

Chapter 34: Association Between CKD and Frailty and Prevention of Functional Losses

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The incidence and prevalence of chronic kidney disease (CKD) is increasing worldwide and more so in the elderly persons. Among individuals 70 yr of age or older, the prevalence of CKD increased from 38% in 1988 to 1994 to 47% in 1999 to 2004.¹ This noted increase in the number of elderly patients with CKD has been associated with new challenges where CKD has become increasingly recognized as an important comorbid condition in elderly individuals leading to death, cardiovascular events, and hospitalizations.²

Recently, less recognized challenges, such as functional impairment and frailty, became more apparent as factors that affect the quality of life and outcomes in the elderly patients with CKD.^{3–6} Fried *et al.*⁵ described an association between CKD on one hand, and the development of functional impairment on the other. Roderick *et al.*⁷ further showed that the strength of the association with measures of morbidity and functional impairment increase as renal function worsened. Identifying the predisposing factors of frailty in these elderly patients with CKD, to help prevent and manage it, is being recognized more as crucial to improve their quality of life and their longevity.

FRAILITY

Definition

Frailty is a term that has been used for some time with variable definitions. Earlier definitions were vague and described an elderly patient who is lacking general strength and is susceptible to diseases. Fried *et al.*⁸ suggested a more precise and standard definition in which three or more of five components (Table 1) would define frailty, whereas the presence of one or two of these frailty components would be termed “prefrailty.” Prefrail elderly persons are more likely than nonfrail elderly persons to develop the whole frailty syndrome.⁸ This is an im-

portant concept because it is believed that intervention at that stage of prefrailty may reverse the frailty syndrome.⁹

Regardless of the definition, it is important to realize two main things. The first is that frailty develops slowly and that it may be initiated by different factors such as lack of activity, inadequate nutritional intake, stress, or triggered by a disease process such as CKD. The second is that the presence of frailty is associated with several adverse health outcomes such as functional decline [worsening mobility, activities of daily living (ADL) disability, recurrent falls, hip and nonspine fractures], hospitalization, and death.^{8,10–12} The recognition of these two issues highlight the importance of early identification of the problem, hopefully at the prefrailty period, and intervening in such a way to minimize the poor outcomes that are associated with the frailty syndrome.

CKD and Frailty

Background.

CKD has long been recognized to be associated with various comorbidities. Rocco *et al.*¹³ showed more than a decade ago that patients with moderate to advanced CKD have a reduced quality of life and an increased frequency and severity of poor symptoms such as tiring easily, weakness, lack of energy, difficulty sleeping, muscle cramps, and easy bruising, as well as psychologic distress. Subsequently, Shidler *et al.*¹⁴ showed higher negative perception of illness to be associated with higher depression scores and lower quality of life, even at early stages of CKD.

Shlipak *et al.*³ expanded further on that concept to show that CKD is also associated with poor func-

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Table 1. Definition of frailty

Unintentional weight loss (10 lbs or more in a year)
Self-reported exhaustion
Weakness (measured by grip strength)
Slow walking speed
Low physical activity

tional status. In their study, Shlipak *et al.* showed that CKD is associated with a greater prevalence of both frailty and disability in the elderly population, with the prevalence of frailty and disability being 15 and 12%, respectively, in elderly with CKD, *versus* only 6 and 7% in the elderly with normal kidney function, respectively. Similarly, frailty was highly prevalent in patients with end-stage kidney disease (ESKD) on hemodialysis (HD).⁶ It increased more as a function of aging. The proportion of frailty gradually increased in patients with ESKD as they aged from 44.4% in patients younger than 40 yr to 66.4% in patients 50 to 60 yr of age to 78.8% in ESKD patients older than 80 yr. Frailty was also noted to be independently associated with high risk of death and high risk of the combined outcome of death and hospitalization in these patients with ESKD on HD.⁶

Mechanism of Frailty in Elderly Patients With CKD.

Frailty is not synonymous with aging; in fact, only 3 to 7% of elderly persons between the ages of 65 to 75 yr are frail.⁹ Shuurmans *et al.*¹⁵ hypothesized that the concept of frailty is more predictive of an outcome than the chronological age *per se*, suggesting that frailty may be a better criterion to identify older persons in need for intervention.

Several factors have been suggested to predispose to frailty in elderly patients in general and more so in elderly patients with CKD, including the following (Table 2).

Increased Inflammatory and Procoagulant Factors.

Walston *et al.*¹⁶ showed that frailty in elderly was associated with increased inflammatory and procoagulant markers and that this increase was independent of the disease status. Similar results were found in elderly patients with CKD, where renal insufficiency was independently associated with elevations in inflammatory and procoagulant biomarkers.¹⁷ Taking these results together, it is suggested that CKD in elderly patients, through its effects on inflammatory and procoagulant markers, may contribute to the frailty noted in these patients. This was further suggested by a pilot study conducted by Swidler *et al.*⁴ on 26 elderly patients with CKD, who showed that these

patients exhibited a high prevalence of frailty in association with elevated inflammatory markers.

Hormonal Changes.

As we age, several changes occur in the hormonal levels and activities, and these hormonal changes are prevalent in patients with CKD and may act as contributing factors in the pathophysiology of frailty noted in the elderly patients with CKD.¹⁸

The levels of both the testosterone hormone levels and vitamin D decline¹⁹ with aging and with CKD, and this decline has been noted to be associated with decrease in muscle mass and strength, as well as poor function in older patients.²⁰ Other endocrinological abnormalities occur with aging and with CKD such as hypo- and hyperthyroidism and diabetes mellitus²⁰ and are also associated with muscle strength and functional decline.

Although growth hormone (GH) levels decrease with aging, its basal levels and the spontaneous secretion of endogenous GH in patients with CKD are either normal or even increased; however, GH action is decreased in these patients with CKD because of insensitivity to GH.^{21,22} Giving GH to elderly patients on chronic HD improved muscle performance, suggesting a role of GH in preserving muscle function.²³ Similarly, thyroid hormonal abnormalities are prevalent in the elderly²⁴ and in patients with renal impairment^{25,26} and are associated with frequent comorbidities²⁷ that can play a role in the noted poor outcomes.

Malnutrition.

Inadequate food intake is a common finding in elderly persons and more so in uremic patients. Alteration in taste, smell, and mental status often found in patients with CKD can lead to malnutrition. This age-related reduction in food intake, accelerated further in uremic individuals, can lead to further weight loss together with an increased loss of muscle mass and strength causing sarcopenia.²⁸ Advanced sarcopenia, associated with malnutrition, is synonymous with physical frailty and is estimated to affect 30% of people older than 60 yr and may affect >50% of those older than 80 yr.²⁹

Anemia.

Anemia is highly prevalent in elderly persons³⁰ and in patients with CKD³¹ and has been shown to be associated with mobility dysfunction, physical limitation, and reduced exercise capacity.^{32,33} The Women's Health and Aging Studies I and II (WHAS) identified anemia as a risk factor for frailty.³⁴ Taking

Table 2. Mechanisms and management of frailty

Mechanisms of Frailty	Management of Frailty
Increase inflammatory markers	Anti-inflammatory/ACEI
Anemia	Erythropoiesis stimulating agents
Anorexia, nausea→poor nutrition, weight loss, sarcopenia	Nutritional support
Hormonal changes	Hormonal replacement
Decrease muscle strength	Exercise/Tai Chi
Depression	Psychotherapy/antidepressants

these studies together, anemia is suggested to be a factor predisposing to frailty in elderly patients with CKD.

Depression.

Depression is highly prevalent in patients with CKD,³⁵ occurring in 20 to 30% of these patients.³⁶ It correlates with both hospitalization and mortality rates³⁷ and has been associated with frailty.³

Management.

Several studies have investigated the effects of intervention on functional decline in elderly population with various results.^{39–42} The first approach in management of elderly patients with CKD is to rule out any underlying disease that could be contributing to the symptoms of frailty such as an occult malignancy, neglect, and alcohol abuse. Identifying patients at the prefrailty stage is very crucial to delay or even prevent further deteriorations. The following measures were suggested for management of both prefrailty and frailty stages (Table 2).

Exercise

The beneficial effects of exercise in the older population have been well documented. Exercise may prevent or slow down the decline in physical functioning.^{43,44} Interestingly, it was noted that elderly who are physical active⁴⁵ and those who undergo resistance exercise⁴⁶ have lower levels of inflammatory markers, suggesting an anti-inflammatory component to exercise.

Studies in the field of renal rehabilitation have shown that exercise training in HD patients improves the aerobic capacity and muscle strength.⁴⁷ Specific types of physical activity have been shown to help reduce frailty.⁴⁸ Tai Chi exercises has been used in China for centuries and consist of a number of stylized movements in which practitioners continuously change posture. These movements address weakness, slow walking speed, and low physical activity, three of the five frailty components.

Nutrition.

Malnutrition is common in patients with CKD⁴⁹ and is associated with low muscle mass and sarcopenia.⁵⁰ Managing malnutrition and supplementation of vitamin D are promising means to alleviate some of the components of frailty. This is more important in patients with CKD who have decreased levels of active vitamin D. Vitamin D was shown to improve balance, reduce falls, improve quadriceps strength, and to predict better neuromuscular performances.^{51,52}

Of interest, chronic inflammation, which is common in patients with CKD,⁴ may contribute to the malnutrition noted in these patients.⁵⁰ Hence, new treatment strategies targeting inflammatory markers may be beneficial to improve the malnutrition and frailty. In this respect, angiotensin converting enzyme inhibitors (ACEIs) have been shown to be associated with a better nutritional status and lower levels of inflammatory markers in patients with CKD,⁵³ as well as improving muscle strength.⁵⁴

Hormonal Replacement.

To combat the progression of sarcopenia, several intervention strategies including replacement or even supplementation doses of hormones such as testosterone,⁵⁵ GH,⁵⁶ insulin-like growth factor (IGF),⁵⁷ and dehydroepiandrosterone (DHEA)⁵⁸ were used.

Testosterone replacement studies have shown an increase in muscle mass in males and improved function in elderly after hospitalization.¹⁹ Similarly, high doses of DHEA improved muscle strength in males.¹⁹ GH treatment to elderly chronic HD patients produced anabolic effects, with improved muscle performance and better nutritional status,²³ increased lean body mass at all dosage levels of GH, and improved the quality of life.⁵⁹

Anemia.

Patients treated with recombinant human erythropoietin had a better quality of life,⁶⁰ significant increases in energy and physical function,⁶¹ significant improvement in work capacity, and an increase in measured exercise capacity.⁶² Thus, identifying and treating anemia may contribute in improving symptoms of frailty in elderly patients with CKD.

Depression.

Recent reports have suggested that depressive symptoms can be ameliorated by psychiatric counseling, cognitive-behavioral therapy, and/or medications.^{63,64} Good psychologic health, including positive affect, was found to significantly lower the risk of frailty.⁴¹ Thus, identifying symptoms of depression by screening tests as the Geriatric Depression Scale (GDS) and adequately managing depression by therapy and medication can be beneficial in the prevention of frailty. However, the treatment of clinical depression in dialysis patients presents various obstacles. First, it is difficult to encourage patients to pursue and complete an appropriate evaluation³⁶; in addition, many patients are reluctant to take additional medications, the medications themselves may have side effects, and the dialysis regimen itself imposes time constraints on patients' willingness to obtain appropriate counseling.

Future Directives.

Several other drugs might have a role in the treatment of frailty and are currently being studied. These include anti-inflammatory and anabolic agents, psycho-stimulants, and selective androgen receptor modulators

CONCLUSIONS

Frailty, an important problem in geriatric medicine, is becoming more recognized in patients with CKD, as well as patients with ESKD, as a factor that can even worsen the prognosis and the quality of life of these patients. It is imperative for the nephrology community, in lieu of the rising numbers of elderly

patients being seen by nephrologists, to recognize this syndrome of frailty and work diligently to manage it.

TAKE HOME POINTS

- Frailty is a prevalent and a newly recognized challenge to patients with CKD that affects the quality of life and outcomes in elderly patients with CKD
- Frailty develops slowly and its presence is associated with several adverse health outcomes as functional decline, hospitalization, and death
- Strength of association with measures of morbidity and functional impairment increase as renal function worsens
- Several mechanisms were suggested to explain the association between frailty and CKD such as the presence of inflammatory markers, anemia, malnutrition, hormonal changes, depression, and decreased muscle strength
- Identifying and treating the underlying mechanisms at the prefrailty stage can help delay or even prevent further deteriorations

DISCLOSURES

None.

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REVIEW QUESTIONS: ASSOCIATION BETWEEN CKD AND FRAILTY AND PREVENTION OF FUNCTIONAL LOSSES

1. The following factors have been suggested to predispose to frailty in elderly patients with CKD except:
 - a. Anemia
 - b. Hypertension
 - c. Depression
 - d. Malnutrition
 - e. Decrease in growth hormone activity
2. The following were suggested to define frailty except:
 - a. Weakness
 - b. Slow walking speed
 - c. Intentional weight loss
 - d. Low physical activity
 - e. Self-reported exhaustion
3. True or False:
 - a. Identifying patients at the prefrailty stage is crucial to delay or even prevent further deteriorations
 - b. Frailty is less prevalent in elderly with CKD versus elderly with normal kidney function
 - c. New treatment strategies as angiotensin converting enzyme inhibitors is associated with a better nutritional status and lower inflammatory markers in patients with CKD, and may be beneficial in improving malnutrition and frailty