Chapter 11
Frailty in Non-Dialysis Chronic Kidney Disease

Malena Colombo, Victoria P. Musso-Enz, María del Pilar Romero, Gustavo Aroca-Martinez, and Carlos G. Musso

Introduction

Frailty status is a condition which is not merely induced by aging but mainly by a progressive and sustained deterioration of several body physiological processes that lead to an increased vulnerability to stressors [1–7]. The main clinical characteristics of frailty status are low physical activity and poor social connections [5, 8].

The prevalence of frailty and pre-frailty status in older individuals ranges from 7% to 15% and 44% to 47%, respectively. This condition is characteristically more prevalent in women and increases steadily with age from 4% in older individuals (65–69 years) to 26% in the oldest old (≥85 years) [9, 10]. Frailty pathophysiology consists of a simultaneous functional reserve decline (below a 30%) of many systems, such as skeletal muscle, nervous, endocrine, and immune systems, with even poor coordination among their functions, leading to an altered homeostatic response, mediated by metabolic imbalance, cytokine over-expression (TNF-alpha, interleukin-6, interleukin-1), and/or hormonal dysfunction [10, 11].

M. Colombo · V. P. Musso-Enz · M. del P. Romero
Physiology Department, Instituto Universitario del Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

G. Aroca-Martinez
Facultad de Ciencias de la Salud, Universidad Simon Bolivar, Barranquilla, Colombia

C. G. Musso (✉)
Physiology Department, Instituto Universitario del Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Facultad de Ciencias de la Salud, Universidad Simon Bolivar, Barranquilla, Colombia

Nephrology Division, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

Ageing Biology Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
e-mail: carlos.musso@hospitalitaliano.org.ar

C. G. Musso et al. (eds.), *Frailty and Kidney Disease*,
https://doi.org/10.1007/978-3-030-53529-2_11

Frailty status prevalence in non-dialysis chronic kidney disease (CKD) patients is around 14% [10], and CKD associated inflammation, increased oxidative stress, protein-energy wasting, and dysregulated methionine transmethylation reactions contribute to the appearance of frailty in this group [10]. Moreover, some pathological conditions have been suggested as common pathways among frailty and CKD, as is the case of altered hemoglobin, interleukin 6, insulin-like growth factor 1 (IGF-1), dehydroepiandrosterone-S (DHEA-S), hemoglobin A1c (Hb A1c), 25-hydroxy vitamin D, vitamin B12, and, carotenoids levels [5, 7, 12].

This chapter describes the relationship between fragility and CKD, its clinical consequences, and adequate therapeutic approach.

Frailty in Chronic Kidney Disease: Senescent Nephropathy

The prevalence of frailty is higher in older individuals with CKD compared to normal kidney ones, and this prevalence increases with worsening kidney function, having worse outcomes than those that are robust with CKD, including an increased falls, hospitalization, dialysis requirement, and mortality [1, 12]. Frailty phenotype prevalence among end-stage renal disease patients is five- to sevenfold higher than in community-dwelling older adults, and it is linked to higher rates of mortality [9, 11]. The inflammatory state, which characterized both frailty and CKD, is associated with their increase in resting energy expenditure that may contribute to the imbalance of muscle protein homeostasis. The signaling of the anabolic hormones (insulin and IGF-1) is impaired by the proinflammatory cytokines by increasing the glucocorticoids activity, and by directly causing skeletal muscle resistance to insulin and IGF-1. This phenomenon incites muscle protein breakdown via the caspase-3 and ubiquitin proteasome system [12].

According to the Health, Aging and Body Composition Study, an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m2 was independently associated with the progressive difficulty in walking one-quarter of a mile or climbing a ten-steps stairs. In a follow-up study, participants found in the highest quartile of cystatin C concentration (≥1.13 mg/L) experienced a significantly higher risk of developing functional limitation than those in the lowest quartile (<0.86 mg/L) [13]. The Heart and Soul Study found that exercise capacity was diminished in patients with eGFR <60 ml/min/1.73 m^2 for low exercise capacity, compared to those with eGFR >90 ml/min/1.73 m^2. Further findings demonstrated that maximum exercise tolerance becomes impaired even in early CKD stages, since participants with eGFR 60–90 ml/min/1.73 m^2 were also more likely to have low exercise capacity [13]. It has been documented that stage 3b CKD patients had defective oxygen consumption during maximal exercise, and they also performed poorly on several tests of day-to-day activities, with maximal gait speed over a short distance 85% and sit-to-stand performance 79% of population norms. The proportion of patients who failed to rise from a chair without using their arms was higher among individuals with lower eGFR, and no patients with eGFR <12 ml/min/1.73 m^2 were able to perform this task [13].

Malnutrition is a prevalent condition in end-stage renal disease (ESRD) patients, which gradually progresses with renal function deterioration prior to renal replacement therapy (RRT) initiation. This phenomenon can be induced by reduced dietary intake, uremic toxins accumulation, RRT catabolic effects, oxidative stress, metabolic and hormonal imbalances, increased insulin resistance, systemic inflammation, and comorbid conditions. All these factors can lead to physical, mental, and social deterioration [14].

As mentioned above, CKD predisposes to frailty through many mechanisms, such as anemia, bone fragility, chronic inflammation, oxidative stress, atherosclerosis, malnutrition, sarcopenia, and even all these factors can also lead to CKD progression, giving place to a dangerous vicious cycle. Consequently, CKD in older patients are more likely to reach frailty, and as CKD disease progresses, the prevalence of frailty increases. Meanwhile, frailty status influences negatively CKD evolution as well as the health conditions that chronic nephropathy patients deal with. Therefore, those patients who suffer from CKD and frailty at the same time are at greater risk of falling, showing fractures, getting hospitalized, and they also have more chances of progressing to dialysis and death. Because of that the coexistence of CKD and frailty phenotype has been considered a particular condition named "senescent nephropathy" (SN). SN is characterized by significant clinical complications, therapeutic demands (e.g., rehabilitation), and worse prognosis, in comparison with robust older CKD patients (Table 11.1) [3, 4, 12].

Moreover, a study that compared the worsening of the health-related quality of life (HRQL) in ESRD documented that frailty was associated with worse HRQL at the follow-up, and that it was the only factor that was associated with it. The same study showed that the overall pattern of change in HRQL suggested that most participants had stable HRQL but when there was a change in HRQL, it was more likely to be worse [15]. There is strong evidence that links HRQL with mortality risk in ESRD patients, but not enough studies examined this relationship with earlier stages of CKD [13].

Table 11.1 Differences between chronic kidney disease (CKD) robust older patients and senescent nephropathy (SN) patients

	CKD	SN
CKD diagnosis	Positive	Positive
Frailty score	Negative	Positive
Therapy	Corresponding CKD therapy (conventional tagets)	Corresponding CKD therapy adjusted to frailty status (conventional or modified targets) + Frail rehabilitation & home assistance
Follow-up	Standard control rate	Tighter control rate
Prognosis	Standard	Worse

Sarcopenia and CKD

Sarcopenia, which is defined as musculoskeletal mass and strength reduction, is an important component of the frailty phenotype. Its diagnosis is based on the evaluation of the muscle mass by imaging techniques (computed tomography or magnetic resonance), bioimpedance analysis (lean body mass), muscle strength (handgrip), and the physical performance assessed by applying clinical test, such as the short physical performance battery or timed get-up-and-go test, and/ or applying clinical scores (Table 11.2) [4, 10, 16]. People tend to lose muscle mass at a rate of 1–2% per year after the age of 50 years, due to a progressive atrophy and loss of type II muscle fibers and motor neurons, as well as an increased variability in fiber size, extracellular space expansion, protein aggregates deposition within the interstitial matrix, and increased infiltration of adipose and connective tissues, all changes which contribute to a decline in the muscle functional capability. In addition, other mechanisms involved in the onset and progression of sarcopenia are the low protein diet, reduced growth hormone and androgens serum levels, insulin resistance, low vitamin D, high cortisol levels, metabolic acidosis, and chronic diseases such as diabetes mellitus, cirrhosis, peripheral vascular disease, and CKD [4, 6, 10]. Moreover, muscle loss is more pronounced in pre-dialysis patients, which may ameliorate once dialysis has been initiated [12]. Skeletal muscle biopsies from patients with advanced chronic nephropathy show lower mitochondrial volume density and mitochondrial DNA copy number than controls, changes that can be reversed by muscles resistance exercise [17]. An important contributor to sarcopenia during kidney injury is the skeletal muscle down-regulation by inflammatory mediators such as IL6 and TNF-like weak inducer of apoptosis (TWEAK), being the exercise beneficial effect mediated by TWEAK modulation [14, 17]. Regarding metabolic acidosis, it activates caspase-3 and the ubiquitin proteasome system, inhibiting the intracellular signaling of insulin and IGF-1 and increasing the adrenal glucocorticoid production, resulting in protein catabolism that activate muscle breakdown cytokines (interleukin-6 and TNF-alpha), which finally induce sarcopenia [12, 14]. It is worth mentioning that, social isolation and depression, usually associated to CKD, are also sarcopenia inducing factors since these behaviors lead to inactivity and loss of muscles function [3, 4].

The highest concern of sarcopenia is altered locomotion, but it can also impair other vital functions such as glucose regulation, hormone production, and muscle tissue mass as the major potassium and amino acids body reservoir. Moreover, sarcopenia increases the risk of numerous adverse outcomes such as physical disability, diminished quality of life, and death [10]. In addition, sarcopenia explains why

Table 11.2 Clinical sarcopenia stages

Sarcopenia	Muscle mass	Muscle strength	Performance
Pre-status	Low	Normal	Normal
Mild-moderate	Low	Low	Normal
Severe	Low	Low	Low

when kidney function is assessed in older people using eGFR equations based on serum creatinine, those patients with the lowest and highest eGFR values were associated with the highest mortality (U-shape curve) [10]. This phenomenon is particularly prominent in octogenarians, and probably can be explained by the fact that higher eGFR can reflect those individuals with lower muscle mass and malnutrition [4].

Frailty Evaluation in CKD

Frailty screening should be routinely performed in CKD patients (young or older) so that targeted management strategies can be offered. The two more popular frailty diagnosing tests are: the Fried Frailty Phenotype and the Frailty Index (FI). The former has a more robust evidence base in terms of predicting outcomes in CKD patients, but is a time-consuming evaluation, thus not practical to be performed routinely to nephrology outpatients [1]. Fried et al. created the concept of frailty phenotype that incorporates disturbances across five clinical domains: shrinking, weakness, poor endurance and energy, slowness, and low physical activity level, in order to identify older people who are at risk of disability, falls, institutionalization, hospitalization, and premature death [4, 10]. Those individuals who have ≥ 3 domains are considered to be frail, those who have one or two altered domains to be vulnerable or pre-frail individuals, and those with no domain to be fit or robust [11]. It is worth pointing out that sarcopenia is usually considered included into the "shrinking" domain; and that social isolation, depression, and cognitive impairment are usually considered as exacerbating conditions of the frailty phenotype [10]. However, as the Fried frailty phenotype was developed in community-dwelling older adults, some components may not be fully applicable to ESRD patients, while there is also some physiological reserve aspect of these patients that are not fully covered by the Fried frailty phenotype [9]. In this sense, since frailty phenotype, comorbidity, and disability are related terms but they should not be used interchangeably, the coexistence of these entities may imply the risk of over-diagnosing frailty phenotype in people whose clinical "domains" are not secondary to their loss of complexity (frailty phenotype) but to their comorbidities (presence of more than three chronic disease) or disability (altered at least one of the daily activities). Thus, to apply Fried frailty score to CKD patients may overreport the true prevalence of frailty in these groups (pseudo-frailty phenotype) [10]. Mitnitski et al. described a holistic approach to assessing frailty in older patient, and Rockwood et al. further developed a frailty diagnostic model, including a total of 70 variables consisting of a variety of medical and psychological conditions and functional impairments. The total number of deficits for an individual patient was divided by all the predetermined clinical variables to calculate in order to obtain a Frailty Index (FI) score. Rockwood et al. then compared the FI with the frailty phenotype, demonstrating that both frailty definitions correlated moderately well with each other. However, FI is hard to implement into routine clinical cares because it requires the assessment of

many variables [3, 5, 12]. The Clinical Frailty Scale (CFS) is a frailty screening tool that consists of a 7-point scale with descriptors for levels of frailty that relies on clinical judgement alone, which then it was updated to nine descriptors including two terminality states. Higher scores on the CFS were associated with an increased risk of death and institutionalization. The CFS is the simplest and clinically useful and validated tool for diagnosing frailty, then it seems to be the most recommended test because it integrates known and unrecognized disturbances in multiple organ systems (cardiovascular, respiratory, nervous, and musculoskeletal systems) many of which affect survival [1]. Alfaadhel et al. demonstrated that high CFS scores at dialysis initiation are associated with mortality, and a subsequent study showed that the CFS performed in patient's pre-dialysis is an independent predictor of mortality. In this sense, Iyasere et al. performed the CFS within their study that compared the quality of life and physical function in older patients on assisted peritoneal dialysis and hemodialysis, documenting that higher CFS scores were associated with worse HRQL scores [3, 4, 12] (Table 11.3). Clarke et al. report that the self-reported measures of physical performance Duke Activity Status Index (physical function) and General Practice Physical Activity Questionnaire (habitual activity regarding walking behavior) were independently associated with survival in non-dialysis CKD [17]. Even though self-report responses are simple to complete, they may be confusing or allow respondents to overestimate their capabilities [18]. For instance, from a group of stage 4–5 CKD patients, only 6% self-identified as frail, while in fact,

Table 11.3 Clinical Frailty Scale (CFS) (If dementia is present, the degree of frailty usually corresponds to the degree of dementia)

CFS score	Clinical characteristics
1 - Very fit	People who are robust, active, energetic, and motivated. These people commonly exercise regularly. They are among the fittest for their age.
2 - Well	People who have no active disease symptoms, but are less fit than category 1. Often, they exercise or are very active occasionally.
3 - Managing well	People whose medical problem are well controlled, but are not regularly active beyond routine walking.
4 - Vulnerable	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up," and/or being tired during the day.
5 - Mildly frail	These people often have more evident slowing and need help in high orders (finances, medication, transportation, heavy housework).
6 - Moderately frail	People need help with all outdoor activities. Indoors, they need help with housekeeping, and often have problems with stairs. They also need help with bathing and might need minimal assistance with dressing.
7 - Severely frail	Completely dependent for personal care, from either cause (physical or cognitive). Even so, they seem stable and not at high risk of dying.
8 - Very severely frail	Completely dependent, and approaching the end of life (within 6 months).
9 - Terminally ill	Approaching the end of life. This category applies to any people with a life expectancy <6 months, who are not otherwise evidently frail.

20% were measured as frail by applying the Fried phenotype. Besides, it has been documented that among ESRD patients, 91% of whom both measured and self-identified as frail, believed that adults with ESRD just like them are more likely to be frail than healthy adults. However, only 58% of participants who measured as frail but not identified that way believed that adults with ESRD are more likely to be frail [9]. Even though it has been suggested that questionnaire-based frailty assessing methods are more likely to overestimate the patient's capability, they still appear to be predictive of outcomes [12]. Regarding the medical-reports, 98% of clinicians think that adults with ESRD are more likely to be frail than healthy adults. There are three Fried frailty components that at least one clinician identifies as not relevant to adults with ESRD: weight loss, slowed walking, and weak strength. The component most frequently identified as not relevant to adults with ESRD was weight loss, since their weight constantly fluctuates [9]. Regarding frailty diagnostic physical test, the walking speed test showed the highest area under the curve (AUC) value (0.97 [95% CI 0.93–1.00]), but the Frailty Phenotype walking speed criterion cut-off was most discriminative with a sensitivity of 0.84 (95% CI 0.62–0.94) and specificity of 0.96 (95% CI 0.88–0.99). Among the non-physical frailty diagnostic tests, the CFS showed the highest AUC value (0.90 [95% CI 0.84–0.97]). It showed good sensitivity and specificity when using a cut-off of ≥5 (0.79 [95% CI 0.57–0.91] and 0.87 [95% CI 0.78–0.93], respectively [1] (Table 11.1)**.** Finally, Iyasere et al. demonstrated that higher CFS scores are associated with worse HRQL in older patients receiving assisted peritoneal dialysis and hemodialysis. The FI had the worst performance with a low and non-significant AUC value (0.63, 95% CI 0.50–0.78) in CKD. Roshanravan et al. demonstrated that walking speed is associated with mortality in patients with CKD, unlike hand grip strength [1].

It should be taken into account that the low level of physical activity usually found in ESRD patients can tend to over-detect frailty phenotype in this group; then, the reliable tests mentioned above can help to avoid misdiagnose [10].

Senescent Nephropathy Treatment

Frailty status trends should be identified since there is a window of opportunity in which clinicians can successfully intervene by referring patients to interventions aimed at decreasing frailty risk and minimizing premature mortality by optimizing nutritional and rehabilitation [18]. The prevention or delay of the appearance of frailty and sarcopenia can be accomplished mainly by low intensity resistance and aerobic physical exercise, an adequate caloric and protein intake, vitamin D supplementation, and avoidance of polypharmacy. In addition, these patients should also receive their CKD corresponding treatment, but even frailty evaluation can contribute to redesigning patient's therapeutic objectives [16].

There is an increased risk of poor outcomes associated with frailty, leading to the analysis of risk to benefit trade-off of standard treatment options (including renal replacement therapies) for the patient. For instance, nephroprevention objectives for

frail CKD older patients should be different from those for robust CKD young patients (Table 11.4) [19]. Therefore, early frailty identification is a vital medical target because of its high and increasing prevalence and to its prognostic importance and influence in the potential medical management (Fig. 11.1) [4].

Table 11.4 Nephroprevention targets (estimative) for chronic kidney disease (CKD) and senescent nephropathy (SN) patients

Nephroprevention targets	CKD conventional targets	SN modified targets (if conventional targets were not tolerated)
Diet	Low sodium Low protein	Normal sodium (to avoid hypotension and/or hyponatremia) Normal protein (to avoid sarcopenia)
Hemoglobin (g/dl)	11	11.5–12 (to avoid cognitive dysfunction and/or falls)
Glycated hemoglobin (HbA_{1C}) (%)	<7	7.5–8.5 (to avoid hypoglycemia)
Blood pressure (mmHg)	≤130–80	≤140/150–80 (to avoid cognitive dysfunction and/or falls) diastolic higher 60 (to avoid coronary event)
Proteinuria (g/day)	<0.5	˂1 (to avoid hyperkalemia, hyponatremia, and /or renal function deterioration induced by antiproteinuric drugs)

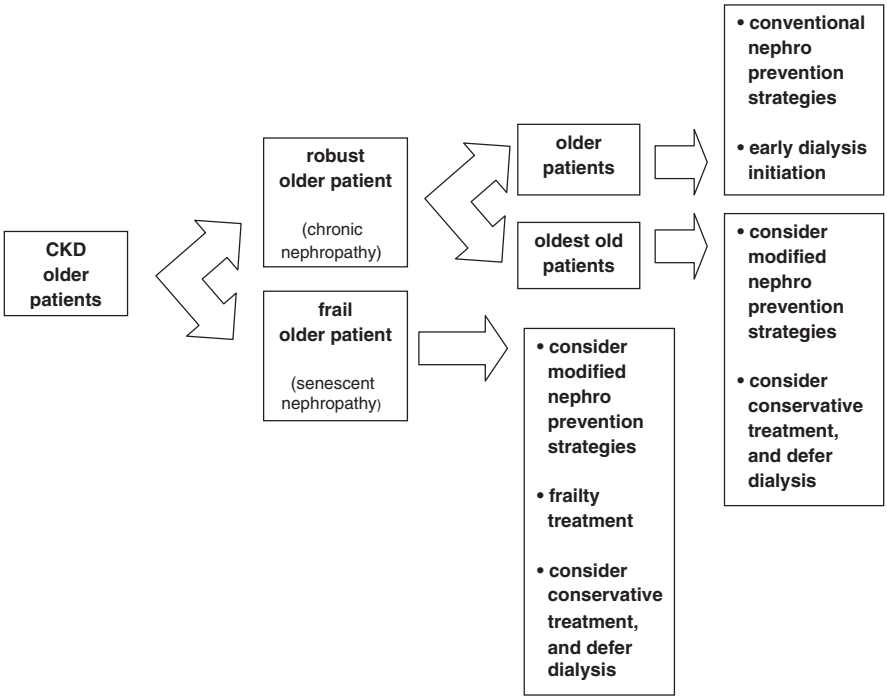

Fig. 11.1 Proposed nephroprevention algorithm in older patients with chronic kidney disease (CKD)

Diet

Patients with advanced CKD often have a reduced energy intake that contributes to sarcopenia and, subsequently, to physical frailty. This is generally due to anorexia which is present in one-third of ESRD patients. This loss of appetite is multifactorial, being its potential contributors the uremic milieu, inflammation, superimposed illnesses, medications, and low mood. Moreover, the uremic toxins accumulation causes defects in the appetite hypothalamic regulation. Cognitive impairment, which is more common in the CKD population, usually leads to reduced food intake. Patients with CKD should maintain an adequate protein and energy intake while restricting dietary phosphate intake to prevent the development of secondary hyperparathyroidism and CKD bone disease [12].

Exercise

Exercise can be used as a treatment for sarcopenia, since its beneficial effect has been associated to improvements in proteolysis, muscle regeneration, and inflammatory cytokines release. Low-intensity resistance and aerobic exercise improved physical fitness, muscular strength, and quality of life not only in ESRD and dialysis patients, but also has positive effects on eGFR and exercise tolerance in stage 3–4 CKD. Unfortunately, limited evidence is available regarding the exercise impact on frailty in earlier stages of CKD [9, 10, 17]. The importance of regular exercise in CKD older patients lies in building up or maintaining their functional capacity and independence [5]. In this sense, an exercise counseling clinic could be an option to prevent the progression of sarcopenia in CKD. This counselling clinic should consist of an active clinical program situated in a medical fitness facility that specialized in dealing with chronic nephropathy. When patients first enter the program, they should be evaluated, after this evaluation, they should be counseled by a certified exercise physiologist who will prescribe an individualized exercise plan, which includes a combination of aerobic and resistance exercise. Then, nephrologists should make a revision of physical exercise for each individual to rule out possible contraindications for these patients. Finally, patients receive periodic motivational counseling, which includes review of the initial exercise prescription, identification of barriers to exercise, and reminder regarding patient's follow-up [8].

Anemia Treatment

A large multicenter cross-sectional study in stage 3–5 CKD performed by Finkelstein et al. showed that higher hemoglobin levels were associated with significantly higher HRQL scores, being the maximal score increase when hemoglobin ranges 10–12 g/dL, with blunted improvements above this level [13, 20].

Androgens

Testosterone deficiency is frequently present in male ESRD patients and is independently associated with adverse outcomes. In earlier stages of CKD, testosterone level was an independent predictor of muscle mass and strength, with low serum levels of testosterone in men which is a significant factor in the sarcopenia and frailty pathophysiology [12]. Since that testosterone has been proposed as a therapeutic alternative, if it is not contraindicated, to treating sarcopenic frailty older patients [10].

Vitamin D

Low 25-hydroxyvitamin D [25(OH)D] levels are associated with frailty in the older individuals. The vitamin acts directly on skeletal muscle influencing contractile muscle function and muscle metabolism. Gordon et al. demonstrated that 1,25(OH) D is a determinant of physical function and muscle size in CKD patients. Therefore, vitamin D deficiency may contribute to developing frailty in CKD, and this vitamin supplementation could be useful for treating this deficit [10, 12].

Other Measurements

Oral sodium bicarbonate treatment can be used to treat mild metabolic acidosis, improving nutritional parameters and muscle strength. Most guidelines currently recommend administering oral sodium bicarbonate when the serum bicarbonate concentration is <22 mmol/L, though the target of bicarbonatemia is not well-defined. It is also important to avoid periods of significant fluid overload that can stimulate the inflammatory cascade and subsequent protein catabolism, thus fluid restriction, diuretic therapy and RRT can be required. Finally, uremia leads to protein catabolism and subsequent sarcopenia, therefore the timing of dialysis initiation is important [12]. Angiotensin-converting enzyme inhibitors may improve the structure and biochemical function of skeletal muscle, and they may halt or slow senile decline in muscle strength. Other substances that may improve muscular function are growth hormone, androgens, and antioxidants [10]. In addition, avoidance of polypharmacy may be another efficient strategy to prevent or delay the onset of both frailty and sarcopenia [10, 12, 21].

There are a number of therapeutic options available for older CKD patients that should be chosen taking into consideration the patient's therapy choice and overall clinical functional status. These are nephroprevention strategies (conventional or modified), conservative treatment, dialysis initiation (early or delayed), or palliative care [4, 10, 22]. Regarding the conservative treatment, it has the

objective of managing non-anuric ESRD patients without prescribing dialysis. It constitutes an alternative for handling non-terminal very old or frail older patients suffering from ESRD who are not adequate candidates for dialytic therapy, due to medical or personal (autonomy) reasons. For CKD conservative treatment many drugs can be used, such as loop diuretics for salt and water overload, potassium binders for hyperkalemia, subcutaneous erythropoietin for anemia, sodium bicarbonate for metabolic acidosis, activated charcoal for high serum urea, calcium supplements for hypocalcemia, and phosphate binders for hyperphosphatemia. Besides, this treatment also includes nutritionist counseling and psychological support [16].

Regarding the palliative treatment, which is used in terminal patients, consists of a symptomatic therapy (oxygen, analgesic, etc.) that includes psychological assistance [16]. In this regard, around 5% of older patients refuse to initiate dialysis and octogenarian patients may not be able to receive treatment due to extreme frailty, such as marked dementia or multiple comorbidities, due to lack of dialitic accesses or even intolerance to the procedure. On the contrary, withdrawal from dialysis is more frequent among nursing home dialysis patients, and discontinuation rate is associated to social and medical reasons, such as severe dementia or terminal oncological disease.

When senescent nephropathy is present, frailty treatment should be initiated based on its inducing condition. For example, whether muscle mass loss is identified as the patient's frailty-inducing factor, a normal diet and muscle exercise should be recommended, instead of a low-protein diet and low daily exercise. Moreover, the CKD therapeutic measures that are usually used should be executed more carefully in cases where frailty coexists with CKD, due to the patient's intolerance. In cases where conventional targets cannot be accomplished due to patient's intolerance to nephroprevention therapy, modified nephroprevention targets, doses ajusted to frailty, and more rigorous medical controls, should be sought (Table 11.4 and Fig. 11.1) [4].

References

1. Nixon AC, Bampouras TM, Pendleton N, Mitra S, Dhaygude AP. Diagnostic accuracy of frailty screening methods in advanced chronic kidney disease. Nephron. 2019;141(3):147–55. https://doi.org/10.1159/000494223.
2. Coppolino G, Bolignano D, Gareri P, Ruberto C, Andreucci M, Ruotolo G, Rocca M, Castagna A. Kidney function and cognitive decline in frail elderly: two faces of the same coin? Int Urol Nephrol. 2018;50(8):1505–10. https://doi.org/10.1007/s11255-018-1900-3.
3. Ali H, Abdelaal F, Baharani J. Assessment of frailty in elderly pre-dialysis population using simple tools. Saudi J Kidney Dis Transpl. 2017;28(4):716–24.
4. Ostuni M, Musso CG. Usefulness of frailty evaluation for handling chronic kidney disease elderly patients: a review and original proposal. Int Urol Nephrol. 2019;51(3):461–5. https://doi.org/10.1007/s11255-018-2061-0.
5. Demircioglu DT. The Association of Vitamin D levels and the frailty phenotype among non-geriatric dialysis patients: a cross-sectional study. Clinics (Sao Paulo). 2018;73:e116. https://doi.org/10.6061/clinics/2018/e116.

6. Musso CG, Vilas M, Onuigbo M. Nephroprevention in the oldest old with chronic kidney disease: special considerations. World J Nephrol. 2015;4(1):1–5. https://doi.org/10.5527/wjn.v4.i1.1.
7. Adame Perez SI, Senior PA, Field CJ, Jindal K, Mager DR. Frailty, health-related quality of life, cognition, depression, vitamin D and health-care utilization in an ambulatory adult population with type 1 or type 2 diabetes mellitus and chronic kidney disease: a cross-sectional analysis. Can J Diabetes. 2019;43(2):90–7. https://doi.org/10.1016/j.jcjd.2018.06.001.
8. Bohm CJ, Storsley LJ, Hiebert BM, Nelko S, Tangri N, Cheskin LJ, McAdams-DeMarco MA, Rigatto C. Impact of exercise counseling on physical function in chronic kidney disease: an observational study. Can J Kidney Health Dis. 2018;5:2054358117753615. https://doi.org/10.1177/2054358117753615.
9. Van Pilsum Rasmussen S, Konel J, Warsame F, Ying H, Buta B, Haugen C, King E, DiBrito S, Varadhan R, Rodríguez-Mañas L, Walston JD, Segev DL, McAdams-DeMarco M. Engaging clinicians and patients to assess and improve frailty measurement in adults with end stage renal disease. BMC Nephrol. 2018;19(1):8. https://doi.org/10.1186/s12882-017-0806-0.
10. Musso CG, Jauregui JR, Macías Núñez JF. Frailty phenotype and chronic kidney disease: a review of the literature. Int Urol Nephrol. 2015;47(11):1801–7. https://doi.org/10.1007/s11255-015-1112-z.
11. McAdams-DeMarco MA, Ying H, Thomas AG, Warsame F, Shaffer AA, Haugen C, Garonzik-Wang JM, Desai NM, Varadhan R, Walston J, Norman SP, Segev DL. Frailty, inflammatory markers, and waitlist mortality among patients with end-stage renal disease in a prospective cohort study. Transplantation. 2018;102(10):1740–6. https://doi.org/10.1097/TP.0000000000002213.
12. Nixon AC, Bampouras TM, Pendleton N, Woywodt A, Mitra S, Dhaygude A. Frailty and chronic kidney disease: current evidence and continuing uncertainties. Clin Kidney J. 2018;11(2):236–45. https://doi.org/10.1093/ckj/sfx134.
13. Kittiskulnam P, Sheshadri A, Johansen K. Consequences of CKD on functioning. Semin Nephrol. 2016;36(4):305–18. https://doi.org/10.1016/j.semnephrol.2016.05.007.
14. Kamijo, Kanda E, Ishibashi Y, Yoshida M. Sarcopenia and frailty in PD: impact on mortality, malnutrition, and inflammation. Perit Dial Int. 2018;38(6):447–54. https://doi.org/10.3747/pdi.2017.00271.
15. McAdams-DeMarco MA, Ying H, Olorundare I, King EA, Desai N, Dagher N, Lonze B, Montgomery R, Walston J, Segev DL. Frailty and health-related quality of life in end stage renal disease patients of all ages. J Frailty Aging. 2016;5(3):174–9.
16. Musso CG, Trigka K, Dousdampanis P, Jauregui J. Therapeutic alternatives and palliative care for advanced renal disease in the very elderly: a review of the literature. Int Urol Nephrol. 2015;47(4):647–54. https://doi.org/10.1007/s11255-014-0886-8.
17. Ortiz A, Sanchez-niño M. Sarcopenia in CKD: a roadmap from basic pathogenetic mechanisms to clinical trials. Clin Kidney J. 2019;12(1):110–2.
18. Sieverdes JC, Rao V, Taber DJ, Noltemeyer Z, McGillicuddy JW, Bergamin M, Thangavel S, Baliga PK. Feasibility and functional testing for frailty in chronic kidney disease. Prog Transplant. 2018;28(3):299–300. https://doi.org/10.1177/1526924818781577.
19. Moffatt H, Moorhouse P, Mallery L, Landry D, Tennankore K. Using the Frailty Assessment for Care Planning Tool (FACT) to screen elderly chronic kidney disease patients for frailty: the nurse experience. Clin Interv Aging. 2018;13:843–52. https://doi.org/10.2147/CIA.S150673.
20. Wawer AA, Jennings A, Fairweather-Tait SJ. Iron status in the elderly: a review of recent evidence. Mech Ageing Dev. 2018;175:55–73. https://doi.org/10.1016/j.mad.2018.07.003.
21. Formica M, Politano P, Marazzi F, Tamagnone M, Serra I, Marengo M, Falconi D, Gherzi M, Tattoli F, Bottaro C, Giuliano D, Tibaldi V, Isaia GC. Acute kidney injury and chronic kidney disease in the elderly and polypharmacy. Blood Purif. 2018;46(4):332–6. https://doi.org/10.1159/000492149.
22. Bansal AD, Leonberg-Yoo A, Schell JO, Scherer JS, Jones CA. Ten tips nephrologists wish the palliative care team knew about caring for patients with kidney disease. J Palliat Med. 2018;21(4):546–51. https://doi.org/10.1089/jpm.2018.0087.