muscles engineered to overexpress the naturally occurring myostatin inhibitor follistatin, or a dominant negative form of main myostatin receptor (ActRIIB) all display similar, if not greater, increases in size [17].

The increased levels of myostatin are widely accepted to lead to muscle wasting including muscle atrophy due to unloading in mice and humans [6] and with severe atrophy in HIV patients. Whether myostatin expression levels increase in sarcopenic muscles have yielded conflicting results [6, 18, 19]. Sarcopenic muscles of mice seem to exhibit the abundant Smad3 (possible myostatin-downstream regulator) but not myostatin [18]. In addition, muscle loading induced more abundant myostatin in satellite cells in type II fibers in older males than in younger males, although myostatin in satellite cells of each muscle fiber is equally expressed regardless of age at baseline [19]. Therefore, it seems that myostatin-dependent signaling is locally activated in sarcopenic mammalian muscles.

Phase 2 humanized mAb against myostatin LY2495655 showed dose-dependent and significant increases in appendicular lean mass at weeks 8 and 16 as compared with placebo after total hip arthroplasty randomized clinical trial of 400 patients [20]. Many researchers have conducted experiments to inhibit myostatin in models of muscle disorders such as cancer cachexia, amyotrophic lateral sclerosis, and Duchenne muscular dystrophy (DMD) [21, 22]. Although several researchers actively try to determine the effect of pharmacological inhibition of myostatin for DMD patients, it is much difficult for obtaining positive effects and few possibilities of clinical application. Indeed, a randomized clinical trial that used the same compound for DMD patients had a trend toward improved muscle mass and performance (6-min walk test) but was stopped early due to nonmuscle side effects (i.e., epistaxis and telangiectasias) [23]. In contrast, several investigators basically examined the effect of inhibiting myostatin to counteract sarcopenia using animals. Lebrasseur et al. [24] showed significantly greater muscle mass and increased performance such as distance to exhaustion and treadmill time in aged mice after treatment with a myostatin inhibitor (PF-354, 24 mg/kg) for 4 weeks. They also observed the decreased levels of phosphorylated Smad3 and Muscle ring-finger protein 1 (MuRF1) in aged muscle after pharmacological myostatin inhibition. In addition, Murphy et al. [22] showed that a lower dose of PF-354 (10 mg/kg) significantly increased the fiber size and in situ force of hindlimb muscle of 21-month-old senescent mice. More recently, Becker et al. [25] conducted a randomized, Phase 2 trial of a myostatin antibody (LY2495655: LY, 315 mg) by subcutaneous injection using worldwide frail elderly aged 75 years or older (the USA, France, Australia, etc.).

At 24 weeks, the LY group significantly increased the least-squares mean change in appendicular lean body mass (LBM) than the placebo group. In addition, treatment with LY for elderly subjects for 24 weeks improved functional characteristics such as stair climbing time and chair rise with arms from the baseline [25]. These lines of evidence clearly highlight the therapeutic potential of the antibody-directed inhibition of myostatin for treating sarcopenia.

In mice and rats with CKD, there is apparent increase in myostatin expression in muscle [26, 27]. There is some report for pharmacological inhibition of myostatin for CKD mice but not those of humans. Subcutaneous injection of an anti-myostatin peptibody into CKD mice reversed the loss of body weight (5–7% increase) and mass of hindlimb muscles such as tibialis anterior, gastrocnemius, extensor digitorum longus, and soleus (~10% increase) [26]. In addition, myostatin inhibition suppressed circulating inflammatory cytokines (interferon-γ [IFNγ], interleukin [IL]-6, tumor necrosis factor-α [TNF-α], macrophage colony-stimulating factor, etc.) and mRNA expression of these cytokines (TNF-α and IL-6) in CKD mice. Furthermore, this treatment enhances the rate of protein synthesis, satellite cell function, and improves IGF-I intracellular signaling [26]. Although the effect of pharmacological myostatin inhibition for CKD was clearly obtained using model mice, there is no clear evidence for CKD human trial by myostatin inhibition. A pilot randomized controlled trial (RCT) study of PINTA 745, an anti-myostatin peptibody, in patients undergoing hemodialysis has completed recruiting, but results are not yet published (www.clinicaltrials.gov NCT01958970). The primary outcome is percentage change in lean mass using Dual-energy X-ray absorptiometry (DXA) after 4 weeks of treatment. To the best of our knowledge, this is the only study in patients with kidney disease. Hopefully, myostatin antagonism will be tested in patients with predialysis CKD in the future.

11.2.2 Anabolic Steroids

In males, levels of testosterone decrease by 1% per year, and those of bioavailable testosterone by 2% per year from age 30 [28]. In women, testosterone levels drop rapidly between the ages of 20 and 45. There is a significant decrease in testosterone level with renal impairment (progressing CKD stage) [29]. The decreased testosterone level in CKD patients had a significant correlation with increased level of sperm cytoplasmic droplets and for total neutral glucosidase activity [29]. Testosterone increases muscle protein synthesis, and its effects on muscle are modulated by several factors including the genetic background, nutrition, and exercise. Systemic reviews [30] have indicated that supplementation with testosterone attenuates some sarcopenic characteristics such as decreases in the grip strength [31] and muscle mass [32]. A study of long-term (6 months) supraphysiological treatment with testosterone in a placebo-controlled study showed increased leg lean body mass and leg and arm strength [33]. Although there are significant increases in strength among elderly males given high doses of testosterone, the potential risks may outweigh the benefits. Thrombotic complication, sleep apnea, and an increased risk of prostate cancer are associated risks with testosterone therapy in older men.

Novel, nonsteroidal compounds, called selective androgen receptor modulators (SARMs), have shown tissue-selective activity and improved pharmacokinetic properties but lower systemic side effects. SARMs have been tested in the healthy elderly patients and in cancer-associated sarcopenia [34, 35]. In fact, improvements in physical function (stair climb speed) and LBM were shown in a Phase 2, double-blind study of enobosarm, a nonsteroidal SARM, in healthy postmenopausal and elderly men [35]. This study showed that only 1 mg of enobosarm increased LBM in advanced cancer patients. In addition, another type of SARM, GSK2881078, was recently investigated in healthy older men and women [36]. Repeated DXA and magnetic resonance imaging cross-sectional thigh scan revealed that treatment with GSK2881078 once daily for 50 days resulted in significant greater lean mass with no serious adverse effects in spite of transient elevations of alanine aminotransferase. Whether these drugs are effective in treating normal and CKD-induced sarcopenia should be determined by further studies with more strict clinical trials.

Using 43 hemodialysis patients, Supasyndh et al. [37] tested a supplementation of oxymetholone, a more mild anabolic steroid, under RCT for a 24-week duration. They observed a significant increase in fat-free mass, subjective scores of physical function, and a grip strength for this treatment. During 24 weeks, these hemodialysis patients exhibited the atrophy of both types I and II muscle fibers and decreased the IGF-I receptor mRNA level under placebo treatment, but these were blocked by treatment with oxymetholone and surprisingly induce hypertrophy of type I fibers. More recently, I found very unique study for this field. Kim et al. [38] determined the effect of oxymetholone (50 mg/kg) for old mice subjected to chronic forced exercise. Chronic annual exercise for 28 days elicited the abundant expression of reactive oxygen species, partially due to downregulation of glutathione, superoxide dismutase, and catalase activity, but it restored these levels at baseline after supplementation with oxymetholone. This treatment elicited the fiber hypertrophy of the gastrocnemius and soleus muscles due to attenuation of the expression of myostatin, sirtuin1, and muscle-atrophy genes [38]. However, there is little report of oxymetholone treatment for sarcopenia or CKD in mice model or humans. Collectively, these facts should be elucidated by many studies to assess benefits versus risks for normal and CKD-induced sarcopenia by treatment with anabolic steroids, androgens, or similar substances.

11.2.3 Ghrelin

Ghrelin, a 28-amino acid peptide, is mainly produced by cells in the intestines, stomach, and hypothalamus. Ghrelin is a natural ligand for the growth hormone (GH)-secretagogue receptor that possesses a unique fatty acid modification. Ghrelin can stimulate GH secretion and modulate energy homeostasis by promoting adiposity and enhancing food intake. In contrast, ghrelin suppresses the production of anorectic proinflammatory cytokines (IL-1β, IL-6, and TNF-α) on T lymphocytes and monocytes [39]. Ghrelin and low-molecular-weight agonists of the ghrelin receptor are considered attractive candidates for the treatment of

cachexia [40]. Nagaya et al. [41] demonstrated that intravenous human ghrelin (2 μg/kg, twice daily, 3 weeks) significantly increased in the lean body mass, hand grip strength, and Karnofsky performance score in patients with chronic obstructive pulmonary disease. In addition, Nagaya et al. [42] demonstrated that similar intravenous treatment with human ghrelin significantly improved several parameters (e.g., lean body mass measured by Dual-energy X-ray Absorption and left ventricular ejection fraction) in patients with chronic heart failure. Pietra et al. [43] demonstrated that oral treatment with anamorelin HCl (ANAM) to rats significantly and dose dependently increased food intake and body weight at all dose levels (3, 10, and 30 mg/kg) compared with the control and significantly increased GH levels at 10 or 30 mg/kg doses. In addition, Phase 3 trials of two types of anamorelin (ROMANA1 and ROMANA2) were conducted in patients with non-small cell lung cancer and cachexia [44]. Twelve weeks of both anamorelin treatments induced significant increases in the LBM but not handgrip strength in these cachectic patients with very low levels of adverse effects. However, a more recent review pointed out that heterogeneity existed in the clinical effects of anamorelin [45]. Intriguingly, such a treatment with ghrelin was tried in elderly people. In a long-term (1 year) placebo-controlled study, an oral ghrelin mimetic (MK-677) was observed to increase an appetite in healthy older adults (over 60 years old), although this study did not show a significant increase in strength or function by the ghrelin mimetic treatment [46]. Anamorelin HCl (ONO-7643) is a potent and selective novel ghrelin receptor agonist that mimics the N-terminal active core of ghrelin [47].

It is possible that unacylated ghrelin (UnAG) lowers several defective symptoms (e.g., oxidative stress), resulting in muscle mass loss. Cappellari et al. [48] determined the effect of treatment with UnAG for 5/6 nephrectomy (Nx) CKD rat model. They demonstrated that UnAG administration (200 μg twice a day) normalizes CKD-induced loss of gastrocnemius muscle mass and a cluster of high tissue mitochondrial reactive oxygen species generation, high proinflammatory cytokines, and low insulin signaling activation. More specifically, UnAG administration ameliorates the downregulation of the amount of activated (phosphorylated) Akt, mammalian target of rapamycin (mTOR), p70 ribosomal protein S6 kinase (p70S6K), GSK3β, and PRAS40 in the muscle of CKD model rats. In addition, 8 weeks' treatment with UnAG (0.1 nmol/g BW) to similar CKD model mice improved all of the declined parameters such as exercise endurance, muscle mass, mitochondrial amount, and the expression of peroxisome proliferator-activated receptor γ coactivator 1 (PGC-1α) [49]. Surprisingly, treatment with ghrelin increased exercise endurance in CKD mice more markedly than those of more popular and general treatment with IGF-I [49]. Very intriguingly, some trial of ghrelin mimetic was conducted using hemodialysis patients. Campbell et al. [50] performed a randomized crossover double-blind study in assessing the effect of MK-0677 versus placebo on IGF-I levels, the primary outcome, in hemodialysis patients (22 subjects, 3-month crossover). Although there is no significant change in many blood parameters such as IL-6, TNF-α, adiponectin, GH, and insulin by treatment with MK-0677, the geometric mean IGF-I blood levels

were 1.76-fold greater following the treatment with ghrelin. Therefore, further validation of this trial is necessary by increasing the sample size, varying the range of doses during treatment, and observing other outcomes.

11.2.4 Ursolic Acid

A pentacyclic triterpenoid, ursolic acid, is the major waxy component in apple peel, and it is also found in many other edible plants. Ursolic acid exerts beneficial effects in animal models of diabetes and hyperlipidemia [51]. Kunkel et al. [52] showed that ursolic acid reduced two skeletal atrophy-inducing models, such as muscle denervation and fasting, by predictive analysis, using connectivity mapping. Under fasting, ursolic acid might increase muscle mass by inhibiting atrophy-promoting muscle gene (atrogin-1 and MuRF1) expression [52]. Chronic administration of ursolic acid for unstressed normal mice with appears to elicit muscle hypertrophy, probably due to the decrease in mRNA expression of atrogin-1 and MuRF1. Ursolic acid may increase skeletal muscle Akt phosphorylation in vivo. Intriguingly, ursolic acid alone was not sufficient to activate the receptor of insulin and IGF-I but done rapidly only by combining with insulin and IGF-I [52]. Thus, ursolic acid's hypertrophy-promoting effect seems to be indirect. Some reports have determined whether the treatment with ursolic acid attenuates sarcopenia in mice. Using 22-month-old mice, Ebert et al. [53] investigated the effect of 0.27% addition of ursolic acid for standard diet to the weight of the body, muscle, or several organs. Although treatment with ursolic acid did not modulate the weight of the body, heart, liver, or epididymal and retroperitoneal fat, this improved the weight of quadriceps, the fiber size of type IIB but not type IIX, grip strength, and specific force. Intriguingly, a subset of the mRNAs repressesd by ursolic acid in aged muscle are positively regulated by activating transcription factor 4 (ATF4) [53]. Thus, it is possible that the attenuating effect of ursolic acid for aged muscle atrophy is modulated via ATF4-dependent signaling. In contrast, using a mouse model of CKD, a long-term (21 days) effect with ursolic acid was verified (oral gavage, 100 mg/kg) [14]. Treatment with ursolic acid has been demonstrated to markedly attenuate CKD-induced muscle atrophy by inhibiting the expression of inflammatory cytokines, such as IL-6 and TNF-α and myostatin, which elicit several muscle-specific ubiquitin ligases (MUSA1, MuRF1, and atrogin-1). In addition, they demonstrated that ursolic acid significantly attenuated the levels of phosphorylation of p38, signal transducer and activator of transcription 3, and NF-κB (p65) in the muscle affected by CKD. However, its hypertrophic effects in humans are less clear. Supplementation with ursolic acid (50 mg/day for loquat leaf extract) did not improve physical performance (balance, 4 m gait speed, and chair-rise ability), muscle mass, and strength (knee extension and handgrip strength) in healthy adults (aged between 19 and 65 years and body mass index ranging from 18.5 to 30.0 kg/m^2) than those who took placebo [54]. In addition, supplementation with ursolic acid (3 g) for resistance-trained men did not modify serum level of insulin and IGF-I and muscle

IGF-I-dependent pathways (IGF-I receptor, Akt, mTOR, and p70S6K) than those adapted to a single bout of resistance training [55]. Further research is needed to elucidate the effect of supplementation with ursolic acid on human skeletal muscle and the attenuation of sarcopenia and CKD.

11.2.5 The Other Candidates

AST-120, a charcoal absorbent, is used in indoxyl sulfate (IS)-targeted therapeutics because it absorbs indole, a precursor of IS, in the gut flora, resulting in a reduced level of IS synthesis in the liver [56]. In CKD mice, the weights of body and several skeletal muscles (tibialis anterior, soleus, and gastrocnemius) were markedly decreased. Compared with sham mice, IL-6 and atrophy-accelerating factors (myostatin and atrogin-1) were significantly enhanced in the skeletal muscle of CKD mice, whereas muscular Akt phosphorylation was decreased [15]. In addition, a reduced exercise capacity was observed for the CKD mice, which was accompanied by an increased muscular autophagy and the decreased expression of muscular PGC-1α and mitochondrial oxidative capacity. An AST-120 treatment (charcoal oral absorbent, 8 w/w% in powder diet) significantly restored these degraded symptoms, including muscle atrophy observed in CKD mice to the sham levels as well as a decrease in IS levels. An L-carnitine (560 mg/kg) or teneligliptin (60 mg/kg) treatment by drinking water also restored them to the sham levels without changing IS levels [15]. There are other reports of AST-120 amelioration for chronic kidney disease in mice model [57, 58]. Intriguingly, treatment with AST-120 for mice subjected to renal failure (RF) significantly downregulated urinary albumin excretion and mRNA expression levels of plasminogen activator inhibitor 1. IS binds to aryl hydrocarbon receptor (AhR), activates cytochrome P450 family 1 subfamily A member 1 (Cyp1a1), and induces vascular inflammation [59]. The skeletal muscle of RF mice, which contained elevated levels of IS, displayed significantly higher Cyp1a1 expression than that of control mice, suggesting that accumulated IS induced Cyp1a1 expression. AST-120 restored Cyp1a1 expression levels in the RF mice to control levels [58].

5-aminolevulinic acid (ALA) is a mitochondria-activating substance, which is synthesized from glycine and succinyl-CoA by the action of ALA synthase in mitochondria. ALA supplementation with sodium ferrous citrate (SFC) has been shown to promote mitochondrial electron transport and increased ATP production [60]. Fujii et al. [16] investigated the effect of supplementation with low- and normal-dose ALA for normal and CKD-induced sarcopenia in mice. Normal dose of ALA (0.03%) significantly increased the grip power and muscle weight in both aged (100 weeks of age) and CKD model 5/6 Nx mice. Surprisingly, low dose of ALA (0.003%) also significantly improved the extent of decrease in running distance in both symptoms probably due to modulation of mitochondrial amount and those of normal dose [16]. The efficacy of ALA on physical performance of elderly women has also been recently reported by Masuki et al. [61]. Since low dose of ALA supplementation is effective for muscle endurance in mice, ALA would be an intriguing candidate for

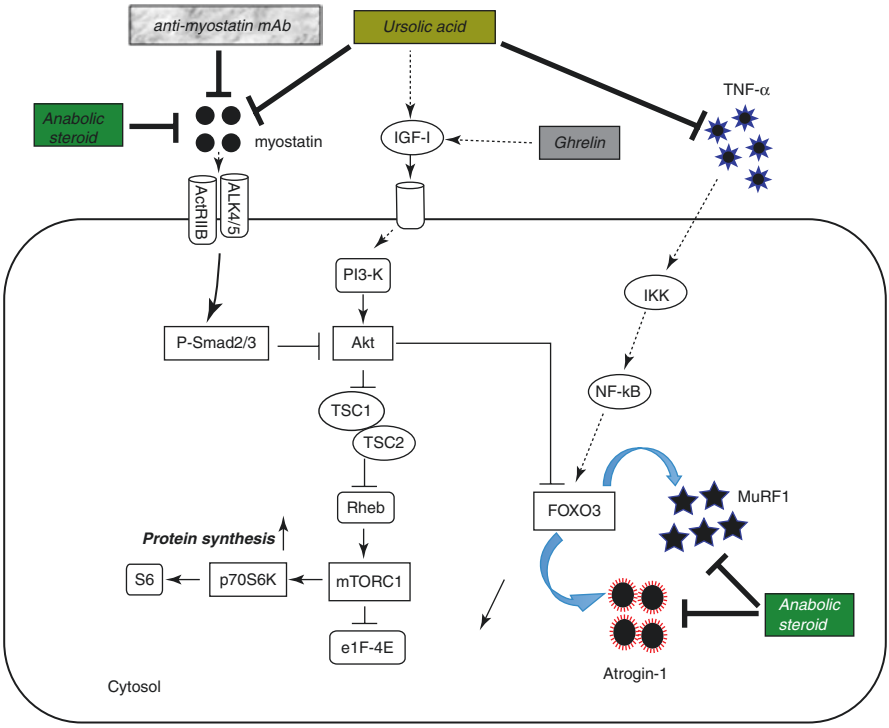

Fig. 11.1 Pharmacological intervention affects different mediators in CKD-induced sarcopenic muscle. Recent findings suggest that the myostatin-Smad pathway inhibits protein synthesis probably due to blocking the functional role of Akt. In animal studies, ursolic acid supplementation blocks the myostatin- and TNF-α-dependent signaling, resulting in the attenuation of muscle atrophy. Treatment with an ursolic acid and ghrelin upregulates the amount of IGF-I and then stimulates protein synthesis by activating the Akt/mTOR/p70S6K pathway. CKD-induced sarcopenic muscle exhibits a marked upregulation of myostatin and several atrogenes, which are effectively ameliorated by anabolic steroids. *ALK* activin receptor-like kinase, *ActRIIB* activin receptor IIB, *IGF-I* insulin-like growth factor I, *TSC* tuberous sclerosis complex, *TORC1* component of TOR signaling complex 1, *Rheb* Ras homolog enriched in brain, *mTORC1* mammalian target of rapamycin complex 1, *eIF4E* eukaryotic initiation factor 4E, p70S6K p70 ribosomal protein S6 kinase, *FOXO* forkhead box O, *TNF-α* tumor necrosis factor-α, *IKK* inhibitor of kB kinase, *NF-κB* nuclear factor-kappaB, *MuRF1* muscle ring-finger protein 1

improving normal and CKD-induced sarcopenia in humans. Figure 11.1 represents an overview of pharmacological interventions for sarcopenia in CKD.

11.3 Conclusion

The recent advances in muscle biology have led to new hopes for hormonal, pharmacological, and nutritional treatment of muscle wasting. In the case of CKD-induced sarcopenia, there are many candidates such as UPS, apoptosis, autophagy,

imbalance between anabolic and catabolic pathway, or inflammatory signaling [5]. In normal sarcopenic mammalian muscles, there is no demonstration for enhancement in UPS, calpain, and inflammatory pathway [6, 7], in spite of an apparent functional defect of autophagy-dependent signaling [8–10]. Although there are several differences in the molecular mechanism between normal and CKD-induced sarcopenia, several candidates (myostatin inhibitor, ghrelin, and ursolic acid) seem to exhibit similar positive effect for both symptoms. Further research is needed to elucidate the effect of these supplementations on these two sarcopenias in humans.

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Conflict of Interest Kunihiro Sakuma and Akihiko Yamaguchi declare that they have no conflict of interest.

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Oral Health Management for the Prevention of Sarcopenia and Frailty

12

Masami Yoshioka

Abstract

Patients with chronic kidney disease (CKD) have a high prevalence of periodontal disease. Periodontal disease is thought to be associated with the progression of CKD through the chronic inflammation burden. CKD patients also have a high risk of tooth loss leading to inadequate occlusion status, which in turn could cause dietary imbalances and a decline in physical activity. Epidemiological studies have suggested that impairment of the functional dentition among older individuals could be a risk factor for protein deficiency and could be associated with sarcopenia and frailty. Functional dentition can be maintained by preventing oral diseases through periodic dental visits and appropriate oral health care. Therefore, oral health management including both professional care and self-care should be recommended for patients with CKD to prevent sarcopenia and frailty.

Keywords

Oral management · Periodontal disease · Tooth loss · Functional dentition · Balanced diet · Protein intake

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12.1 Introduction

Recently, the association between oral health status and sarcopenia/frailty among older individuals has garnered much attention, including a systematic review [1]. Recent reports have suggested that a slight decline in oral function (i.e., oral frailty) might be a risk factor for physical frailty and mortality [2].

Patients with CKD have a high risk of developing dry mouth, dental caries, and periodontitis [3, 4]. Epidemiological studies have suggested that diabetic dialysis patients have fewer teeth and a higher prevalence of periodontitis than the non-diabetic patients [5, 6]. Tooth loss leads to reduced biting force and/or masticatory function, which increases the risk of malnutrition.

Therefore, oral health management to maintain and improve oral hygiene and function is very important for CKD patients. In this chapter, I would like to introduce oral health management for the prevention of sarcopenia and frailty.

12.2 Oral Health Status and CKD

12.2.1 Oral Health Condition in CKD Patients

12.2.1.1 Pre-dialysis Patients

An area of concern in pre-dialysis patients is that CKD is thought to be associated with hyposalivation and increased prevalence and severity of periodontal disease. In a study conducted in stage 4–5 CKD pre-dialysis patients, the secretion rate of stimulated saliva was significantly lower in patients with CKD compared with control subjects [3]. In another cross-sectional study conducted on patients with different kinds of kidney disease at the pre-dialysis stage, it was revealed that patients with diabetic nephropathy had more dental caries and lower salivary flow than other CKD patients [4].

A cross-sectional study conducted in more than 5000 community residents showed that initial/severe periodontal disease was associated with a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 compared with the GFR of patients with healthy gingiva or gingivitis after adjustment for important risk factors for CKD [7]. Brawski et al. reported that the severity of periodontal disease in pre-dialysis patients with stage 2–5 CKD was higher than that of the general population [8].

Fisher et al. investigated an association between a moderate to severe decrease in kidney function (GFR: 15–59 mL/min/1.73 m^2) and periodontal disease in the Third National Health and Nutrition Examination Survey (NHANES III) [9]. They found that adults with periodontal disease or edentulous adults were twice as likely to have CKD after simultaneously adjusting for other traditional and nontraditional risk factors such as socioeconomic status, health status, and health behavior [9].

Recently, Nylund et al. demonstrated findings obtained from a longitudinal clinical study (follow-up time ranged from 20 to 157 months) which aimed to compare oral health at the pre-dialysis (baseline) and post-transplantation (follow-up) stages

[10]. This study also aimed to investigate differences in oral health between patients with diabetic nephropathy and those with other kidney diseases at follow-up [10]. They found that patients often had more calculus and deep periodontal pockets at the pre-dialysis stage, and that salivary flow rate was significantly higher compared with follow-up. Additionally, it was revealed that diabetic nephropathy patients often had more Candida growth, more plaque, used more drugs, and had lower stimulated salivary flow than patients with other kidney diseases [10]. In conclusion, oral health was better at follow-up than at the pre-dialysis stage; hence, they emphasized the importance of treating oral infectious foci at the pre-dialysis stage to prevent adverse outcomes after kidney transplantation [10].

12.2.1.2 Patients on Dialysis

Patients on dialysis often have a dry mouth because of water-intake restrictions and/or salivary gland hypofunction, a frequent side effect of medication. Because saliva washes out the oral cavity, hyposalivation causes accumulation of debris, increasing the risk of oral infectious diseases. Dry mouth also causes speech and swallowing problems, oral pain and burning, and denture fitting problems. Oral symptoms such as dysgeusia and mucosal petechia/ecchymosis are also reported in patients on dialysis. A systematic review concerning the prevalence and severity of oral disease in patients with CKD demonstrated that the rate of edentulousness and the number of decayed teeth are higher in patients on dialysis, while the number of filled teeth is lower than that of the general population, which may reflect lower use of dental services [11]. The review also indicated that patients on dialysis have poor oral hygiene and more frequent periodontitis than patients with less severe CKD [11].

12.2.1.3 Diabetic Patients on Dialysis

Diabetic nephropathy is a common primary kidney disease of patients on dialysis. In Japan, more than 30% of patients on dialysis are derived from diabetic nephropathy [12]. Diabetes is a risk factor both for dental caries and periodontal disease [13, 14].

Recently, Almusawi et al. demonstrated that dental caries risk factors (exposed root surfaces, heavy plaque, xerostomia, and cariogenic bacteria in saliva) were significantly associated with fasting blood glucose, salivary glucose, and HbA1c [13]. In that study, they suggested that routine monitoring of dialysis patients for oral health and creating awareness about dental hygiene and healthy dietary habits are important for preventing caries development [13].

Periodontitis is declared as the sixth major complication of diabetes, and diabetes is a risk factor for gingivitis and periodontitis. Conversely, it is known that inflammatory cytokines such as TNF-alpha produced in periodontal lesions cause deterioration of glycemic control [14].

The studies discussed above indicate that the prevalence and severity of dental caries and periodontitis in dialysis patients with diabetes are thought to be higher than those in dialysis patients without diabetes. An epidemiological study that compared diabetic dialysis patients and non-diabetic dialysis patients reported that diabetic dialysis patients had a higher DMFT index (the sum of decayed, missing, or filled

permanent teeth) and a higher prevalence of periodontal disease [5]. A study conducted in Japan found that diabetic dialysis patients had fewer remaining teeth and a higher prevalence of periodontitis compared with non-diabetic dialysis patients [6].

12.2.2 Association Between Oral Health and CKD

12.2.2.1 Possible Effects of Chronic Inflammation in Periodontal Lesions on the Progression of CKD

Akar et al. reviewed the possible contribution of poor oral health to systemic consequences including infectious diseases, atherosclerotic complications, and protein-energy wasting in patients with CKD [15]. They proposed a hypothetical model in which periodontitis acts as a potential cause of local and systemic inflammation via endotoxemia and/or bacteremia [15]. This model is supported by findings in many other studies. A study conducted with dentate hemodialysis patients by Rahmati et al. found that serum levels of IgG against the periodontal pathogen, *Porphyromonas gingivalis,* were correlated with increased C-reactive protein (CRP) levels [16]. Bastos et al. showed that the frequency of *P. gingivalis, Tannerella forsythia*, and *Treponema denticola* in subgingival plaque was higher in periodontitis patients with CKD than in those without CKD [17]. Ismail et al. reported in a review article that moderate to severe periodontitis can contribute to the inflammatory burden by increasing serum CRP levels and may increase the prevalence of atherosclerotic events, and that effective periodontal therapy may decrease serum CRP levels [18].

Several epidemiological studies conducted with older individuals suggested that periodontitis is a risk factor for a deterioration in renal function. Iwasaki et al. reported that elevated serum antibodies to *P. gingivalis* were significantly associated with decreased kidney function (GFR 15–59 ml/min/1.73 m^2) in a community-based cohort of older Japanese people [19]. In another cohort study of older Japanese people, Iwasaki et al. showed that the highest periodontal inflamed surface area (PISA) quartile was significantly associated with a greater cumulative incidence of decreased kidney function than the other three quartiles after adjusting for covariates [20]. Wahid et al. suggested in a review article that patients with CKD had a higher prevalence of periodontal disease compared with the healthy population, while non-surgical periodontal therapy has been shown to decrease the systemic inflammatory burden in patients with CKD, especially those undergoing hemodialysis [21]. Furthermore, several clinical studies support the view that periodontal treatment has a statistically significant positive effect on eGFR [22, 23].

12.2.2.2 Oral Health and Mortality in Hemodialysis Patients

The relationship between oral health and mortality in patients treated with maintenance hemodialysis has been reported in several studies. According to a multinational cohort study by Palmer et al., edentulousness and a high DMFT index were associated with early all-cause mortality, while favorable oral health attitudes (i.e., dental flossing, using mouthwash, brushing teeth daily, spending at least 2 min on oral hygiene daily, changing a toothbrush at least every 3 months, and visiting a

dentist within the past 6 months) were associated with better survival [24]. Several studies reported that moderate to severe periodontitis was significantly associated with a higher risk of death compared with mild and no periodontal disease [25, 26]. Because chronic inflammation in a periodontal lesion is associated with an increased serum CRP concentration and greater intima-media thickness in hemodialysis patients, it is thought that periodontitis may induce a systemic process that exacerbates atherosclerosis [27].

However, one research article refutes the association between periodontitis and increased risk of early death in adults treated with hemodialysis [28]. More interventional clinical studies that evaluate whether periodontal treatment results in decreased all-cause and cardiovascular mortality will be necessary to confirm that association.

12.2.2.3 Possible Effects of the Progression of CKD on the Progression of Periodontitis

Ioannidou et al. demonstrated that patients with CKD had a higher prevalence of moderate periodontitis compared with individuals without CKD using the NHANES III dataset [29]. They observed a significant dose–response association between the prevalence of moderate periodontitis and CKD stage among non-Hispanic Blacks and Mexican-Americans [29]. In an epidemiological study conducted in older Japanese people in Niigata, Yoshihara et al. also demonstrated a significant association between an impairment of renal function and the severity of periodontal disease [30].

A possible mechanism by which CKD induces the progression of periodontal disease is that impaired renal function leads to osteoporosis and a consequent increased risk of bone resorption in the periodontium, and that the state of uremia that is accompanied by an altered immune system results in a decreased host response to the subgingival gram-negative microbial challenge [18].

A systematic review and meta-analysis of observational studies published recently showed much substantial evidence that supports an association between periodontitis and CKD [31]. However, it also noted the limitations of the studies and concluded that well-designed prospective studies with longer follow-ups in representative communities are needed to clarify the directional association [31].

However, Deschamps-Lenhardt et al. mentioned in their review article that it is important to identify new modifiable or treatable risk factors for CKD, which is difficult to manage and remains a major cause of mortality and cardiovascular morbidity worldwide [32]. They suggested that periodontitis may be a novel modifiable risk factor and proposed that periodontal screening, through referral to a dentist, should be included in the multidisciplinary management of CKD [32].

12.2.3 Need for Special Care in Oral Health Management of Patients with CKD at Each Stage

As shown in Table 12.1, there are plausible reasons why patients with CKD should receive oral health management appropriate for each stage.

Table 12.1 Reasons why oral health management is especially recommended for patients with chronic kidney disease (CKD)

	Pre-CKD with diabetes	CKD stage (G1–G4)	Dialysis	Kidney transplant
Oral prophylaxis/ dental treatment	Manage high risk of infectious disease including dental caries and periodontal disease	Manage difficulty in dosing renal excretory medication such as antibiotics	Manage difficulty in invasive procedures such as tooth extraction and oral surgery	Manage gingival proliferation as a side effect of immunosuppressants
Infection control of periodontium	Reduce inflammatory cytokines which interfere with glycemic control	Reduce inflammatory cytokines which induce atherosclerosis	Reduce chronic inflammatory burden which affects prognosis	Eliminate the source of infection prior to operation and during administration of immunosuppressant
Food control	Correct eating habits such as overeating and/ or fast eating leading to obesity		Support balanced nutrition intake to prevent protein-energy malnutrition	

In pre-CKD patients with diabetes, inflammation control in the periodontium should be emphasized because of its effects on glycemic control. A functional dentition is also important for dietary therapy of patients with diabetes.

CKD patients with impairment of renal function should be advised of the importance of oral prophylaxis to prevent deep dental caries and severe periodontitis which requires prescribed drugs, because many antibacterial drugs are excreted by the kidneys. Simultaneously, infection control of the periodontium is also crucial for suppressing the inflammatory cytokines that induce atherosclerosis.

Patients with CKD who are medicated with steroids long-term are at high risk of steroidal osteoporosis. To prevent osteoporosis, bone modifying agents (BMAs) such as bisphosphonate are often used. Steroids have an immunosuppressive effect, and the BMA could cause BMA-related osteonecrosis of the jaw. Therefore, care should be taken when undertaking invasive dental procedures in patients with CKD who have a history of steroid and/or BMA use.

Reduction of the chronic inflammatory burden is crucial for patients with end-stage CKD, because it could influence their prognosis. In patients on hemodialysis, bleeding diathesis caused by anticoagulants makes it difficult to perform invasive procedures such as tooth extractions. Therefore, hemodialysis patients should make every effort to prevent dental disease so as to avoid any invasive treatment. Furthermore, to prevent protein energy malnutrition, which is often seen in patients on dialysis, the oral environment should be set up to support a balanced nutritional intake.

In patients who have had a kidney transplant, elimination of any infectious lesions prior to the surgery is vital, and careful infection control is required during administration of immunosuppressants. Additionally, cyclosporin, a traditional immunosuppressant, may cause gum proliferations as an adverse effect.

As described above, all patients with CKD in each stage are at a high risk of oral disease and invasive dental treatment, and oral infection might precede CKD. Therefore, all patients with CKD and their medical doctors and co-medical staff should insist on oral prophylaxis throughout all CKD stages.

12.3 Oral Health Status and Sarcopenia/Frailty

12.3.1 Association Between Oral Health Status and Diet/Nutrition Intake

Several studies have suggested that the number of remaining teeth and the occlusion affect food diversity and protein intake, which could be related to sarcopenia and/or frailty in older people [33–35].

Yoshihara et al. assessed whether tooth loss was related to nutrient intake in older Japanese subjects [35]. They reported that the older group with fewer than 20 teeth consumed less vitamin D and protein, and as food groups, less vegetables and seafood than the control group with 20 or more teeth [35]. Yoshida et al. examined nutritional intake from the point of view of whether the molar occlusion of the natural teeth was retained [34]. They found that the group who had lost molar contact reported significantly lower consumption of vegetables and higher consumption of confectionary (food rich in sugar) than did the group who retained molar contact [34].

Most studies investigating a correlation between oral health status and nutritional status were conducted among community-dwelling older people. Yamasaki et al. investigated an association between oral health conditions and nutritional status in hemodialysis patients [36]. They demonstrated significant correlations between the number of remaining teeth or occlusion status and the normalized protein catabolic rate (nPCR) [36]. This suggested that nPCR could be attributed to the number of remaining natural teeth and the Eichner index (occlusion status) by logistic regression analysis [36]. Because nPCR is an indicator used for monitoring protein intake among dialysis patients, tooth loss and an inadequate occlusion status might lead to decreased protein intake in hemodialysis patients.

Bastos et al. investigated a correlation between serum levels of vitamin D and chronic periodontitis in pre-dialysis CKD patients [37]. They revealed that the serum 25(H)D levels of CKD patients with chronic periodontitis were significantly lower than those of CKD patients without chronic periodontitis [37]. They suggested that vitamin D insufficiency/deficiency could induce chronic periodontitis, because vitamin D has important functions in immune and inflammatory responses [37]. Although vitamin D insufficiency/deficiency is thought to be a risk factor for periodontal disease [38], it is also a risk factor for incident frailty in older women

[39]. Therefore, vitamin D insufficiency/deficiency might be a risk factor common to both periodontitis and frailty in patients with CKD.

12.3.2 Association Between Oral Health Status and Physical Activity

Many epidemiological studies have demonstrated correlations between oral health status (e.g., number of teeth, occlusion status) and physical fitness or body balance. However, most of these studies are cross-sectional studies; therefore, a causal relationship has not yet been fully elucidated.

Okuyama et al. investigated the influence of dental occlusion on physical fitness decline in an 8-year cohort study of community members aged 70 at the baseline [40]. They suggested that partial or complete loss of occlusion was associated with a decline in leg extensor power or a decrease in the one-leg standing time with eyes open, and concluded that maintenance of the dental occlusion could prevent a decrease in the activities of daily life in older people [40]. Moriya et al. found a significant relationship between perceived chewing ability and muscle strength among independent older residents [41]. In a 1-year cohort study conducted in community-dwelling older people, Moriya et al. reported that physical performance such as one-leg standing time with eyes open increased significantly in subjects with improved masticatory ability after dental treatment [42].

Sakai et al. investigated associations between tongue strength and muscle function, nutritional status, and dysphagia among older inpatients of a rehabilitation hospital [43]. They showed that isometric tongue strength was independently associated with grip strength, nutritional status as measured by the Mini Nutritional Assessment-Short Form (MNA-SF), and the functional oral intake scale (FOIS) [43]. These findings suggest that direct interventions, apart from exercise therapy and nutritional therapy, might be effective in dysphagia rehabilitation in older inpatients to maintain and improve tongue strength in association with sarcopenic dysphagia [43].

12.3.3 Association Between Oral Health Status and Sarcopenia/Frailty

The association between oral health status and sarcopenia/frailty among older individuals has been reported in several epidemiological studies.

Tanimoto et al. investigated factors related to sarcopenia in community-dwelling older subjects in Japan [44]. They divided the subjects into three groups—"sarcopenic," "intermediate," or "normal"—using three measurements: appendicular muscle mass (measured by bioelectrical impedance analysis), grip strength, and usual walking speed [44]. They demonstrated that a large population of subjects with sarcopenia had poor masticatory ability and a low dietary variety score

compared with the other two groups among men, and that a large population of subjects with sarcopenia had poor masticatory ability compared with the other two groups among women [44]. Using multiple logistic regression analysis, they showed that age and dietary variety in men, and age and masticatory ability in women, were associated with sarcopenia [44].

Murakami et al. examined the relationship between chewing ability and sarcopenia in Japanese community-dwelling older adults [45]. They showed significant correlations of sarcopenia with age, body mass index, and chewing ability [45]. Because this study was cross-sectional, these findings did not prove the decline in chewing ability to be a cause of sarcopenia. However, they mentioned that it might be meaningful to consider solutions to suppressing sarcopenia in older adults in terms of dentistry in future [45].

Several studies have been conducted concerning the association between oral health status and frailty in terms of denture use and denture fit [46, 47]. Sato et al. evaluated the association of tooth loss, denture use, and self-perceived denture fit with frailty in community-dwelling older Japanese adults [47]. They indicated that tooth loss, the presence of 20 teeth or more, denture non-use, and self-perceived ill-fitting dentures were significantly correlated with frailty by a multivariable logistic regression analysis [47]. Andrade et al. examined the relationship between oral health and frailty in community-dwelling older individuals in Brazil [46]. They found that older individuals with a need for dental prostheses were significantly more likely to be pre-frail or frail, while participants with 20 or more teeth had a lower chance of being frail than edentulous individuals [46]. Interestingly, the use of dental prostheses was not related to being frail [46]. Based on these findings, possessing a functional dentition is a substantial indicator for prevention of frailty.

Horibe et al. performed a comprehensive examination including masticatory function tests (evaluating maximum occlusal force, mixing ability, and self-reported chewing ability) to clarify the association between masticatory function and frailty [48]. They demonstrated that all three masticatory functions were significantly associated with pre-frailty or frailty in community-dwelling older Japanese people [48]. Another 2-year cohort study was conducted with community-dwelling individuals aged 65 years and over, in which Horibe et al. revealed that comfortable walking speed, Self-Rating Depression Scale (SDS) score, Mini-Mental State Examination (MMSE) score, and masticatory function were significantly related to the progression to frailty or pre-frailty [49]. Of the three masticatory function items evaluated, mixing ability and subjective chewing ability were most closely related to frailty progression [49].

Iwasaki et al. examined a longitudinal association between oral function and the development of frailty in community-dwelling older adults in a 5-year prospective cohort study [50, 51]. They showed that poor oral function as indicated by low maximum bite force increased the risk of development of frailty [51], and that a functional dentition (defined by the presence of 20 or more teeth with nine or more occluding pairs of teeth) was significantly associated with a lower risk of frailty [50].

12.4 Oral Frailty

12.4.1 Oral Frailty as a Presage of General Frailty

Oral frailty is a sign of decline in oral function. Oral frailty is an original word proposed by a Japanese research group of the Ministry of Health, Labor and Welfare Project for Health Promotion for the Elderly in FY 2013. Although the definition of the phrase is not fixed, oral frailty is known currently as "a state of weakness in the oral cavity, with the main symptoms of impaired articulation, spilling a little when eating, and increased amounts of unchewable food." Oral frailty often proceeds after tooth loss caused by dental caries and/or periodontal disease, which reflects poor oral health literacy. Therefore, the phrase "oral frailty" is often used as a key word in oral health promotion to prevent a decline in oral function in Japan [52].

The research group named four stages of general frailty in terms of oral health conditions: "pre-frailty," "oral frailty," "sarcopenia/locomotive syndrome," and "frailty." The oral frailty stage is a reversible stage that could transition to the next stage, but could return to the previous stage with appropriate intervention. Therefore, the research group intends to make people conscious of the risk of oral frailty, with the aim of improving self-care for oral function and oral health literacy prior to progression to frailty.

12.4.2 Oral Frailty as a Possible Predictor of General Frailty

Tanaka et al. investigated whether poor oral status can predict physical weakening (physical frailty, sarcopenia, and subsequent disability) among community-dwelling older adults [2]. They revealed that poor oral status as determined by the number of natural teeth, chewing ability, articulatory oral motor skill, tongue pressure, and subjective difficulty in eating and swallowing significantly predicted further physical weakening [2]. When oral frailty was defined as co-existing poor status in three or more of these six measures, oral frailty posed more than twice the risk of physical frailty, sarcopenia, disability, and mortality [2].

Older people with frailty are thought to have poorer oral function compared with robust older people. Watanabe et al. divided community-dwelling older people into three groups (frail, pre-frail, and robust groups) and investigated the relationship between oral function and frailty [53]. They showed that frail older individuals had significantly poorer oral function than pre-frail and robust individuals, and that the risk of frailty was associated with lower occlusal force, masseter muscle thickness, and the oral diadochokinesis rate [53].

12.4.3 A Comprehensive View of the Prevention of Oral Frailty

For older individuals, appropriate oral health is significant in maintaining not only oral function but also quality of life. Rouxel et al. reported that deterioration in oral

health and oral health-related quality of life increased the risk of depressive symptoms among older adults and highlighted the importance of oral health as a determinant of subjective well-being in later life [54]. Major chronic diseases, including CKD and oral disease, have common risk factors such as obesity, diabetes, and tobacco use. Therefore, all health professionals should recognize the importance of oral disease prevention.

Recently, The European College of Gerodontology and the European Geriatric Medicine Society published European Policy Recommendations on Oral Health in Older Adults [55]. The aim of this recommendation was to improve the oral health status of older adults, particularly frail/care-dependent persons, who find it difficult to access professional dental care [55]. Based on the competencies described in these recommendations, they published practical guidelines for physicians to promote oral health in frail older adults [56]. The guidelines mention that all physicians should appreciate the importance of oral health and incorporate an initial oral health screening into routine medical assessment and care [56]. As all patients with CKD are at a high risk of oral health deterioration, the doctor in charge should perform a risk assessment on oral deterioration and refer the patient to a dentist if required [56].

12.5 What Patients with CKD Need to Prevent Sarcopenia/Frailty

12.5.1 Periodic Checkup by a Primary Care Dentist

Periodic dental checkups are thought to reduce tooth loss. According to a position paper entitled "Periodontal maintenance" approved by the Board of Trustees of the American Academy of Periodontology in 2003, tooth loss and periodontal attachment loss are reduced in patients receiving periodic periodontal maintenance when compared with patients not receiving periodic maintenance [57]. Axelsson et al. conducted a 30-year study in a group of carefully monitored subjects who underwent preventive dental treatment on a regular basis and found that the rate of tooth loss and the incidence of caries and periodontal disease were low [58].

At the periodic dental checkup, a patient will receive not only professional mechanical tooth cleaning, but also additional education in self-care focused on proper plaque control measures, including the use of toothbrushes and interdental cleaning devices, according to individual needs. For maintaining dental health, effective plaque control by both daily self-care and professional care is essential. Therefore, improving the quality of self-care is crucial.

In patients with CKD and diabetes, impairment of infection control and wound healing means that periodontal management is more problematic. Patients on hemodialysis need to master proper self-care measures to manage the risk of bleeding derived from the administration of anticoagulants and their compromised condition.

Patients on hemodialysis should be treated with special consideration when undergoing dental treatment. For invasive procedures with a high risk of infection

and bleeding, the dentist must decide on a treatment plan, when to treat, and what medications should be administered prior to and/or after the procedure, based on information about the patient's general condition shared by the patient's medical doctor.

These complicating factors demonstrate why dialysis patients should be encouraged to use a preventive dental service to avoid invasive and risky dental procedures. Despite these circumstances, dialysis patients are less likely to visit a dental office for periodic checkups and are also less likely to be referred to a preventive dentist by a medical practitioner [59, 60].

12.5.2 Review of the Oral Environment and Dietary Habits

To prevent frailty and sarcopenia, a balanced diet and an adequate protein intake are essential. Tooth loss impairs masticatory ability, leading to poorly balanced meals and a lower protein intake [34, 35]. Reduced masticatory ability tends to attract patients towards easy-to-chew foods, and as a result, the amount of fibrous food and/or protein decreases in individuals with missing teeth.

In patients experiencing problems with their food intake because of tooth loss, a tailored dietary intervention together with replacement dentures can positively change dietary behavior [61]. Bradbury et al. performed a randomized controlled trial of the dietary behavior of patients receiving replacement complete dentures through a tailored dietary intervention and revealed that nutrition counseling increased fruit and vegetable intake in the edentulous [61].

12.5.3 Efforts to Maintain Oral Hygiene and Oral Function

The main causes of tooth loss are dental caries and periodontal disease. Plaque control is the most important measure for preventing these diseases. To maintain excellent oral hygiene, both home self-care and professional oral care at regular checkups are necessary. To maintain oral function, a healthy and well-maintained dentition and functional chewing and/or swallowing muscles are necessary. Therefore, to maintain a functional dentition that enables the patient to eat a healthy diet, we need to consider two aspects: oral hygiene and masticatory/swallowing functions.

Older adults are thought to be at high risk of a decline in oral function as a result of muscle weakness and/or decreased reflection function. Therefore, older adults need to expend additional effort to maintain and improve oral function. Table 12.2 shows a range of exercises designed for older adults to maintain and improve oral function. Some exercises are easy to do by themselves, but it should be understood that each movement is designed to strengthen related muscles.

As mentioned in the previous section, a slight decline in oral function may be unnoticed by the patient. At periodic dental examinations, older patients should be assessed for a possible decline in oral function and instructed about functional oral care aimed at maintaining/improving oral function.

Table 12.2 Exercises for maintaining and improving oral function

Facial muscle exercises
Lip stretching
Lip corner stretching
Orbicularis oris muscle stretching
Cheek stretching
Tongue exercises
Tongue stretching (energetically move tongue forward, in a circle and from side to side)
Swallowing exercises
Conscious swallow
Supraglottic swallow
Shaker exercise
Speaking exercises
Pronounce Pa, Ta, Ka, La sounds
Salivary gland massage
Massage the glands softly with fingers

12.5.4 Use of Public Health Services

Castrejon-Pere et al. performed a cross-sectional study to identify associations between oral health conditions and frailty status among older Mexican community-dwelling adults [62]. They found that those who gave a low rating for their oral health and those who did not use dental services had a higher probability of being frail (OR = 3.2, 2.1, respectively) [62]. They concluded that the use of dental services and self-perception of oral health were associated with a higher probability of being frail [62].

In an observational study on factors associated with regular dental visits among hemodialysis patients, the common reasons cited by dialysis patients for not seeking dental care were lack of concern and/or lack of awareness of the importance of preventive dental visits [60]. Because medical practitioners rarely refer dialysis patients for dental care, medical health providers are expected to promote dental visits among dialysis patients [60].

In Japan, an oral function promotion program for pre-frail older adults has been provided as part of community health services by municipalities since 2006. It includes instruction on mouth cleaning, salivary gland massage to stimulate saliva secretion, and facial muscle and tongue exercises to improve swallowing function. Positive effects of the oral function promotion program have already been demonstrated on both objective and subjective oral conditions [63, 64]. This program would be valuable for many older individuals; however, the rate of participation to date has been low.

In a cross-sectional study, Matsushita et al. reported that dry mouth could be an independent determinant of physical pre-frailty among healthy Japanese older adults [65]. The oral function promotion program including salivary gland massage and mouth exercises is a useful measure to improve the condition of salivary hypofunction, and the same activities can be incorporated into daily self-care exercises at

home. These benefits can also be used for CKD patients with dry mouth. In a clinical study conducted with older hemodialysis patients, it was found that long-term (more than 4 weeks) oral functional training including salivary gland massage and tongue movement exercises could increase resting saliva secretion [66].

In Japan, the dental fee for inspection and management of declining oral function was incorporated into medical insurance in April 2018. Hence, elderly individuals can receive medical services to maintain and improve oral function as part of their insured medical treatment in Japan. Because patients with CKD are likely to be frail/sarcopenic and suffering from oral diseases, these oral health promotion services should be actively recommended to achieve improvement in the functional dentition.

As mentioned above, the maintenance of oral health is thought to slow the progression of sarcopenia and frailty by enabling patients to maintain adequate nutrition.

Kamdem et al. demonstrated that self-reported oral pain and chewing impairment had a significant relationship with frailty and its components, not only through a nutritional pathway of involuntary weight loss [67]. Oral pain and difficulty in eating could cause patients to lose the motivation to go out to eat, with a consequent reduction in opportunities for social participation. Frailty stems from not only a physical but also a social and psychological point of view.

12.6 Conclusion

Oral health management in patients with CKD is aimed at infection control to reduce the systemic inflammation burden and support of favorable dietary habits. Oral hygiene and masticatory function should be checked up periodically by a primary care dentist. Medical practitioners and ancillary staff also need to be educated about the importance of preventive dental treatment for patients with CKD. Efforts to maintain oral health are critical components of health literacy of which patients with CKD should be made aware.

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Frailty and Cognitive Impairment in Chronic Kidney Disease

13

Kazuhiko Tsuruya

Abstract

Recently, accumulating evidence has been published on cognitive impairment in patients with chronic kidney disease (CKD). It has been shown that brain atrophy is prominent in patients receiving hemodialysis or peritoneal dialysis, and the significant association between brain atrophy and frequency of rapid decline in blood pressure during the hemodialysis session was documented. Recently, we reported a close association between gray matter atrophy and executive dysfunction in CKD patients, suggesting the importance of preventing brain atrophy for the prevention of cognitive impairment. It has been reported that frailty, a common geriatric syndrome that embodies an elevated risk of catastrophic declines in health and function among older adults, is associated with poor cognitive function, cognitive decline, and dementia in older adults with and without CKD. A number of traditional and nontraditional vascular factors and nonvascular factors are strongly implicated in the pathophysiological relationship among CKD, cognitive decline, and frailty. Several recent randomized controlled trials of elderly individuals without dementia have demonstrated that exercise training improved cognitive function with an increase in brain volume. Experimental studies have shown that exercise decreased the amount of β-amyloid (Aβ) oligomers in addition to depositing Aβ in the brain. Alternatively, some other studies have demonstrated that physical training increases angiogenesis, synaptogenesis, and neurogenesis, especially in hippocampus and in gyrus dentatus and initiates the upregulation of numerous neurotrophic factors such as BDNF and IGF-1 in the brain, especially in hippocampus. Accordingly, physical exercise training should be implemented to prevent and treat frailty and cognitive impairment in the elderly CKD patients.

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Albuminuria · Anemia · Brain atrophy · BDNF · Cognitive impairment · Exercise training · Frailty · Oxidative stress · Renin-angiotensin system · Uremic toxin

13.1 Introduction

Recently, accumulating evidence has been published on cognitive impairment in patients with chronic kidney disease (CKD), especially in patients receiving hemodialysis (HD) and peritoneal dialysis (PD). It has become clear that the prevalence of cognitive impairment is increased in not only dialysis patients, but also in non-dialysis-dependent CKD (NDD-CKD) patients [1, 2]. The symptoms and characteristics of cognitive impairment in patients with CKD are characterized by vascular cognitive impairment, believed to be caused by damaged blood vessels in the brain, or cerebrovascular disease, rather than Alzheimer-type dementia [3, 4]. In this article, I discuss cognitive impairment in CKD patients with regard to brain atrophy, factors associated with cognitive impairment, and the association of dialysis modality with cognitive impairment in the first half of this article, and the association between frailty and cognitive impairment in the second half.

13.2 Cognitive Impairment in CKD Patients

13.2.1 Brain Atrophy in Patients Receiving HD

Dialysis patients have a higher prevalence of brain atrophy, even at younger age, than the general population. This suggests the involvement of a mechanism that cannot be explained only by aging. We previously assessed the extent of brain atrophy in 55 HD patients without clinically overt neurological signs and symptoms, with a mean age of 52 ± 11 (SD) years and a mean HD duration of 7 ± 6 (SD) years and in 35 healthy individuals, with a mean age of 42 ± 14 (SD) years. Brain atrophy was assessed by the ventricular–brain ratio (VBR), calculated as the ratio of the ventricular area to the whole brain area on the maximum MRI slice and compared between the two groups. The severity of periventricular hyperintensity (PVH) and the number of lacunae were also regarded as ischemic brain lesions. The VBRs at all age groups were significantly higher in HD than in controls. The results showed that HD patients had significantly higher number of lacunae and had more advanced PVH than did controls. Both the number of lacunae and the severity of PVH were significantly correlated to VBR in HD. According to these findings, we concluded that the rapid progression of brain atrophy was related to the asymptomatic ischemic brain lesions in our HD patients. Such data indicated that cerebral ischemia might be a causative mechanism of brain atrophy in chronic HD patients (Fig. 13.1) [5].

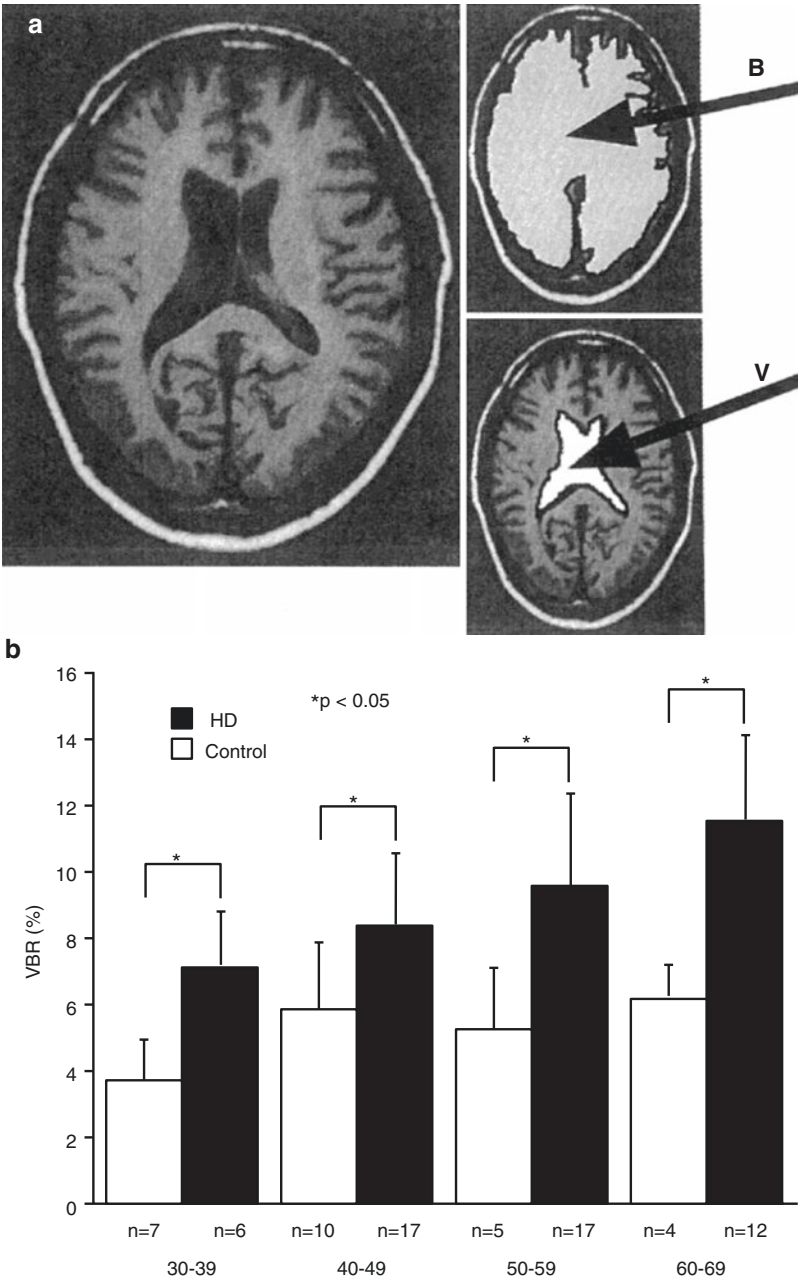

Fig. 13.1 Severe brain atrophy in hemodialysis patients compared to healthy individuals. (**a**) Planimetric outline of the ventricles and brain drawn on to the NIH images. To obtain the VBR, cross-sectional area of the lateral ventricle (V) is divided by the brain cross-sectional area (B). (**b**) VBR size of hemodialysis and controls according to age decades. All mean VBR values are higher in hemodialysis than controls (Student's *t* test, $P < 0.05$). *NIH* national institutes of health, *VBR* ventricular brain ratio. (Reproduced from [5])

It is supposed that hypotension during HD sessions might decrease brain blood flow and induce brain infarction, resulting in brain atrophy. Thus, we examined the role of HD-related hypotension in brain atrophy in patients on chronic HD using MRI. Frontal brain atrophy was assessed by the frontal atrophy index calculated by frontal brain area/intracranial frontal space as described previously [6]. The number of lacunae was also counted. We studied 32 HD patients without symptomatic neurological abnormalities or diabetes mellitus: male/female ratio 19/13; mean age 53 ± 10 (SD) years; and mean HD duration 11 ± 6 (SD) years. All dialysis-related hypotension episodes during the same period were identified from the medical records and counted. The results showed a positive association between the numbers of dialysis-related hypotension episodes, that is, a sudden drop in blood pressure during HD, was arbitrarily defined as a fall in systolic blood pressure >50 mmHg within 30 min of HD, associated with clinical symptoms such as fatigue, clouding of consciousness, muscle cramps, or other symptoms associated with hypoperfusion of the peripheral or central nervous system, identified from the medical records during 3 years with progression of frontal brain atrophy [7]. These results suggest that dialysis-related hypotension plays a role in progressive frontal lobe atrophy in HD patients.

13.2.2 Brain Atrophy in Patients Receiving PD

In patients receiving PD, unlike HD patients, a rapid decline in blood pressure and brain blood flow cannot occur. Therefore, there is a possibility that brain atrophy is less severe in PD patients than HD patients; however, little is known regarding brain atrophy in those patients. Therefore, we examined brain volume and its annual change over 2 years in PD patients. A recent analysis of brain MR images using the statistical parametric mapping (SPM) approach showed that gray matter volume decreases with aging, while white matter volume remains unchanged [8]. We analyzed brain MRI images of patients with NDD-CKD and those of patients undergoing PD using SPM to compare the brain volumes and percentage changes in brain volume between these two groups. T1-weighted magnetic resonance images were analyzed. Total gray matter volume (GMV), total white matter volume (WMV), and cerebrospinal fluid space volume were segmented, and each volume was quantified using statistical parametric mapping software. Normalized GMV (GMV ratio: GMR) and normalized WMV (WMV ratio: WMR) values were calculated by division of GMV and WMV by intracranial volume to adjust for variations in head size. We compared GMR and WMR between PD patients and patients with NDD-CKD in the cross-sectional study and the annual change in GMR between them in the longitudinal study.

An initial cross-sectional analysis in 69 patients with NDD-CKD (mean age 61 ± 10 years, 37 males and 32 females, estimated glomerular filtration rate [eGFR]: 39 ± 12 mL/min/1.73 m^2) and 62 patients undergoing PD (mean age 60 ± 12 years, 41 males and 21 females) with no history of cerebrovascular disease showed a significant inverse correlation between age and GMR, but not

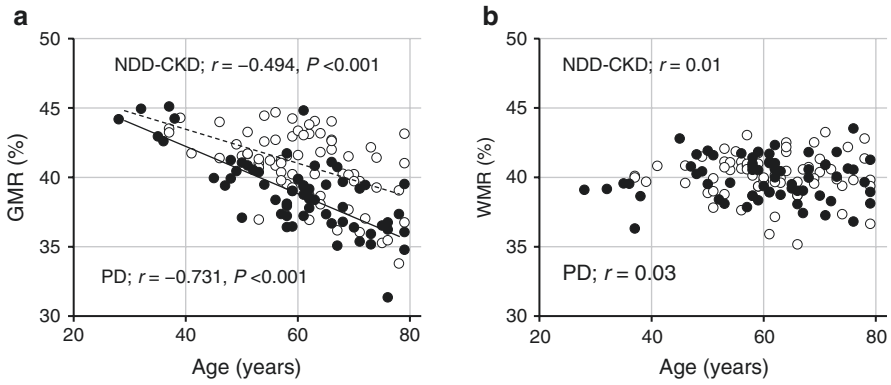

Fig. 13.2 Inverse association of GMR, but not WMR, with age. The association of the GMR and WMR with age in PD (closed circles; $n = 62$) and NDD-CKD patients (open circles; $n = 69$) are shown. GMRs, but not WMRs, are inversely associated with age in PD and NDD-CKD patients. *GMR* gray matter volume ratio, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *PD* peritoneal dialysis, *WMR* white matter volume ratio. (Reproduced from [9])

WMR. In terms of the relationship between GMR and age, the regression line for PD patients was below that of NDD-CKD patients, meaning lower GMR in PD patients in the same age group, and the difference became larger with increasing age (Fig. 13.2) [9].

Next, when the annual change in GMR was compared between 61 NDD-CKD patients (mean age 61 ± 10 [SD] years, 32 males and 29 females, eGFR: 39 ± 12 [SD] mL/min/1.73 m^2) and 34 PD patients (mean age 60 ± 11 [SD] years, 21 males and 13 females) who underwent another brain MRI 2 years later, the least square mean (± SE) of the annual change in GMR was −0.38 ± 0.10% in NDD-CKD and −0.83 ± 0.14% in PD patients, indicating progression of brain atrophy to be faster, that is by a rate of more than twofold, in PD patients (Fig. 13.3) [9]. Given that the GMR in normal individuals decreases with age at a rate of 0.2–0.3%/year, as reported by Taki et al. [8], brain atrophy in PD patients progresses three times faster than that in normal individuals.

13.2.3 Association Between Brain Atrophy and Cognitive Function in CKD Patients

It is well known that cognitive impairment in patients with CKD is characterized by executive dysfunction, rather than memory dysfunction, although the precise mechanism of this remains to be elucidated. The trail making test (TMT) is commonly used to detect any decline in executive function due to frontal lobe dysfunction and yields three measures: TMT-A, TMT-B, and ΔTMT. The TMT-A test uses a dedicated form on which numbers from 1 to 25 are randomly located and measures the amount of time required for subjects to draw a line to connect the numbers in numerical orders. The TMT-B test uses a form on which numbers

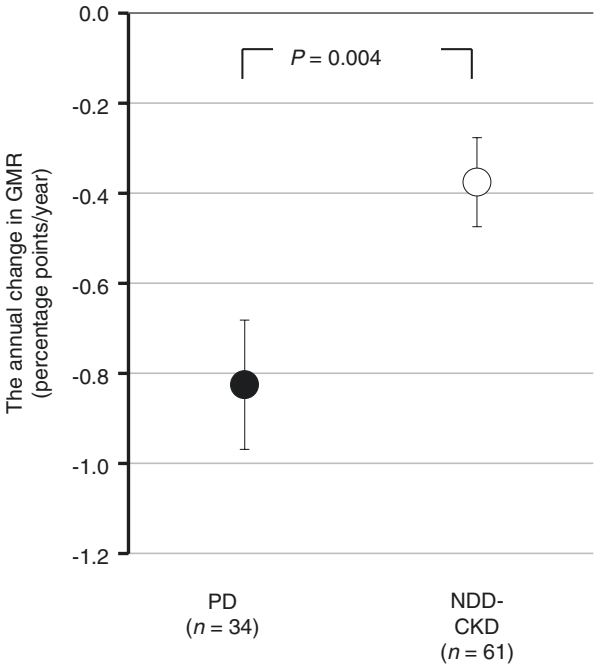

Fig. 13.3 Comparison of the annual change in GMR between PD and NDD-CKD patients. The annual change in GMR as determined by subtraction of the baseline GMR from the GMR after 2 years is significantly higher in PD patients than in NDD-CKD patients. Data are least square mean ± standard error, closed circles: PD patients, open circles: NDD-CKD patients. *GMR* gray matter volume ratio, *NDD-CKD* non-dialysis-dependent chronic kidney disease, *PD* peritoneal dialysis. (Reproduced from [9])

from 1 to 13 and Japanese kana characters from "a" to "shi" are randomly located and measures the amount of time required for subjects to draw a line to connect the numbers (in ascending order) and the kana characters (in the Japanese syllabary order) alternately. Finally, ΔTMT is defined as the difference between TMT-B and TMT-A.

Few reports are available regarding the relationship between brain atrophy and cognitive function. Thus, we performed brain MRI as well as conducting the TMT on 95 NDD-CKD patients with no history of cerebrovascular disease and assessed the correlation between GMR and TMT using multivariable regression analysis. The results showed that GMR was significantly inversely correlated to the scores of TMT-A, TMT-B, and ΔTMT. These correlations remained significant even after adjustment for confounding factors including age, sex, diabetes, eGFR, educational level, systolic blood pressure, smoking/drinking habits, hemoglobin level, history of cardiovascular disease, and urinary protein excretion (Table 13.1) [10].

We stratified the participants by eGFR (<45 vs. ≥45 mL/min/1.73 m^2) and examined the associations between GMR and TMT scores. Then, multivariable associations were observed in participants with eGFR <45 mL/min/1.73 m^2, but not in participants with eGFR ≥45 mL/min/1.73 m^2. According to this finding, it is considered that the correlation of brain atrophy with executive dysfunction is more robust in patients with severe renal dysfunction. Furthermore, when stratified by age (<65 vs. ≥65 years), multivariable associations were observed in participants ≥65 years, but not in participants <65 years. We suppose that the smaller GMR (more severe

Table 13.1 Univariable and multivariable-adjusted regression analyses of correlation between whole-brain GMR and TMT scores in all participants

		TMT-A	TMT-B	ΔTMT
Univariable analysis	*Standardized β*	−0.490	−0.516	−0.476
	P	<0.001	<0.001	<0.001
Model I	*Standardized β*	−0.442	−0.467	−0.432
	P	<0.001	<0.001	<0.001
Model II	*Standardized β*	−0.394	−0.423	−0.393
	P	0.002	<0.001	0.003
Model III	*Standardized β*	−0.349	−0.362	−0.332
	P	0.012	0.006	0.013

GMR gray matter volume ratio, *TMT* trail making test
Model I: Multivariable analysis adjusted for sex and age. Model II: Model I + diabetes mellitus, estimated glomerular filtration rate, and education. Model III: Model II + systolic blood pressure, smoking habits, drinking habits, hemoglobin, previous history of cardiovascular disease, and log-transformed urinary protein to creatinine ratio

brain atrophy) and the higher TMT scores (more severe executive dysfunction) in the elderly compared with younger participants might attribute to the more robust association between them in the elderly probably due to the threshold effect reported in the neuropsychological correlates of white matter lesions in healthy elderly subjects [11].

We then divided the brain into four regions, that is, the frontal, temporal, parietal, and occipital lobes, and examined whether GMR correlated with TMT-A, TMT-B, and/or ΔTMT in each of these regions. Interestingly, significant inverse correlations were observed after multivariable adjustment in the frontal and temporal lobes, but not in the parietal and occipital lobes [10]. These findings suggested that atrophy of the frontal and temporal lobes affects frontal lobe function (i.e., executive function), which was consistent with our hypothesis.

13.2.4 Factors Associated with Cognitive Impairment

Although the mechanisms by which CKD leads to cognitive and functional decline are still not fully elucidated, various factors are believed to be involved in the pathogenesis of cognitive impairment in CKD [12], including vascular risk factors, such as cerebrovascular disorder, hypertension, diabetes, dyslipidemia, myocardial infarction, atrial fibrillation, and smoking habits [13, 14] as well as in the general population [15–21].

Nonvascular risk factors such as anemia, albumin, education, level of physical, social, and mentally stimulating activities, and depressive symptoms are also documented to be important risk factors for cognitive impairment and dementia [22–29] and are also frequently present in patients with CKD. Other nontraditional vascular factors and nonvascular factors such as hemostatic and coagulation abnormalities, inflammatory cytokines, oxidative stress, hyperhomocysteinemia,

and hyperparathyroidism [4, 30–33] may also explain the greater risk of cognitive impairment and dementia in individuals with CKD.

13.2.4.1 Anemia

Despite the lack of clinically apparent neurological symptoms or morphological abnormalities, patients with CKD accompanied by anemia present with impairment in cerebral blood flow (CBF) and oxygen metabolism, which is reportedly prominent in the frontal cortex [34–36]. Meanwhile, renal anemia correction with recombinant human erythropoietin (rHuEPO) has been shown to improve brain function. Using the Wechsler Adult Intelligence Scale (WAIS), Temple et al. [37] reported that brain function was significantly improved by correction of anemia with rHuEPO therapy (hemoglobin 5.8 g/dL → 9.3 g/dL) in nine patients of the treatment group, but not in the nine control patients matched with the treatment group for age, educational status, and social class, who did not receive rHuEPO. Grimm et al. [38] measured event-related EEG potentials (P300) of the brain, stimulus-related evoked potentials, in 15 patients undergoing chronic HD and found that anemia correction with rHuEPO therapy from a hematocrit of 22.7%–30.6% significantly decreased P300 peak latency and improved higher brain function (Fig. 13.4). P300 is considered to be potentially associated with intellectual information processing, such as stimulus perception, discrimination, and task execution, whereas its peak latency is an indicator of stimulus evaluation time in intracerebral information processing. P300 latency is reportedly prolonged with aging and neurological diseases, and it is also known to be markedly prolonged particularly in patients with dementia. In addition, P300 latency has been shown to correlate with scores of general

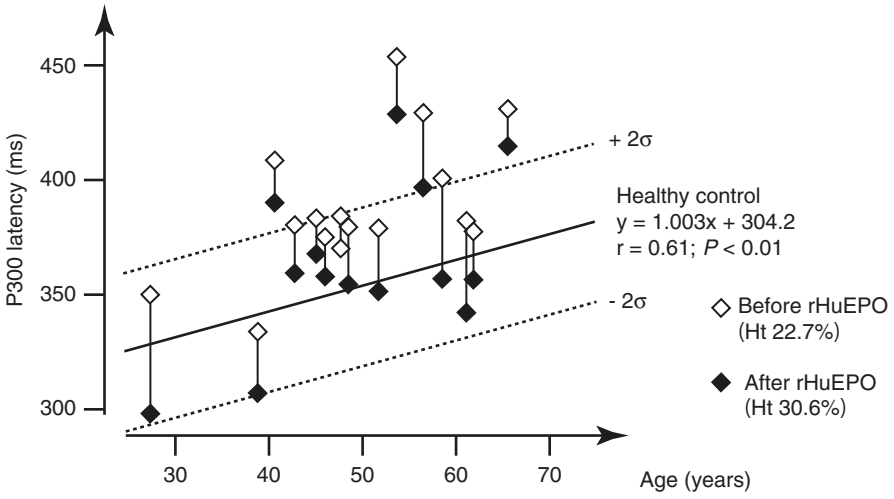

Fig. 13.4 Effect of anemia correction on cognitive impairment evaluated by P300 latency. In 15 patients undergoing chronic hemodialysis, after the start of rHuEPO therapy (4.7 ± 1.2 months), P300 peak latency significantly decreased as anemia was corrected (hematocrit, 22.7% → 30.6%). *rHuEPO* recombinant human erythropoietin. (Reproduced from Ref. [38])

intellectual functioning tests, such as Mini-Mental State Examination (MMSE) and the revised Hasegawa dementia scale, and with CBF. Moreover, although P300 latency is prolonged in some individuals without neurological abnormalities but with almost normal intellectual function, P300 latency may be used to detect early-stage dementia or latent cognitive impairment. These results indicate that anemia makes a reversible contribution to uremic cognitive dysfunction.

13.2.4.2 Albuminuria and Decreased Kidney Function

The relationship between CKD and dementia was investigated in the Hisayama Study. Takae et al. [39] investigated the association between albuminuria and the development of dementia based on the results of a follow-up study in the residents of the town of Hisayama in Fukuoka Prefecture, Japan. Of all the residents ≥60 years of age who underwent the health screening program for elderly residents of the town in 2002, 1562 community-dwelling Japanese subjects aged ≥60 years without dementia were followed up for 10 years, and the association between the urinary albumin/creatinine ratio (UACR) and dementia development was examined using the Cox proportional hazards model. UACR was categorized as normoalbuminuria (UACR <30 mg/g) and albuminuria (UACR ≥30 mg/g), and UACR in the normoalbuminuria range was further divided into the following tertile categories: low-normal (≤6.9 mg/g), medium-normal (7.0–12.7 mg/g), and high-normal (12.8–29.9 mg/g). After multivariable adjustment, the incidence of all-cause dementia rose significantly with increasing UACR, with the hazard ratios for all-cause dementia being 1.12 (95% CI, 0.78–1.60), 1.65 (1.18–2.30), and 1.56 (1.11–2.19) in those with UACR of 7.0–12.7 mg/g, 12.8–29.9 mg/g, and ≥ 30.0 mg/g, respectively, as compared with subjects with UACR of ≤6.9 mg/g. When the outcome was divided by the type of dementia, that is, Alzheimer's disease and vascular dementia, the risk for both types of dementia rose significantly with increasing UACR, with the hazard ratios for the development of Alzheimer's disease being 1.20 (95% CI, 0.77–1.86), 1.75 (1.16–2.64), and 1.58 (1.03–2.41), and the hazard ratios for the development of vascular dementia being 1.03 (0.46–2.29), 1.94 (0.96–3.95), and 2.19 (1.09–4.38) in those with UACR of 7.0–12.7 mg/g, 12.8–29.9 mg/g, and ≥ 30.0 mg/g, respectively, as compared with subjects with UACR of ≤6.9 mg/g. In terms of the relationship between kidney function and dementia, a significant increase in the risk of vascular dementia was observed in patients with an eGFR of <60 mL/min/1.73 m^2, while no such association was observed for Alzheimer's dementia.

13.2.4.3 Oxidative Stress

To elucidate the mechanism of cognitive impairment development in CKD, we conducted the following experiment using 5/6 nephrectomized CKD mice [40]. Working memory performance was tested by the radial arm water maze test. We examined the working memory test and histological examination of mouse brains after 4 and 8 weeks. Next, we investigated the effect of tempol (TMP) against uremia-induced neurodegeneration and oxidative stress in the mouse brain. Eight weeks after CKD induction, vehicle-treated mice made significantly more errors than sham-operated

control mice, while TMP improved working memory performance in CKD mice (Fig. 13.5). CKD was associated with accumulation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) in the hippocampal neuronal cells, but not in TMP-treated CKD mice. The numbers of pyknotic neuronal cells were increased in the hippocampus of CKD mice at 8 weeks, but not in CKD mice treated with TMP. According to these findings, we concluded that uremia is associated with spatial working memory dysfunction in mice and that treatment with TMP protects against cerebral oxidative stress and improves cognitive dysfunction in uremic mice, suggesting their potential usefulness for the treatment of cognitive dysfunction in uremia. These results suggest the involvement of CKD-induced oxidative stress as the primary cause of neuronal cell damage and decreased learning function in CKD.

13.2.4.4 Renin-Angiotensin System

The source of oxidative stress was considered to be uremic toxins, but this remains unclear. Thus, we examined whether the brain renin-angiotensin system was activated in the CKD mouse model, and whether it contributed to cognitive impairment [41]. Errors in the radial arm water maze test were significantly increased in the untreated CKD mice, but were not increased in the CKD mice treated with telmisartan. Tissue brain AII concentrations, accumulation of 8-OHdG and lipid peroxidation in the brain, and the appearance of pyknotic cells were also increased in the untreated CKD mice, but not in the CKD mice treated with telmisartan. These results suggest the involvement of the renin-angiotensin system in oxidative stress production in the brains of CKD mice. It is noteworthy that the dose of telmisartan used in this experiment was comparable to the regular clinical dose. A meta-analysis also demonstrated the inhibitory effect of renin-angiotensin system inhibitors on cognitive impairment associated with Alzheimer's disease or aging in clinical practice [42], suggesting a promising effect of these agents for the prevention of cognitive impairment in CKD.

13.2.4.5 Uremic Toxins

The higher incidence of cognitive impairment in patients with end-stage kidney disease has been attributed to both vascular causes and neurodegenerative causes due to progressive accumulation of uremic toxins [2]. Several studies have attempted to treat cognitive impairment by targeting uremic toxins. Nocturnal daily HD improved CI symptoms, such as psychomotor efficiency, attention, and working memory, in a small longitudinal pilot study [43]. Longer dialysis sessions have also been suggested to improve cognitive function. Ok et al. [44] followed up 247 patients who consented to receive 8-h dialysis therapy three times per week; the control group was matched for age, sex, diabetic status, and dialysis vintage (receiving 4-h dialysis therapy three times per week) for 12 months, and their outcomes, cognitive function, quality of life, and so on, were compared. They reported that the capacity to memorize was significantly improved in patients receiving longer dialysis session length. However, some other studies showed that more intensive dialysis with a more effective clearance of uremic solutes, that is, six times per week, has not been found effective in improving cognitive function [45, 46].

Because serum levels of uremic toxins are remarkably decreased after kidney transplantation [47], it is considered that cognitive function in posttransplant

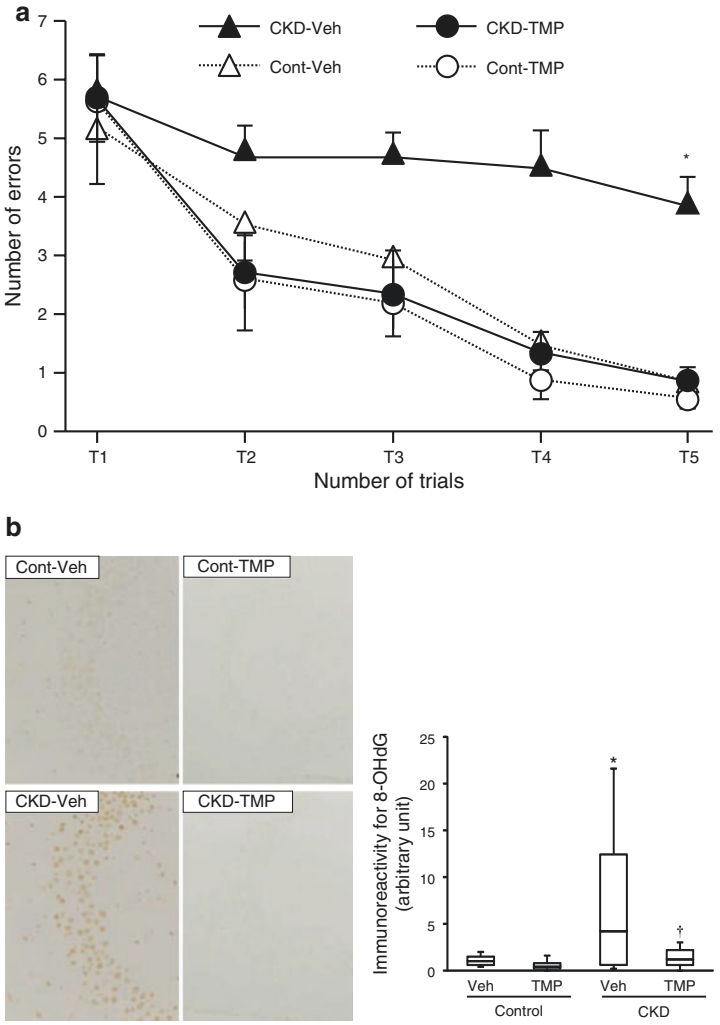

Fig. 13.5 Effect of tempol on prevention of uremia-induced spatial working memory dysfunction and inhibition of 8-OHdG accumulation in the hippocampal CA3 region. (**a**) The numbers of errors during radial arm water maze test on the fifth day in Cont-Veh (white triangle), CKD-Veh (black triangle), Cont-TMP (white circle), and CKD-TMP (black circle) mice are shown. The number of errors in CKD-TMP mice is significantly decreased to levels similar to those observed in control mice, and significantly lower than CKD-Veh mice. The ends of the box represent the upper and lower quartiles; thus, the box spans the interquartile range. The median is marked by a vertical line inside the box. The two lines outside the box that extend to the highest and lowest observations represent the whiskers. $^{*}P < 0.05$ versus the other three groups. (**b**) Effect of TMP on prevention of oxidative DNA damage generation. Representative microphotographs of 8-OHdG immunostaining in the hippocampal CA3 region from each group are shown. Magnification: 200×. Quantitative analysis of 8-OHdG-positive neurons in the hippocampal CA3 region is shown. 8-OHdG immunoreactivity in the hippocampal CA3 region is significantly higher in CKD-Veh mice than TMP-treated CKD mice. The ends of the box represent the upper and lower quartiles; thus, the box spans the interquartile range. The median is marked by a vertical line inside the box. The two lines outside the box that extend to the highest and lowest observations represent the whiskers. $^{*}P < 0.05$ versus Cont-Veh mice. $^{\dagger}P < 0.05$ versus CKD-Veh mice. *CA3* cornu ammonis 3, *CKD* chronic kidney disease, *Cont* control, *8-OHdG* 8-hydroxydeoxyguanosine, *TMP* tempol, *Veh* vehicle. (Reproduced from [40])

patients is superior to that in dialysis patients. Indeed, a significant improvement in cognitive function, including attention, memory, executive functions, the pace of data processing, and language functions, was reported in CKD patients after kidney transplantation [48–55]. Harciarek et al. [49] reported that a kidney transplant was associated with improved neuropsychological performance in patients with end-stage kidney disease. It was reported that the early beneficial effects of transplantation on cognitive function were not transient and were still evident after 1 year following transplantation [49, 50].

13.2.5 Dialysis Modalities and Cognitive Impairment

Association between dialysis modalities and cognitive impairment has also been pointed out. Wolfgram et al. [56] compared the incidence of dementia between 112,960 patients undergoing HD and 8663 patients undergoing PD and reported that the incidence was significantly lower in patients undergoing PD and remained significantly lower even after adjustment in the multivariate analysis, while the significant difference was maintained after propensity score matching. A meta-analysis O'Lone et al. [57] revealed that cognitive function was insignificantly better in patients undergoing PD. Recently, Tian et al. [58] conducted a meta-analysis of 15 cohort or cross-sectional studies, comparing the cognitive functions using neuropsychological tests and covering the executive function, memory, orientation, attention, etc. By qualitative analysis, it showed that more studies are inclined to PD compared with HD with better cognitive functions. By quantitative analysis, PD showed better performance in the tests of MMSE, Montreal Cognitive Assessment (MoCA), and Stroop interference test and exhibited lower risk of dementia compared with HD.

13.3 Association Between Frailty and Cognitive Impairment

Frailty is a common geriatric syndrome that embodies an elevated risk of catastrophic declines in health and function among older adults. This state was initially described and validated by Fried et al. [59] in a geriatric population but is emerging as an important risk factor in patients with CKD.

13.3.1 Non-CKD Patients

Frailty has been associated with poor cognitive function, cognitive decline, and dementia in older adults without kidney disease. Current evidence in the literature from cross-sectional and longitudinal studies has shown relationships between frailty and cognitive disorders.

Recently, several systematic reviews and meta-analyses of observational, cohort, and cross-sectional studies on the association of frailty with cognitive impairment

were performed and reported [60–62]. To analyze the relationship between cognition and frailty in the elderly, Brigola et al. [60] performed a systematic review on the currently existing literature concerning the subject was carried out. A total of 19 studies were selected for review, from which 10 were cross sectional and 9 longitudinal. There was a relationship between components of frailty and the cognitive domains. Risk of mild cognitive impairment (MCI), dementia, and mortality were all evidenced in the relationship between frailty and cognitive impairment. According to the results of the reviewed studies, the authors illustrated a model of association between factors, frailty, cognitive impairment, and their outcomes in older adults in order to better understand the frailty-associated factors (Fig. 13.6). Furtado et al. [61] also performed a systematic review of prospective studies published from 2000 to 2017 to analyze the magnitude of the effect size of the cognitive status of populations over 60 years of age, when comparing nonfrail versus prefrail and nonfrail versus frail subgroups. After applying additional search criteria, 14 studies (26,798 old participants) were selected. When comparing the scores of

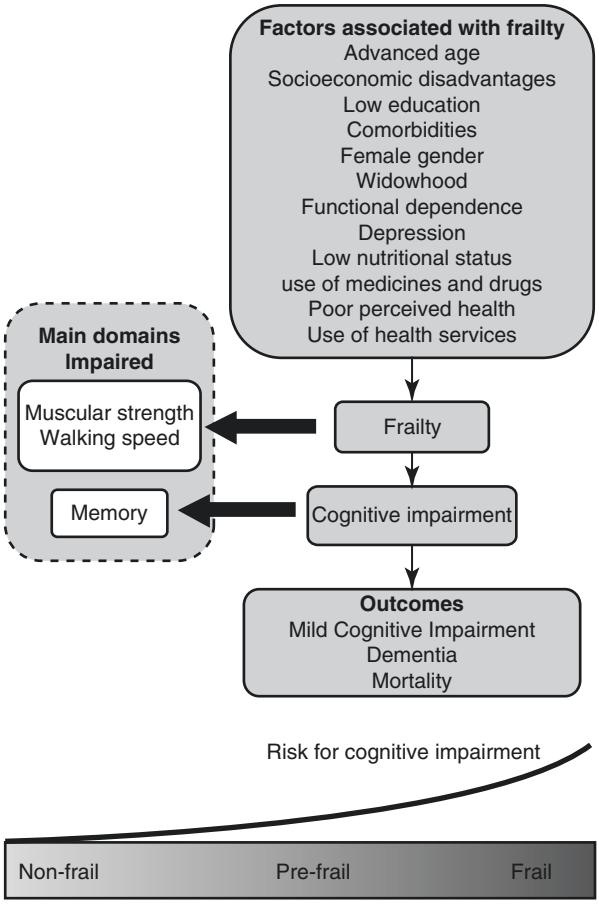

Fig. 13.6 Model of association between factors, frailty, cognitive impairment, and their outcomes in older adults. (Reproduced from Ref. [60])

cognitive status (MMSE score) of the participants who were nonfrail versus prefrail and nonfrail versus frail subgroups, significant statistical differences were found for both comparisons. More recently, Borges et al. [62] examined the risk of cognitive disorders associated with physical frailty in older adults from community-based studies using a systematic review and meta-analysis of cohort and longitudinal studies, which assessed dementia and cognitive impairment as a primary or secondary outcome. The results showed that baseline frailty was significantly associated with an increased risk of geriatric cognitive disorders.

Handgrip strength is an easy, noninvasive, and inexpensive measure of muscle strength in the elderly, which has been reported to be well correlated with the muscle strength of limbs and the human trunk [63, 64]. Weak handgrip strength is a risk factor for disability, morbidity, and mortality and is central to the definitions of sarcopenia and frailty [65, 66]. The measurement of handgrip strength may be especially useful in the context of multimorbidity to identify patients at high risk of adverse outcomes, who may benefit from closer clinical attention [67]. Recently, the association between decline in handgrip strength and development of dementia was examined in the Hisayama Study. Hatabe et al. [68] estimated the risk conferred by a decline in handgrip strength over a 15-year period on the development of dementia using a Cox proportional hazards model. A total of 1055 Japanese community dwellers without dementia aged 60–79 years were followed for 24 years; 835 of them had participated in a health examination in 1973–1974 (mean age, 53 years). The age- and sex-adjusted incidence of total dementia increased significantly with greater decline in handgrip strength. A greater decline in handgrip strength was significantly associated with higher risk of total dementia after adjusting for potential confounding factors; subjects with severely decreased handgrip strength had 1.51-fold increased risk of total dementia compared to those with increased or unchanged handgrip strength.

13.3.2 CKD Patients

The association between frailty and cognitive impairment has also been reported in CKD patients including NDD-CKD and dialysis patients and also in kidney transplant patients [69–75].

13.3.2.1 NDD-CKD Patients

To evaluate the prevalence of MCI and the relationship between MCI and physical function among older adults with predialysis CKD, Otobe et al. [69] conducted a cross-sectional study of 120 patients, aged ≥65 years, with NDD-CKD without dementia. Physical, clinical, and biochemical parameters were compared between normal and MCI patients using the Japanese version of the MoCA-J. Logistic and linear regression analyses showed gait speed was significantly associated with MCI even after adjustment for multivariable covariates. They also conducted a 2-year prospective cohort study enrolling 131 patients ≥65 years with non-dialysis-dependent CKD who were classified into four groups: patients with mild-to-moderate (eGFR

≥30 mL/min per 1.73 m^2) or severe (eGFR <30 mL/min per 1.73 m^2) CKD and high (handgrip strength ≥26 for men and ≥18 kgf for women and gait speed ≥0.8 m/s) or low (handgrip strength <26 for men and <18 kgf for women and/or gait speed <0.8 m/s) physical function [70]. Multivariate logistic regression analysis showed that the combination of severe CKD and low physical function was significantly associated with cognitive decline defined as a %MoCA-J value in the lowest quartile (a %MoCA-J of <92%), although no significant cognitive decline was observed in patients with either severe CKD or low physical function alone.

Coppolino et al. [71] examined the entity of functional, general health and cognitive impairment and the possible relationship between these types of dysfunction and the severity of renal impairment in a series of frail individuals with nonadvanced CKD. Among 2229 geriatric subjects, 271 subjects (162 women and 109 men) were diagnosed as frail and CKD. Cognitive capacities significantly decreased across CKD stages (P for trend <0.0001). In fully adjusted multivariate analyses, cognitive status remained an independent predictor of eGFR ($\beta = 0.465$; $P < 0.0001$). The authors conclude that mild-to-moderate CKD is highly pervasive among frail elderly individuals, and the severity of renal dysfunction is independently correlated with that of cognitive impairment.

13.3.2.2 HD Patients

To investigate whether frailty is associated with poor cognitive function in adults of all ages undergoing HD, McAdams-DeMarco et al. [72] conducted a longitudinal cohort study using 324 adult incident HD patients. At HD initiation, the patients were classified into three groups (frail, intermediately frail, and nonfrail) based on the Fried frailty phenotype, and global cognitive function (modified mini-mental state [3MS]) and speed/attention (TMT-A and TMT-B) were assessed at cohort entry and 1-year follow-up. The results showed that frailty was independently associated with lower cognitive function at cohort entry for all three measures and with worse 3MS at 1-year follow-up. To examine the relationships between patient-reported (subjective) and objective cognitive functioning and everyday functioning of dialysis patients, Song et al. [73] performed a longitudinal observational study in 135 patients who completed a telephone-based neuropsychological battery (Brief Test of Adult Cognition by Telephone, a measure of objective cognitive functioning), subjective cognitive functioning (Patient's Assessment of Own Functioning Inventory), and everyday functioning. Multivariate logistic regression models showed subjective, but not objective, cognitive functioning was a significant predictor of everyday functioning. The authors concluded that the study findings point to the importance of assessing patients' subjective cognitive functioning, not as a stand-alone screening tool, but to optimize clinical assessment and management.

13.3.2.3 PD Patients

The association between frailty and cognitive impairment has not been reported in patients on PD until recently. However, more recently, Yi et al. [74] investigated the prevalence of coexisting frailty and cognitive impairment and its association with clinical outcomes in 784 patients on PD. The authors demonstrated that patients

with cognitive impairment were more than those with frailty (55.5% vs. 27.6%), clinical frailty scale was negatively associated with MoCA score, and coexisting frailty and cognitive impairment decreased patient survival rate and increased peritonitis rate.

13.3.2.4 Kidney Transplant Patients

It is considered that restoration of kidney function after kidney transplant generally improves cognitive function, but it is unclear whether frail recipients achieve such cognitive improvements as same as nonfrail ones. To investigate potential short- and medium-term effects of frailty on posttransplant cognitive trajectories, Chu et al. [75] compared posttransplant cognitive function assessed by 3MS between 100 frail and 565 nonfrail recipients aged ≥18 years old using a mixed effects model with random slope (time) and intercept (person) up to 4 years posttransplant. Although both recipients experienced short-term cognitive improvement up to 3 months, improvements plateaued among nonfrail recipients, whereas cognitive function declined among frail recipients between 1 and 4 years. Finally, cognitive scores were significantly lower for frail recipients compared with nonfrail recipients after 4 years of kidney transplantation.

13.3.3 Mechanism of the Association of Frailty with Cognitive Impairment

A number of traditional and nontraditional vascular factors and nonvascular factors are strongly implicated in the pathophysiological relationship between renal dysfunction and cognitive decline and frailty [76]. When considering the mechanism of the association of frailty with cognitive impairment, it seems better to consider the mechanism of protective influence of physical activity on cognitive impairment. Several possible mechanisms may underlie the protective influence of physical activity on the risk of dementia. Several recent randomized controlled trials (RCTs) of elderly individuals without dementia have demonstrated that exercise training increased brain volume and improved cognitive function [77–79].

Experimental studies using amyloid precursor protein-overexpressing transgenic mice have shown that exercise decreased the amount of β-amyloid (Aβ) oligomers in addition to depositing Aβ in the brain [5, 42, 74]. Liang et al. [80] have also reported that among 69 older adults with normal cognitive function, physically active individuals who met or exceeded the exercise recommended by American Heart Association had significantly lower levels of Aβ deposition measured with positron emission tomography and higher levels of $A\beta_{42}$ in the cerebrospinal fluid compared with inactive individuals who did not meet the recommendation. Alternatively, some other animal studies have demonstrated that physical training increases angiogenesis, synaptogenesis, and neurogenesis,

especially in hippocampus and in gyrus dentatus, and initiates the upregulation of numerous neurotrophic factors in the brain [81, 82], especially in hippocampus [83, 84].

Another important mechanism which explains the effect of physical exercise on cognition includes an endogenous substance which plays a central role in the health status of neurons and called brain-derived neurotrophic factor (BDNF). BDNF is a neurotrophic growth factor that plays an important role in maturation, synaptic connection, neuronal repair, and plasticity of the central nervous system [85, 86]. An increase in BDNF concentrations is associated with an increase in hippocampal size and an improvement in the performance of spatial memory and learning [87]. Insulin-like growth factor-1 (IGF-1) is shown to increase BDNF signaling in response to activity stimulation. Exercise-induced neurogenesis in the rat hippocampus is inhibited following injection of a serum that blocks IGF-1 from leaving the bloodstream and entering the cerebrospinal fluid [88]. IGF-1 also contributes greatly to the exercise-induced effects of BDNF on recall [89]. Neuronal uptake of IGF-1 is stimulated by exercise, and these neurons then show signs of activity and increase their expression of BDNF [90].

13.4 Effect of Exercise on Cognitive Function

13.4.1 Non-CKD Patients

Physical activity has a promising role in delaying cognitive impairment in general population [91]. A lot of clinical studies have shown that exercise intervention has a beneficial role in improving cognition in healthy elderly participants with and without MCI [78, 79, 92–103]. Lautenschlager et al. [103] conducted an RCT of a 24-week physical activity intervention in 138 participants aged 50 years or older who reported memory problems but did not meet criteria for dementia. Participants were randomly allocated to an education and usual care group or to a 24-week home-based program of physical activity. Cognitive function was modestly improved in participants in the intervention group, whereas was deteriorated in the usual care group. Shimada et al. [79] conducted a single-blind RCT in a population-based study of participants and evaluated 945 adults 65 years or older with MCI, enrolled 308, and randomly assigned them to the combined activity group in which subjects underwent weekly 90-min sessions focused on physical and cognitive activities including aerobic exercise, muscle strength training, postural balance retraining, and dual-task training (n = 154) or the health education control group (n = 154) for 40 weeks. Compared with the control group, the combined activity group showed significantly greater scores on the MMSE and Wechsler Memory Scale-Revised-Logical Memory II.

However, several studies [104–107] have reported no improvement in cognitive function by physical exercise. Thus, Cai et al. [108] conducted a meta-analysis and systematic review of RCTs that evaluated the effect of exercise on cognitive function compared with control group for people with chronic diseases (e.g., arthritis, asthma, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, or acquired immunodeficiency syndrome) in 35 studies with 3113 participants. The main analysis revealed a positive overall random effect of exercise intervention on cognitive

function in patients with chronic diseases, and the secondary analysis revealed that aerobic exercise interventions, but not resistance exercise interventions, had a positive effect on cognition in patients with chronic diseases. Northey et al. [109] also performed a systematic review with multilevel meta-analysis of the randomized controlled trials of physical exercise interventions in community-dwelling adults >50 years, with an outcome measure of cognitive function to examine the effects of a multicomponent exercise program on the cognitive function of older adults with amnestic MCI. Analysis of 333 dependent effect sizes from 36 studies showed that physical exercise interventions including aerobic exercise, resistance training, multicomponent training, and tai chi improved cognitive function. Exercise appears to prevent brain atrophy or even increase hippocampal volume in the general population [77, 78]. To examine whether aerobic fitness training of older humans can increase brain volume in regions associated with age-related decline in both brain structure and cognition, Colcombe et al. [77] conducted an RCT in 59 healthy, but sedentary community-dwelling volunteers, aged 60–79 years. Half of the older adults served in the aerobic training group, the other half of the older adults participated in the toning and stretching control group. High spatial resolution estimates of gray and white matter volume, derived from 3D spoiled gradient recalled acquisition MRI images, were collected before and after the 6-month fitness intervention. The results showed that significant increases in brain volume, in both gray and white matter regions, were found as a function of fitness training for the older adults who participated in the aerobic fitness training, but not for the older adults who participated in the stretching and toning (nonaerobic) control group, suggesting that cardiovascular fitness is associated with the sparing of brain tissue in aging humans.

Erickson et al. [78] performed a single-blind RCT in which 120 older adults were randomly assigned to receive either moderate-intensity aerobic exercise 3 day/week or stretching and toning exercises that served as a control. Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1–2 years. Hippocampal volume declined in the control group, but higher physical fitness partially attenuated the decline, suggesting that aerobic exercise training is effective at reversing hippocampal volume loss in late adulthood, which is accompanied by improved memory function. According to these findings, the authors concluded that aerobic exercise is neuroprotective and starting an exercise regimen later in life is not futile for either enhancing cognition or augmenting brain volume. A recent RCT [79] also demonstrated the effect of combined activity against left medial temporal lobe atrophy.

13.4.2 CKD Patients

It is conceivable that physical activity and fitness levels are related to cognitive function in patients with chronic kidney disease, but there have been limited studies in this area. In a study by Parsons et al. [110] using the Kidney Disease Quality of Life (KDQOL) questionnaire, no changes in cognitive function score were found in patients on HD who attended a 5-month intradialytic aerobic exercise program three

times a week (cycle ergometer and mini-stepper) for 30 min in each of the first 2 h of HD, while increased physical performance was found. It is considered that the use of inappropriate instrument for assessing cognitive function and the low-intensity intradialytic exercise training seem to be the main reasons for the luck of changes in parameters related to cognitive function [111]. Meanwhile, Martins et al. [112] compared cognitive function assessed by 3MS between 37 inactive patients and 49 patients participating physical performance program for at least 3 months. The exercise training program consisted of two weekly 20- to 30-min sessions of combined strengthening and peripheral muscle resistance exercises and stretching performed before the initialization of the HD sessions and lasted 6 months. The results showed that better cognitive function was observed in active patients as compared to the inactive ones. According to the results, the authors concluded that patients with better cognitive responses are more physically active and/or physical activity contributes to better cognitive function. Unfortunately, however, this study was not an RCT, and the 3MS is not a sensitive measure for change in global cognition, which limits any conclusions.

Recently, this effect has been evaluated by RCTs [113–115]. Manfredini et al. [113] conducted a multicenter RCT, EXCITE trial, in which, cognitive function and quality of life (QOL) were evaluated by KDQOL-SF in addition to the physical performance to examine whether a simple, personalized walking exercise program at home improves functional status in adult patients on dialysis. A total of 296 patients were randomized to normal physical activity (control; $n = 145$) or walking exercise ($n = 151$). The results showed that the cognitive function score and QOL, as well the physical performance, were improved significantly in the exercise arm compared with the control arm. Baggetta et al. [114] reanalyzed the data of the EXCITE trial to elucidate whether physical exercise program improves physical and cognitive function in elderly HD patients. In this study, 115 patients of the EXCITE trial aged >65 years (active arm, $n = 53$; control arm, $n = 62$) were submitted in random order to a home-based, low-intensity physical exercise program. The cognitive function dimension of QOL significantly reduced in the control arm ($P = 0.04$), while it remained unchanged in the active arm ($P = 0.78$) (between groups difference $P = 0.05$). This secondary analysis of the EXCITE trial shows that a home-based, exercise program improves physical and cognitive performance and is well tolerated in elderly HD patients. McAdams-DeMarco et al. [115] conducted a pilot RCT of 20 HD patients to study the impact of 3 months of intradialytic cognitive training (tablet-based brain games), exercise training (foot peddlers), or standard care on cognitive function. Patients with standard care experienced a decrease in psychomotor speed and executive function, assessed by TMT-A, TMT-B, and ΔTMT, while this decline was not seen among those with cognitive training or exercise training (Fig. 13.7).

As a mechanism of the effect of exercise training on the improvement of cognitive function in HD patients, an increase in cerebral blood flow has been suggested [116]. A pilot RCT was conducted to evaluate the effect of intradialytic aerobic training on cerebral blood flow and cognitive impairment in HD. Cognitive function and blood flow velocity were compared between 15 patients who underwent intradialytic aerobic training three times a week for 4 months with another 15 control patients. Trained

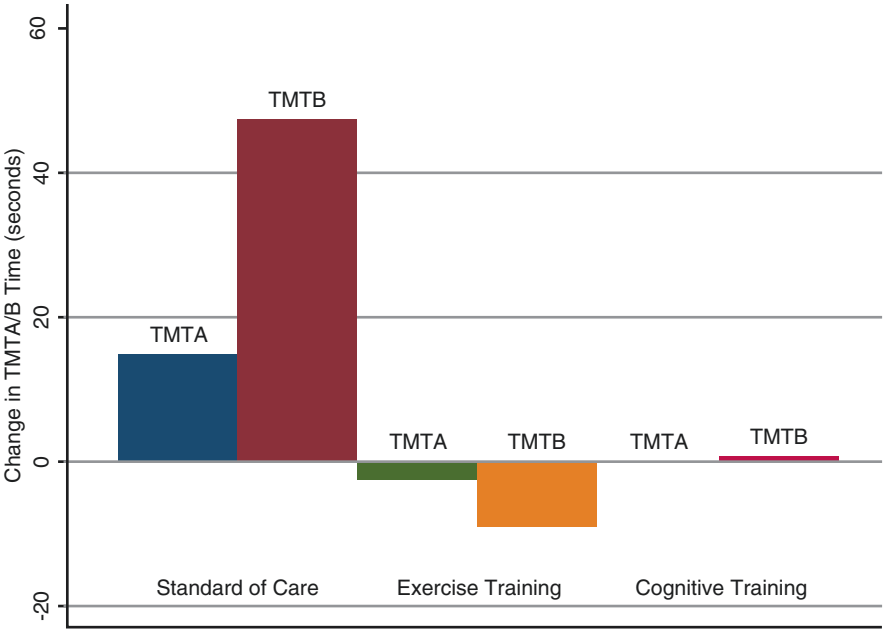

Fig. 13.7 Mean change in psychomotor speed (TMT-A and TMT-B) at 3 months for those with cognitive training, exercise training, and standard of care. *TMT* trail making test. (Reproduced from [115])

patients had a statistically significant improvement of cognitive impairment and basilar maximum blood flow velocity. Intradialytic aerobic training improved cognitive impairment and cerebral blood flow of patients in HD, suggesting a possible mechanism improving cognitive impairment by physical training in HD [116].

13.5 Conclusion

Frailty and cognitive impairment are both highly prevalent in CKD patients and are associated with each other. Both conditions have been identified as incremental risk factors for mortality and when they coexist, the risk is higher than when either of them exists alone. Physical exercise training is reported to be effective in preventing and treating both frailty and cognitive impairment, and thus should be implemented in the elderly CKD patients.

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Polypharmacy and Frailty in Chronic Kidney Disease

14

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Abstract

The prognoses of various diseases have improved because of progress in the field of medicine and clinical practice guidelines developed in countries around the world. However, polypharmacy and frailty have become a global public health concern because of the increase in longevity. Although polypharmacy and frailty are associated with a broad range of negative outcomes, they occur concurrently in patients with chronic kidney disease (CKD) at a higher rate. Elderly patients with CKD usually require multiple medications to prevent CKD progression and complications, and their conditions are generally complicated. In this article, we outline polypharmacy and frailty, which frequently occur in patients with CKD and introduce notes and approaches to overcome these issues.

Keywords

Polypharmacy · Frailty · CKD · Elderly · Multimorbidity · PIMs · ADRs · ADEs Prescribing cascade

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14.1 Introduction

Patients with chronic kidney disease (CKD) usually require multiple medications to prevent the progression of CKD and the complications associated with the disease. Therefore, they easily fall into polypharmacy, which has recently become a major public health concern worldwide. Polypharmacy often occurs when a person has been diagnosed with multiple chronic diseases requiring long-term treatment with multiple medications. The number of chronic diseases an individual suffers from accumulates with age; hence, older adults are at a higher risk for polypharmacy [1]. In addition, polypharmacy has been reported to be strongly associated with frailty [2], and they can be mutually exacerbated. In addition, patients with CKD also experience frailty. Frailty exists at a higher rate in elderly patients with CKD than in elderly patients without CKD, and frailty increases as the CKD stage progresses [3]. In this article, we outline the relationship between polypharmacy and frailty which frequently occurs concurrently in elderly patients with CKD.

14.2 Polypharmacy

Clinical practice guidelines for various diseases have been developed by countries around the world, which has clarified how medicine is recommended and improved disease prognoses. However, the number of patients who survive to be elderly increases, and polypharmacy is becoming a major public health problem since the use of multiple medications is increasingly common among older adults and the elderly population continues will increase. Although the number of prescribed drugs per disease slightly changes with age, elderly adults generally have multiple medications due to multimorbidity. Polypharmacy represents the state of multidrug use. Most literature defines polypharmacy as the use of five or more medications, and the use of ten or more medications as hyper-polypharmacy [4–6]. There is heterogeneity in the definition of polypharmacy. Recently, all complications associated with the use of drugs, such as adverse drug events (ADEs), adverse drug reactions (ADRs), depressed medication adequacy, unnecessary prescriptions, no prescription for required medicines, overdose, and redundant administration, have been interpreted as inappropriate polypharmacy. Taken together, polypharmacy is the "various problems associated with the use of multiple drugs." In addition to the increase in ADEs and ADRs, polypharmacy also adversely affects the economy by increasing the financial burden and quality of life of the affected individuals. As described above, polypharmacy has become a central problem in health care.

Polypharmacy is known to be linked to a broad range of negative health outcomes, including falls, frailty, and mortality [2, 7, 8]. A majority of the reviewed studies supported the theory of a positive association between polypharmacy and frailty, and polypharmacy was found to reduce physical function (e.g., gait speed, chair rise, and grip strength) in older adults [9]. Although the definition of

polypharmacy slightly differs by geographic area, the prevalence of polypharmacy is increasing worldwide and ranges from 39.0% to 60.4% [9]. There are several causes of polypharmacy, and begin by describing them as below.

14.2.1 Cause of Polypharmacy: Elderly and CKD

Polypharmacy is common among elderly patients. The characteristics of elderly patients are listed as follows: (1) a broad range of individual differences in age-related changes in physical and cognitive function, (2) multiple diseases in one individual, (3) disease pathology differs from that of younger individuals, (4) symptoms are atypical in many cases, (5) inspection results depend on individual differences, (6) patients often develop complications unrelated to the disease being treated, (7) the effect of treatment differs from that of younger patients, and (8) the inability to completely curing the disease. The overlap in causal factors as described above induces polypharmacy in elderly patients. On the other hand, CKD patients require multiple medications to prevent the progression of CKD itself. Furthermore, as renal function declines, more medications are preferentially prescribed to control the complications of CKD such as severe high blood pressure, fluid retention, metabolic disorders, mineral bone disorders, anemia, dyslipidemias, and cardiovascular diseases [10]. In addition, a patient with CKD has a greater chance of experiencing negative drug interactions and ADRs due to the pharmacodynamics and pharmacokinetics of the combination of drugs [11]. Therefore, CKD patients tend to experience polypharmacy, and there are several reports that refer to a relationship between CKD and polypharmacy [4, 10, 12–16]. Furthermore, a population-based study found that a long duration of polypharmacy was associated with a higher risk of acute renal failure [17].

14.2.2 Cause of Polypharmacy: Multimorbidity

The most common cause of polypharmacy is multimorbidity, which is mainly due to the combination of lifestyle diseases and chronic diseases and is difficult to eliminate. Long-term treatment is necessary to control high blood pressure and diabetes, and in the case of poor control and increasing number of drugs tend to be prescribed. CKD is the terminal state of these chronic diseases; in addition to the diseases originally suffered from, treatment of body fluid control, mineral abnormality, and anemia are additionally required. Furthermore, the types and doses of each medication can be restricted based on renal function; hence, the prescription of a patient with CKD tends to be more complex. When a patient suffers from heart failure and/or ischemic heart disease, the required number of drugs increases and polypharmacy exacerbates. Such chain of diseases, as often seen in patients with CKD, leads to multimorbidity, resulting in polypharmacy. This tendency is more common in the elderly and patients with low adherence. Polypharmacy, and the use of multiple single-disease

guidelines, tends to make drug regimens increasingly complex, which can lower adherence, and has been linked to a higher rate of negative outcomes [9].

14.2.3 Cause of Polypharmacy: ADRs, ADEs, Prescribing Cascade, and PIMs

The risk of potential drug-drug interactions increases almost exponentially with the number of drugs in use [18]. Hence, polypharmacy is a key risk factor for drug-drug interactions. Additionally, the use of single-disease clinical guidelines in older adults with multimorbidity can result in potentially serious drug-disease interactions [19]. The prevalence of clinically important drug-disease interactions has been reported to be about 15% in a sample of frail older adult veterans in the United States [20]. Such ADRs have been proposed to be the leading cause of hospitalizations in older adults. The use of multiple medications can cause ADEs. Falls and subsequent fractures have been linked to polypharmacy in several studies. The risk of falls increases with the number of drugs in use in a dose-dependent fashion [21]. There are many cases in which additional drugs are required to reduce the symptoms of ADRs and ADEs.

Polypharmacy is sometimes the result of a prescribing cascade. The prescribing cascade develops in an attempt to treat a particular ADE with other drugs. A prescribing cascade begins when a drug is prescribed, an adverse drug event occurs that is misinterpreted as a new medical condition, and a subsequent drug is prescribed to treat this drug-induced adverse event [22]. For example, a cough has been treated with an antitussive agent without notification of the side effects of ACE inhibitors, resulting in unexpected health damage (Fig. 14.1) [23]. Such a

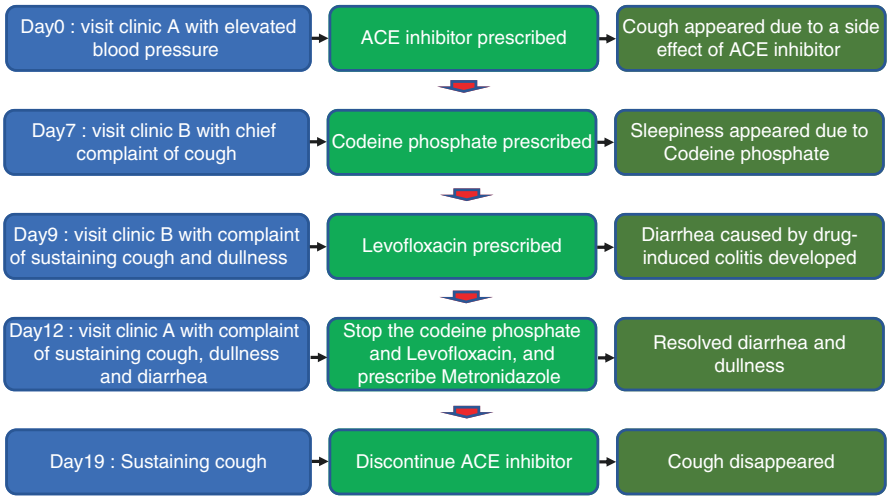

Fig. 14.1 Example of prescribing cascade. (Reviewed from Liu et al. [23])

case is called a prescribing cascade and is often led to incomplete information about drug history. To prevent this kind of incident, it is important to consider each new sign and symptom as a potential adverse effect, particularly if a new drug was recently added to the dose regimen or if the dose was recently changed. Accurately collecting a patient's drug history is also important, and a complete review of drug therapy, over-the-counter medications, and natural health products should be conducted at each medical appointment. When doctors prescribe additional treatment, low doses should first be prescribed first to reduce the risk of side effects, particularly in elderly patients with CKD. Patient education is a key factor in the detection and diagnosis of adverse reactions. Physicians and pharmacists should inform patients of the most likely ADEs and ADRs and prompt them to consult a doctor or a healthcare provider if these or any other type of reactions occur. At follow-up visits, physicians should question the patient on the efficacy and side effects of the drugs.

In addition, with polypharmacy, there can be potentially inappropriate medications (PIMs) that increase the risk of ADRs and ADEs. Polypharmacy is strongly associated with the prescription of PIMs [24]. There are several well-established and validated strategies to evaluate the medical regimen and identifying PIMs. The Beers and STOPP (Screening Tool of Older Persons'' potentially inappropriate Prescription) criteria are common tools used to screen for PIMs [25, 26], and STOPP-J was created for the Japanese population [27]. They include a list of PIMs, which are useful for screening PIMs in case of patient malfunctions. STOPP-J not only lists PIMs but also has algorithms that are used when considering drug changes, which is very helpful when reviewing the patient's medication. When changing the prescribed drug, it may be appropriate to carefully examine the effects and risks associated with the drug based on the algorithm depicted in Fig. 14.2.

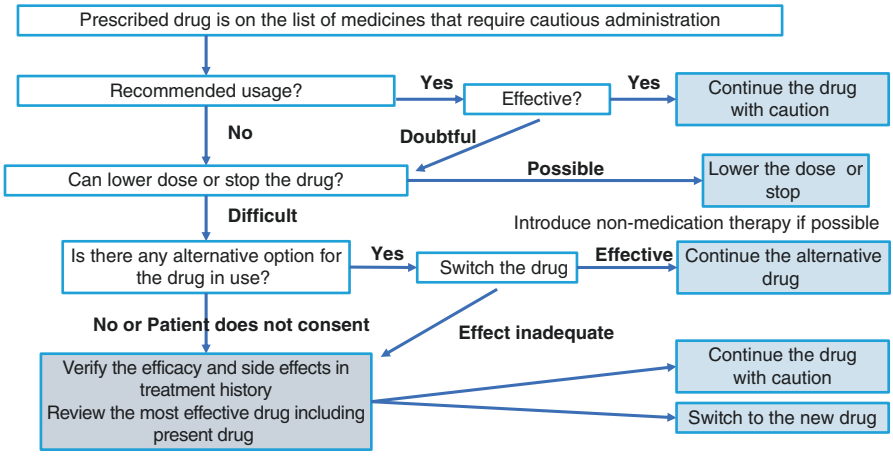

Fig. 14.2 Algorithm of medication review. (Modified from Kojima et al. [27])

14.3 Frailty in CKD

We would like to introduce briefly the relationships between frailty and CKD in this part, since the details are given to the other sections.

Frailty is usually defined as "a state of increased vulnerability to stressors resulting from a decrease in physiologic reserves in multiple organ systems causing limited capacity to maintain homeostasis" [28]. Frailty has been associated with an increased risk of several deleterious outcomes in older people, including disability, falls, hospitalization, institutionalization, and death [28].

CKD patients are prone to frailty. The prevalence of frailty in patients with CKD is reported to be about 14% [29], while the prevalence in the elderly who do not have CKD ranges from 7% to 10% [28, 30, 31]. CKD patients easily develop protein-energy wasting (PEW), accompanied by malnutrition and a reduction in the muscle mass [32]. Loss of muscle mass, as investigated by the biological impedance method, was frequently observed with a reduced eGFR or in albuminuria-positive patients [33]. Dialysis patients may age 15 years faster than healthy individual, based on the Gompertz equation model [34]. Several reports describe that the toxic factors in a uremic state accelerates aging and leads to progressively impaired organ function [35]. In addition, anorexia caused by uremic toxins, dialysate and urine nutrient losses, catabolic effect, chronic low-grade inflammation, deficiency or resistance to anabolic hormone, and physical inactivity have been reported to induce PEW and frailty [36]. Furthermore, physical activity is known to decrease in patients with hemodialysis (HD), due to the maintenance of HD and fatigue after HD, leading to physical deconditioning. Accordingly, these findings indicate that CKD and HD patients are particularly susceptible to frailty. Indeed, the prevalence of frailty increases as CKD stages progress by 1.47% without CKD, 5.94% with CKD stage 1/2, 10.74% with CKD stage 3a, and 20.90% with CKD stage 3b/4/5 [3]. In particular, among CKD, those with diabetic nephropathy and peripheral artery disease are frequently found to experience frailty, and in dialysis patients, frailty is observed in young patients [16, 37, 38]. In the analysis of data from the US Renal Data System (USRDS), 67.7% of the 2275 dialysis patients were considered as frailty [39]. Furthermore, in the population undergoing HD, there was a substantial number of non-elderly patients with frailty, and frailty is a strong and independent predictor of mortality and hospitalization, regardless of age [39, 40]. Frailty is also associated with the progression of CKD stage and initiation of dialysis [41, 42]. Elderly patients with CKD are not typical CKD patients. They have a number of complex problems, such as motor dysfunction, decline of cognitive function, along with various comorbidities [43]. Therefore, they are prone to frailty, which inhibits their independence, and exacerbates their QOL, healthy life expectancy, and prognosis.

When evaluating frailty, there is controversy regarding the indicator of kidney function. In the past, many studies have relied on serum creatinine for estimating kidney function. However, frail individuals often suffer from sarcopenia; thus, serum creatinine may overestimate kidney function, since serum creatinine correlates with muscle mass volume. Cystatin C is less influenced by muscle mass and may be suitable for evaluating kidney function in patients with sarcopenia, physical

frailty, limb amputation, low muscle mass, or elderly people with exercise habits less than that of other generally healthy elderly individuals. Indeed, eGFRcys has been shown to have a stronger association with prognosis than eGFRcr in the elderly population [44]. Several studies have examined the relationship between frailty and kidney function measured by cystatin C, and these studies concluded that eGFRcys may be a better marker of kidney function in frail individuals than eGFRcr [4, 42, 45] in non-dialysis patients with CKD. However, in patients undergoing dialysis, serum creatinine concentration before dialysis depends on muscle mass; therefore, serum creatinine before dialysis can predict frailty. The concentrations of serum creatinine in patients with HD were 10.76 mg/dL without frailty, 9.44 mg/dL with prefrailty, and 8.35 mg/dL with frailty [16].

In summary, frailty increases as the CKD stage progresses, and it is possible to predict frailty to some extent using indicators of renal function. As an indicator, cystatin C is more suitable in cases with patients who are not undergoing dialysis; conversely, creatinine is more suitable when patients are on dialysis.

14.4 Intertwining Relationships Among Frailty, Polypharmacy, and CKD

It is clear that multimorbidity is the common risk associated with polypharmacy, frailty, and CKD; thus, it is common for these three conditions to exist simultaneously. Multimorbidity is defined by two or more long-term conditions and increases with age [46]. As described above, multimorbidity is the cause of polypharmacy, and CKD is the terminal of multimorbidity. The prevalence of multimorbidity increases substantially with age, ranging from 55% to 98% in people aged 65 or older [47]. Frailty is strongly associated with multimorbidity, and many studies suggest a bidirectional association between multimorbidity and frailty [46, 48, 49]. Although the direct influence of polypharmacy on CKD is unclear, it seems that a relationship, as shown in Fig. 14.3, may be established among these three pathologies. These chronic conditions, which are particularly prevalent simultaneously and synergistically, seem to exacerbate the other and increase the risk for a negative outcome such as hospitalization, disability, and mortality.

14.4.1 Polypharmacy Associated with Frailty and CKD

Many studies have shown that polypharmacy is a risk factor for frailty. For example, in a 3-year cohort study in a community with a population between the ages of 50 and 75 years old, there was a dose-dependent influence for frailty risk. The odds ratio (OR) for frailty with oral administration of five or more drugs was 2.30 (95% CI: 1.60–3.31), and OR with ten or more drugs was 4.97 (95% CI: 2.97–8.32) [50].

Patients with CKD require multiple medications to treat the medical conditions that accompany the development of CKD. They often suffer from various chronic diseases simultaneously, such as hypertension, dyslipidemia, diabetes mellitus,

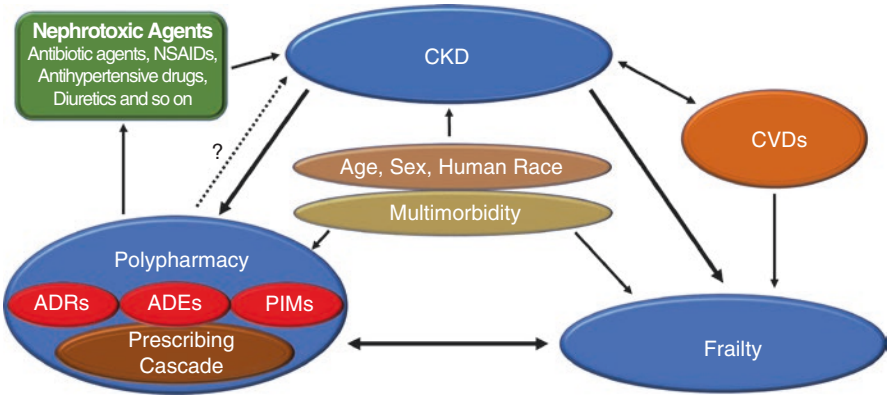

Fig. 14.3 The relationships among CKD, polypharmacy, and frailty

and cardiovascular disease. As CKD stage progress, body fluid regulation, control of bone and mineral metabolism disorders, adjustment of potassium, and acidosis and treatment of anemia become more complicated; therefore, patients with late stage of CKD naturally fall into polypharmacy. In many cases, it is necessary for polypharmacy, it is difficult to reduce the number of drugs, and sometimes the reduction of drugs causes an exacerbation of the medical condition. Polypharmacy has been correlated with decrease of eGFR and increase of ACR [4, 12]. In the CRIC study, most patients with CKD are administered more than nine drugs [14], and in the ARIC study, 84% of the participants with CKD were polypharmacy; furthermore, 54% of CKD participants with frailty was hyper-polypharmacy [4]. Patients on dialysis took from 10 to 14 or more drugs on average [13, 16], and then polypharmacy was also strongly associated with frailty [16]. Thus, the more drugs are required as the CKD condition become more severe, while there are many drugs that require dose adjustment according to the renal function, although renal function may vary from time to time. Therefore, PIMs and ADRs develop easily. It is known that PIMs are generally caused by drugs with anticholinergic activity, benzodiazepines, nonbenzodiazepines, antidepressants, and H1 and H2 receptor antagonists, while in case of CKD it is reported that the drugs that need to be adjusted base on renal function, including antibiotics, antihypertensives, antidiabetics, antiarrhythmics, and diuretics often develop PIMs and ADRs [15]. Hence, we must pay attention to renal function when treating patients with CKD and to review the prescription frequently.

14.4.2 Drugs That Require Attention When Used to Treat Elderly CKD Patients

Elderly adults tend to have reduced lean body mass and body water content and potentially have impaired renal function. Therefore, they are pharmacodynamically

high-risk group of drug-induced kidney injury (DKI), and prevention and early detection of DKI are important. In addition, their tubular function tends to be also reduced; thus, it is easy to cause water electrolyte abnormalities. When using renal excretory drugs for elderly people with CKD, it is necessary to reduce the dose and extend administration interval according to their renal function. When evaluating the elderly with low muscle mass, Cystatin C is recommended for evaluation of renal function as described earlier.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat the elderly. NSAIDs inhibit prostaglandin (PG) production by inhibition of cyclooxygenase (COX). When renal hemodynamics decrease due to dehydration, the production of PG, which has an antagonistic activity for vasoconstriction due to sympathetic nervous system activation or renin-angiotensin system (RAS) activation, is enhanced in kidney tissue; thus a compensatory mechanism works to maintain renal blood flow [51]. If NSAIDs are taken continuously when renal hemodynamics decrease, PG production is reduced and renal blood flow cannot be maintained. NSAIDs are high-risk drugs, which cause renal dysfunction for elderly with CKD; therefore, it is desirable to avoid long-term and regularly use and to use low doses occasionally. When comparing COX-2 selective with non-selective NSAIDs in clinical studies for the elderly, there was no significant difference in the effect on renal injury [52].

It is common to use acetaminophen to avoid the use of NSAIDs as an analgesic in patients with CKD. However, no specific opinion has been obtained on the safety of acetaminophen for renal injury. Acetaminophen has also been reported to be at high risk for renal injury as same as NSAIDs [53], and it is desirable to minimize their use. Acetaminophen-induced renal injury is not acute renal injury but chronic renal injury due to renal papillary necrosis, calcification, and chronic interstitial nephritis. However, it is not clear whether such renal injury develops after the use of acetaminophen alone, and in most cases, it is caused by long-term daily use of multiple analgesics containing acetaminophen. Although the details of the pathogenesis of renal injury caused by acetaminophen are unknown, the combination of drugs with the NSAIDs causes an increased concentration of acetaminophen in the renal medulla, and it is speculated that direct toxicity via *N*-acetyl-*p*-benzoquinone imine, which is an intermediate active metabolite of acetaminophen, causes renal injury [54]. For diagnostic purposes, it is necessary to confirm atrophy and contour irregularities of both kidneys and papillary calcification by plain CT examination. In general, renal papillary necrosis is irreversible; thus, the prevention at the early stage is important.

RAS inhibitors are highly effective at reducing urinary protein by expanding glomerular efferent arteries and are expected to suppress the development of renal injury with urinary protein. However, in the case of the elderly with CKD, it is important to pay attention to renal function decline, since they often suffer from renal sclerosis due to arteriosclerosis and ischemic nephropathy. Excessive blood pressure reduction in such patients may result in decreased renal blood flow and may cause acute kidney injury. In addition, if excessive depression of intraglomerular pressure is caused using an RAS inhibitor, it may also cause acute kidney injury even though blood pressure is normal; hence, caution is required when starting these

patients on RAS inhibitors. The use of low doses is desirable for elderly patients with CKD, and careful monitoring is required to circumvent the development hyperkalemia.

Thiazide diuretics have been reported to be useful in the elderly and are also the first choice for the treatment of hypertension. The distal tubule on which the thiazide diuretic acts actively transports sodium chloride from the lumen to the blood, and if a decrease in plasma volume accompanied by antidiuretic hormone secretion develops, it is easy for the elderly to develop hyponatremia when using thiazide diuretics [55]. In addition, thiazide diuretics enhance calcium reabsorption. When vitamin D or calcium preparations are taken as a treatment for osteoporosis in the elderly, hypercalcemia easily develops and results in developing renal failure accompanied by impaired consciousness.

The elderly patients frequently suffer from infections. When using antibiotics in patients with CKD, renal function should be assessed and dosage should be adjusted based on renal function. If the route of elimination of antibiotics is renal excretion, it is necessary to reduce the dose of the administered drug. Monitoring of blood levels of the drug prescribed is recommended when administering aminoglycosides or vancomycin. When using antibiotics, renal injury may more likely result depending on the medical condition of the CKD patient, such as older age, reduction of circulating plasma volume, use of diuretics, and the combined use with drugs that easily cause renal injury. It is also necessary to pay attention to antiviral drugs, such as acyclovir and ganciclovir. They have low solubility; therefore, the crystals may be deposited in the distal tubule and collecting duct and causing post-renal nephropathy. Furthermore, increased blood concentration of antiviral drug makes central nervous system disorders. Therefore, sufficient fluid load and dose reduction are necessary at the time of administration of antiviral drugs for elderly with CKD. It is also necessary to pay attention to anti-influenza drugs depending on renal function.

14.4.3 Drugs Related with Frailty

While there is an increasing number of studies on the prognosis of elderly people with frailty, there are still few studies that investigate the direct relationship between medication and frailty.

In a cohort study of elderly women without frailty, approximately 15% of 27,652 subjects developed frailty within 3 years; furthermore, subjects who were taking antidepressants had a significantly higher OR for frailty than those who did not, 1.73 (95% CI: 1.41–2.12). Additionally, regardless of the degree of depression, it suggested that oral administration of any type of antidepressant is associated with the incidence of frailty [56]. In the cohort study of elderly without dementia, a higher cumulative anticholinergic use was found to be associated with an increased risk for dementia [57]. Thus, it is suggested that anticholinergic use increases the risk of psychological frailty.

Benzodiazepines increase the risk of cognitive decline and falling and also increase the risk of frailty. In a cohort study where subjects were followed up for

15 years, the hazard ratio for dementia was 1.60 (95% CI: 1.08–2.38) in patients treated with benzodiazepines compared to non-user [58]. Similar to anticholinergics, it is suggested that benzodiazepines can cause psychological frailty. Furthermore, benzodiazepines are also drugs that can cause fall and bone fracture [59]. Nonbenzodiazepine sedatives also have the significantly increased risk of hospitalization due to falling [60].

As described above, antidepressants, anticholinergics, benzodiazepines, or nonbenzodiazepines are related to frailty; hence, it is necessary to avoid their use. If their use in unavoidable, it is acceptable to limit the number of drugs to less than two.

14.5 The Approach to Polypharmacy in CKD

Interventions aimed at reducing inappropriate polypharmacy or the risk of negative outcomes associated with polypharmacy have been unsuccessful at impacting clinically relevant endpoints. Furthermore, many of these interventions are complex and may therefore have limited scalability [9]. In a large cluster-randomized trial, the intervention did not reduce the number of drugs, 11.0 (8.0–15.0) in the usual care group vs 11.0 (8.0–15.0) in the intervention group, treatment burden, or medication adherence [61]. In contrast, the interventions aimed at reducing ADRs were successful, and a recent systematic review found a 35% risk reduction in ADRs for interventions led by a pharmacist [62].

Most patients with CKD need multiple medications that can result in polypharmacy. This situation can cause ADRs, thereby accelerating frailty or exacerbating CKD and polypharmacy itself as a result. As described above, in reference to Fig. 14.2, a clinical medication review analyzing renal function more frequently in patients with CKD than non-CKD patients is recommended when considering a change or addition of medication.

The most important point is to collect detailed medication and treatment history including information from other treatment centers when considering adding additional medication to a prescription regimen. In addition to doctors and pharmacists, it is also important to collect information on drugs from other clinical professionals such as nurses. It is important to follow up on a patient's status when medication is cancelled or changed and to evaluate their symptoms after the cancellation or change. It is also necessary to monitor symptoms for expected adverse events with treatment discontinuation. If polypharmacy is necessary for a patient, it is important to maintain appropriate polypharmacy and continue to carefully observe and monitor the patient. In addition, we postulate that it is possible to take measures against polypharmacy relatively smoothly by performing a series of these processes with a team consisting of a range of medical staff. In the case of elderly CKD patients, it is essential to constantly pay attention to renal function, since it is likely to change with the passage of time and review the medication each time according to the renal function. As described above, to evaluate renal function, cystatin C also needs to be analyzed if muscle mass is considered to be less than what is considered normal for the elderly.

Recently, computerized decision support systems for the optimization of drug therapy for older adults were developed. Moreover, decision support systems have been found to reduce the risk of PIM use [63]. Nonetheless, decision support systems will be useful and helpful tools, since they can be optimized or refined by AI technology.

14.6 Conclusion

Polypharmacy and frailty frequently occur concurrently in patients with CKD. Elderly patients with CKD have multiple diseases that are generally chronic and are very difficult to resolve; thus, multimorbidity easily develops. Multimorbidity is a common cause of CKD progression, frailty, and polypharmacy; therefore, their relationship, as depicted in Fig. 14.3, can be established. Since it is very difficult to treat multiple pathological conditions with a single medication, it is important to maintain appropriate polypharmacy by frequently monitoring the condition of the patient. Monitoring renal function and collecting accurate clinical data with the help of pharmacists and nurses is necessary to prevent ADRs, ADEs, PIMs, and prescription cascades that exacerbate CKD, frailty, and polypharmacy. The prevalence of polypharmacy in patients with CKD is expected to continue to increase; however, computerized decision support systems for the optimization of drug therapy for older adults have been recently developed and will be an important tool. We must make every effort, including developing support systems in the near future, to protect patients with CKD from unfortunate complications and adverse events caused by frailty and polypharmacy.

Declaration of Interest The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Anemia Management and QOL and Frailty in CKD

15

Mariko Miyazaki

Abstract

The strategy to improve health related quality of life (HRQOL) not only renal survival is crucial for chronic kidney disease (CKD) patients. Pathophysiology of anemia is closely associated with heart failure, malnutrition and inflammation which deteriorate HRQOL. Kidney Disease: Improving Global Outcome recommended that the erythropoiesis-stimulating agent (ESA) not be used to maintain Hb concentration above 11.5 g/dL in 2012. Updated systematic reviews for the treatment of anemia and HRQOL outcome mentioned that comparison between baseline Hb < 10 g/dL and partial correction over ≥ 10 g/dL showed the improvement of physical components of HRQOL in dialysis dependent CKD patients. In pre-dialysis CKD patients, aiming for lower Hb target with ESAs not only resulted in better HRQOL but lower healthcare resource utilization than control. However, higher Hb target above 12 g/dL lead to modest improvement of HRQOL with uncertain clinical significance.

Further investigations are required to individualize of the patients that 11.5–13.0 g/dL Hb target is effective for clinically meaningful HRQOL improvement without increasing the risks.

Keywords

Anemia · Cardio-renal-anemia syndrome · Erythropoiesis-stimulating agent · Frailty · Hemoglobin target · Health related quality of life · Malnutrition-inflammation-anemia syndrome · Minimal clinically important difference

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15.1 Introduction

Advanced CKD patients are growing worldwide, furthermore, average life expectancy was extended and elder population has increased in many advanced countries. For example, total number of Japanese patients newly started dialysis are growing to 2600 per million population [1] despite 74 or younger patients who depending renal replacement therapy are decreasing [1]. Therefore, we are forced to construct measures for CKD considering the elderly both pre-dialysis and dialysis dependent. In 2018, the Ministry of Health, Labor and Welfare of Japan released the action plan to overcome of CKD for next 10 years [2]. According to this, the incidence of end stage kidney disease (ESKD) patients starting renal replacement therapy should reduce to 35,000 patients from 40,000 in 2017 by 2028. Additionally, the strategy to improve health related quality of life (HRQOL) is important for CKD patients not only renal survival in the action plan.

15.2 Pathophysiology of Involvement HRQOL in CKD and Anemia

In recent years, the investigations focused on HRQOL are interested in the field of clinical nephrology. Pathophysiology of renal anemia is concerned as the major cause of poor HRQOL in CKD patients but treatable using erythropoiesis stimulating agents (ESA) with or without iron supplementation. Anemia increases circulating plasma volume, cardiac overload, and affected a hypoxic condition of organs. Heart failure and anemia constrict a vessel and renal ischemia via acceleration of a renin angiotensin system. It causes further kidney dysfunction including erythropoietin producing. Consequently, treating renal anemia is possible to break the vicious cycle in cardio-renal-anemia interaction [3, 4].

Metabolic acidosis, overhydration and organ congestion as described above are observed in advanced CKD. Inflammatory cytokines are revealed to affect the hematogenous functions in kidney dysfunction [5–8]. Moreover, dietary restrictions may be performed in order to prevent accumulation of sodium, potassium, phosphate, or urea nitrogen. These restrictions and metabolic disorder are the cause of malnutrition. The inflammation, malnutrition and the iron use interact the hematogenous functions in renal anemia. The role of erythropoietin (EPO) is controlling the apoptosis between maturity from proerythroblast to orthochromatic erythroblast in process of hematogenesis. Hepcidin is controlling whether stimulate iron use or storage in hematopoietic system. Hepcidin is down-regulated in situations where iron utilization proceeds, and in inflammatory conditions hepcidin is increased and iron is channeled into the liver. Steinvinkel advocated those condition as MIA syndrome which affected erythropoietin response in treatment of CKD [9]. Furthermore, the experimental studies revealed the association between uremic toxin such as indoxyl sulfate and myofibroblasts [10, 11] or erythropoiesis [12–14]. Anemia and physical weakness are closely related each other via uremic toxin in CKD patients like this.

In 2001, Fried suggested the definition of frailty in older adults as follows; weight loss, exhaustion, weakness, slow walking speed and low physical activity [15]. The comorbidity is an etiologic risk factor for frailty, and disability is an outcome of frailty. Several studies described anemia was associated to the development of frailty [16]. Ng et al. developed a frailty risk prediction tool including low hemoglobin, eGFR < 60 (ml/min/1.73 m^2), and WBC (×109) ≥6.5, and externally validated using community based two cohorts [17].

Increased white blood cell count is associated to chronic inflammation. Chronic inflammation observed in geriatric patients is known as "inflammaging" with the risks of disability, falls, hospitalization by aging even if without CKD [18]. Inframmaging means that age-related upregulation of the inflammatory response.

Original criteria of frailty was based of biological characteristics, however, the influence of "Inframmaging" should be considered to evaluate the risk of frailty [17, 19]. Therefore, aging and uremic status complicatedly injured the health of elder CKD patients.

15.3 Hemoglobin Target and HRQOL

There have been many reports that anemia deteriorated the physical activity described above, the relationship between hemoglobin concentration and HRQOL has been also evaluated in CKD. HRQOL is consisted with the physical, psychological and social domains of health.

HRQOL is variously evaluated with the instruments to measure the impact of disease and treatment. The medical outcomes study 36-Item Short Form (SF-36) is well known as generic HRQOL tool which can compare across disease. Additionally, KDQ is disease specific QOL tool for kidney disease. It makes difficult to compare directly the HRQOL in outcome studies with different tools. Further concerns is whether the change of HRQOL score is clinically meaningful for the patients or clinician [20]. Minimal clinically important difference was 5–10 points in SF-36, or 0.2–0.5 of effect size in KDQ. In HRQOL evaluation, there are large differences of socio-economic status, healthcare system for end stage kidney disease among the societies [21]. Therefore, the improvement of physical component such as SF-36 vitality, KDQ fatigue, and NHP energy seemed to be major instruments for HRQOL in management of CKD or renal anemia in systematic reviews.

Though the treatment of anemia has contributed to improve morbidity and mortality in CKD both dialysis and pre-dialysis [22–24], Kidney Disease improving Global Outcomes (KDIGO) guideline recommended a target hemoglobin below 11.5 g/L because of cardiovascular event risk in further high target Hb [25]. Those recommendations were based on previous studies that complete correction of anemia did not reduce the risk of cardiovascular events nor HRQOL [26, 27]. After the publication of KDIGO guideline in 2012, practical target Hb was decreased especially in US but little changed in Japan.

The benefit of target Hb range of 11.5–13.0 is controversial because the risk of cardiovascular event in CKD has considerable differences among background of patients such as races, history of CVD or Diabetes.

The incidence of cardiovascular disease was lower in Japanese pre-dialysis CKD patients [26]. It is possible that some individual patients such as younger, without serious comorbidities may bring great wellbeing. Vitality and left ventricular mass index (LVMI) of pre-dialysis patients improved in stratifying Hb 10–11 g/dL, and over 11 g/dL than <10 g/dL reported by Hirakata [27]. Their study had the limitation that darbepoetin was administered every 2 or 4 weeks for higher target Hb but epoetin alfa was need to weekly or every 2 weeks' administration for lower target as conventional methods. For many CKD patients without severe complications, frequent clinical assessment was possible to somewhat affect their QOL beyond LVMI.

Tsubakihara et al. investigated that renal function were preserved in higher hemoglobin group (11.0–13.0 g/dL) than low hemoglobin group (9.0–11.0 g/dL) treated with darbepoetin alfa [28]. Although HRQOL outcome was not included in the study, preserved renal function seems to bring better QOL for advanced CKD patients.

Seven systematic reviews on anemia management and QOL have ever been published.

Clement et al. suggested that Hb target over than 12.0 g/dL did not lead to clinically meaningful improvements of HRQOL in both pre-dialysis and dialysis patients reviewed 11 studies [29]. Collister et al. attempted meta-analysis of 12 pre-dialysis, 4 of dialysis, and 1 both CKD subject to reveal whether the change in HRQOL between baseline and another point was significant by high or low Hb target. They described that ESA treatment of anemia achieving higher Hb level did not show difference in HRQOL, and emphasized the importance of minimal clinically important difference to treat renal anemia and target Hb [30]. They also mentioned that cost-effectiveness consideration in policymakers. Then, economic burden and HRQOL analysis of both dialysis and pre-dialysis setting were published as shown below.

Systematic reviews on maintenance dialysis therapy setting was three [31, 32], Studies in baseline Hb < 10 g/dL and partial correction over ≥10 g/dL showed the improvement of exercise tolerance [31] and fatigue outcomes [32] in dialysis patients by the reviews. Spinowitz et al. highlighted that the economic burden of renal anemia and improvement of HRQOL. In their review, minimal clinically important difference was observed in some studies 11.5–13 g/dL of Hb target. The improvement of HRQOL in higher Hb target resulted in uncertain clinical significance in maintenance dialysis therapy setting [33].

Pre-dialysis setting systematic review was two [34, 35], Gandra identified 14 studies [34]. Ten of them achieved minimal clinically important difference in treated with ESA, one study was not, three studies were not evaluated minimal clinically important difference. They concluded that physical components of HRQOL were improved in pre-dialysis patients.

In 2019, economic burden and HRQOL were also considered in pre-dialysis patients [35].

Untreated anemia leads to lower HRQOL compared with initiating anemia treatment. Furthermore, higher healthcare resource utilization and higher cost were necessary to care in population untreated anemia. Biosimilar ESAs are available to treat renal anemia as a cost-lowering alternative strategy.

15.4 Conclusion

Moderate to advanced CKD patients lose their HRQOL by multiple factors based on the contents described above. One of effective intervention to improve their HRQOL is control of renal anemia and cardiovascular adverse event within safety Hb target.

Nevertheless most physician may consent that therapeutic goal should be based on individual condition with the un-proved benefits in spite of potential risk of higher hemoglobin target as the comment by Wyatt to this systematic review [36]. The individualized therapeutic goals of slightly higher Hb level (11.5–13.0 g/dL) might be considered based on discussion about the risk and benefits. Furthermore, effective and safe medical intervention strategy in CKD with anemia should be further investigated to acquire clinically meaningful change in HRQOL from the point of view both of the patient and the clinician.

Disclosure None.

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