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Sarcopenia and Frailty: Challenges in Mainstream Nephrology Practice

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Sarcopenia and frailty are prevalent in the chronic kidney disease (CKD) population. Sarcopenia is characterised by the loss of muscle mass and function, while frailty is defined as a multi-system impairment associated with increased vulnerability to stressors. There is substantial overlap between the 2 conditions, particularly with regards to physical aspects: low grip strength, gait speed and low muscle mass. Both sarcopenia and frailty have been associated with a wide range of adverse health outcomes. Although there is no recommended pharmacological treatment as yet, it is widely accepted that exercise training and nutritional supplementation are the key interventions to maintain skeletal muscle mass and strength. This review aims to present a comprehensive overview of sarcopenia and frailty in patients with CKD.

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Sarcopenia is derived from Greek (sarcx for "flesh" and penia for "loss") and was first described by Irwin Rosenberg in 1988.[1] More recent definitions include the functional loss of muscle strength and performance that occurs with aging.[2,3] Sarcopenia has only recently gained recognition as a disease entity with an International Classification of Diseases Tenth Revision Clinical Modification (ICD-10-CM) (M62.84) code in 2016.[4] It incurs a substantial financial burden to healthcare systems and was estimated to have a direct healthcare cost of $18.5 billion in the United States.[5] Frailty, a clinical condition first established by geriatricians, is a syndrome characterized by a reduction in functional reserve, with an increased susceptibility for developing adverse outcomes upon exposure to stressors.[6] Encompassing physical, cognitive, and social components, frailty constitutes a broader functional spectrum than sarcopenia.[7] Nevertheless, there is considerable overlap between the 2 conditions, primarily the physical aspects of frailty—weak grip strength, slow walking speed, and weight loss (as a proxy for loss of muscle mass), as defined by the Fried criteria.[8]

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Profound progress has been made in our understanding of both conditions over the past decade, and there has been an exponential growth in the number of scientific publications on sarcopenia and frailty. Furthermore, there is emerging evidence linking sarcopenia and frailty with greater mortality risk in patients with chronic kidney disease (CKD). Importantly, nephrologists frequently encounter younger patients infirmed by multiple comorbidities who present with features consistent with sarcopenia and/or frailty in clinical practice. Therefore sarcopenia and frailty are not necessarily limited to the older population. This review provides a comprehensive overview of sarcopenia and frailty in CKD and discusses the latest developments in therapeutic interventions.

Epidemiology

Sarcopenia is twice as common as frailty in the general population.[9] Sarcopenia may lead to frailty; however, not all patients with sarcopenia are frail. Over the age of 50, muscle mass declines by 1% to 2% per year, while muscle strength decreases at a rate of 1.5% per year, increasing to 3% after age 60 years.[10] In the general population, the prevalence of sarcopenia in adults aged 60 to 70 years ranges between 5% and 13%, increasing to 11% to 50% in those aged 80 years or more.[9] In CKD patients, the reported prevalence of sarcopenia varies markedly from 3.9% to 98.5%,[11–16] a variance thought due to both heterogeneous study

populations and methodological inconsistencies used to evaluate sarcopenia or muscle wasting before the proposition of a unified definition and diagnostic criteria by the European and North American working groups on sarcopenia.[2,3,17] Similarly, the prevalence of frailty in CKD patients is higher than in the general population (15%−21% vs. 3%−6%),[18,19] and among those who are dialysis dependent, the prevalence of frailty varies between 14% and 73%.[20]

Diagnosis—Definition and Assessment

In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as the presence of low appendicular lean skeletal muscle mass with low muscle strength and/or low physical performance and this was subsequently revised in 2018 to include specific cut-off points for measures to characterize sarcopenia.[2,3] Other international groups have also developed similar definitions for sarcopenia, and the cut-offs for the definitions are ethnically specific and are summarized in Table 1.[21,22] There are many techniques for evaluating muscle quantity, including bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA), computed tomography (CT), magnetic resonance imaging (MRI), and anthropometry measurements such as mid-arm and calf circumference. Although both CT and MRI are regarded as the criterion standards for noninvasive muscle quantity assessment,[23] they are not widely used because of high costs, requirements for highly trained personnel, and poorly established cut-off values to define low muscle mass. Both BIA and DEXA are more readily available for routine patient assessment; however, the accuracy of muscle mass estimation by these methods may possibly be affected by the fluid status of patients with CKD or end-stage kidney disease (ESKD). Nonetheless, several measures could be taken to improve the reliability and reproducibility of measurements, including performing BIA after a time interval of 15 to 20 minutes following the end of the mid-week hemodialysis session[24,25] or when the abdomen is free of dialysate in peritoneal dialysis patients,[25,26] to reflect a "dry-weight" state. Multi-frequency BIA (5−500 kHz) might be preferable to single-frequency BIA (50 kHz) in the assessment of muscle mass, as it is less influenced by fluid overload.[27] Importantly, by recognizing the technological limits in defining muscle quantity and quality, low muscle strength has now become the primary parameter of sarcopenia in the 2018 revised European Working Group on Sarcopenia in Older People (EWGSOP2) guidelines as a more reliable measure of muscle function. It is also a better indicator than muscle mass in predicting adverse outcomes.[3]

On the other hand, at least 67 measurement scales have been used to assess frailty in population-based studies.[28] Broadly, there are 2 distinct models to conceptualize frailty, which has led to different measurement approaches: (i) the frailty index (FI) model, developed by Rockwood *et al.*,[7,29] defines frailty as an accumulation of deficits across multiple organ systems including cognition and mood; and (ii) the frailty phenotype (FP) model,[8] also known as the Fried phenotype, which identifies sarcopenia as a critical pathophysiological feature in which frailty is defined by the presence of 3 or more of the 5 criteria comprising weakness, slowness, shrinkage, exhaustion, and low physical activity. Although the FI model is more widely accepted in the geriatrics community, the Fried phenotype is the most commonly used tool in clinical studies for frailty assessment in the CKD population (accounting for 72% of all studies).[20] Several studies have also used the modified Fried criteria for frailty assessment by substituting the measurement of grip strength and gait speed with questionnaire-based

Table 1. Proposed criteria and cut-offs of measurements for different operational definitions of sarcopenia and Fried model for frailty

Parameter	EWGSOP (2010)[2]	EWGSOP2 (2018)[3]	FNIH (2014)[17]	AWGS (2014)[22]	AWGS (2019)[21]	Fried model (2001)[8]
Muscle mass						Shrinking: at least 5% unintentional weight loss in 12 months Exhaustion: self-report using the CES-D scale Weakness: poor grip strength, stratified by sex and BMI quartiles Slowness: gait speed, stratified by sex and height Low physical activity: <383 kcal/wk (M) or <270 kcal/wk (F) (3 or more of the above criteria to diagnose frailty)
DXA (ASM/height^2)	<7.26 kg/m^2 (M) <5.5 kg/m^2 (F)	<7.0 kg/m^2 (M) <5.5 kg/m^2 (F)	<0.789 m^2 (M)[a] <0.512 m^2 (F)[a]	<7.0 kg/m^2 (M) <5.4 kg/m^2 (F)	<7.0 kg/m^2 (M) <5.4 kg/m^2 (F)	
BIA (ASM/height^2)	<8.87 kg/m^2 (M) <6.42 kg/m^2 (F)			<7.0 kg/m^2 (M) <5.7 kg/m^2 (F)	<7.0 kg/m^2 (M) <5.7 kg/m^2 (F)	
Muscle strength						
Hand grip strength	<30 kg (M) <20 kg (F)	<27 kg (M) <16 kg (F)	<26 kg (M) <16 kg (F)	<26 kg (M) <18 kg (F)	<28 kg (M) <18 kg (F)	
5-Times chair stand test		≥15 s				
Muscle performance						
Gait speed (4-m)	<0.8 m/s	≤0.8 m/s	<0.8 m/s	<0.8 m/s	<1.0 m/s[b]	
400-m Walk test		Non-completion or ≥6 min for completion				
5-Times chair stand test					≥12 s	

ASM, appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BIA, bioelectrical impedance analysis; BMI, body mass index; CES-D, Centre for Epidemiological Studies depression scale; DEXA, dual-energy X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older People; F, female; FNIH, Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project; M, male; SM, skeletal muscle mass.
[a]FNIH defines low lean muscle mass using appendicular skeletal muscle mass adjusted for body mass index.
[b]6-Meter walk: <1.0 m/s.

physical function assessments, probably because of the relative ease and time-efficiency of using such questionnaires. Other, simpler tools to detect frailty in clinical settings include the Short Physical Performance Battery (SPPB), which consists of 3 components (balance, gait speed and chair standing), or gait speed alone, both of which have been independently validated to predict adverse outcomes.[30,31]

Pathogenesis of Sarcopenia and Frailty

Although the relationship between sarcopenia and frailty has not been fully characterized, both conditions share many commonalities in the proposed underlying mechanisms involving a complex interplay between multiple systems and pathophysiologic processes,[32] including aging, immunosenescence, hormonal imbalance, sedentary lifestyle, and poor nutritional status, as well as other comorbidities. Specifically in CKD, metabolic acidosis, accumulation of uremic toxins, and chronic state of catabolism in clinically stable maintenance dialysis patients have been suggested to cause an imbalance of protein generation and degradation, but have not been proved to contribute to the early onset of sarcopenia. Figure 1 shows a simplified illustration of the current understanding of the proposed pathogenesis of sarcopenia and frailty.

Primary sarcopenia is age-related degeneration of the lean body muscle mass and overall musculoskeletal system. The current theoretical understanding of aging suggests that it is caused by the accumulation of unrepaired molecular and cellular damage throughout life due to the limitations of the complex network of maintenance and repair functions.[33] With age, the rate of muscle injury from normal contraction exceeds that of repair and regeneration. Furthermore, a combination of decreased satellite cell (muscle stem cell) proliferative and renewal capability and accumulation of mitochondrial DNA mutations result in altered inter- and intracellular environments that sustain catabolism.[34-36] Furthermore, the aging brain is associated with characteristic structural and physiological changes, leading to cognitive impairment and dementia. Frailty correlates with more rapid cognitive decline, and 2 extensive prospective studies have consistently demonstrated an independent association between frailty and Alzheimer's disease. This entity has been denominated as "cognitive frailty."[37,38]

Immunosenescence is defined as an age-related decline in the immune system's ability to generate effective cellular and antibody responses, resulting in diminished responses to vaccination and increased susceptibility to infections, neoplasia, and autoimmune diseases. The hallmarks of immunosenescence include a reduction in the number of peripheral blood naive cells, with a relative increase in the frequency of memory cells and "inflammaging," a chronic state of low-grade inflammation.[39] In 2002, in a pilot study, Leng *et al*. first reported the association between elevated circulating interleukin-6 (IL-6, a pro-inflammatory cytokine) and frailty,[40] which was subsequently demonstrated in a number of studies that also investigated different inflammatory markers (neutrophils, C-reactive protein [CRP], tumor necrosis factor−α [TNFα], and CXC chemokine ligand 10 [CXCL-10]) and in CKD patients with sarcopenia.[18,41-46] Moreover, a

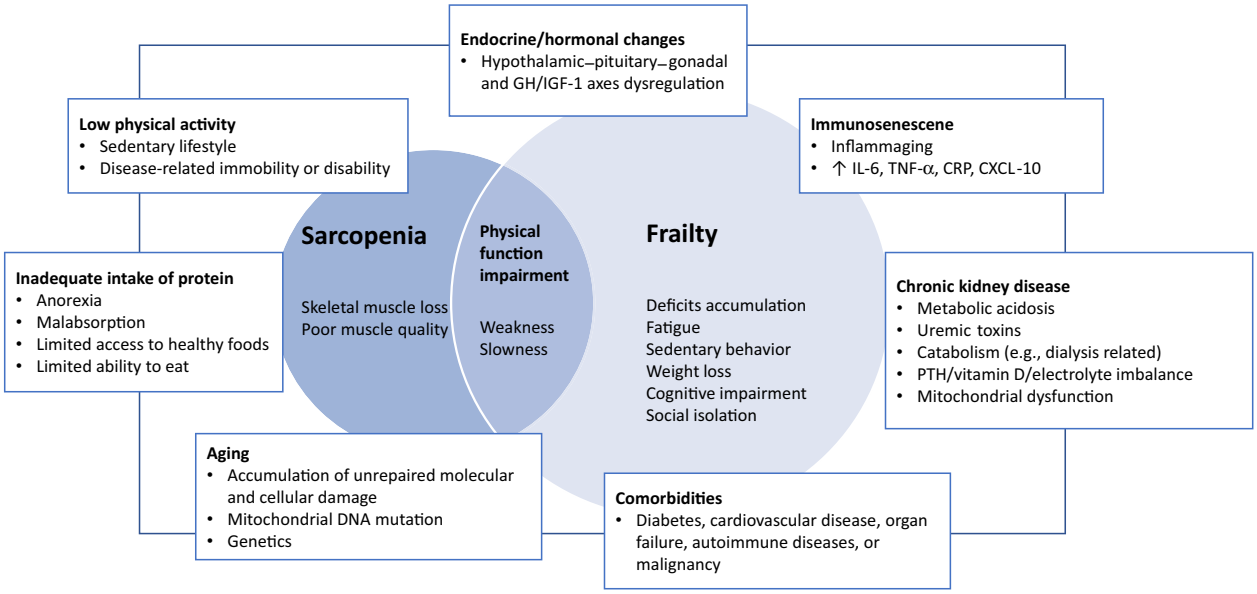

Figure 1. A simplified illustration of the current understanding of the proposed pathogenesis of sarcopenia and frailty. GH/IGF-1, growth hormone/insulin growth factor−1; IL-6, interleukin-6; TNF, tumor necrosis factor; CRP, C-reactive protein; PTH, parathyroid hormone.

significant systemic inflammatory response was observed in the lipopolysaccharide-induced sepsis rat model, along with increased expressions of IL-6 and TNFα in the skeletal muscle associated with loss of muscle mass and strength,[47] which were suppressed by concomitant administration of low-dose dexamethasone.[48] TNFα upregulates the NF-κB pathway via Iκβ kinase (IKK) and induces MuRF-1 expression, which causes myofibril degradation via the ubiquitin−proteasome pathway.[49,50] Similarly, secondary sarcopenia occurs in other systemic diseases that could invoke inflammatory processes: for example, malignancy, CKD, chronic obstructive pulmonary disease, and rheumatoid arthritis. Taken together, immune activation could potentially be a preceding process leading to chronic inflammation in the pathogenesis of sarcopenia and frailty. However, evidence of a direct causal relationship remains to be proved.

The alterations of growth hormone (GH)/insulin growth factor−1 (IGF-1) axis, sex hormone, and cortisol have been regarded as important risk factors for sarcopenia and frailty. Substantially lower serum levels of IGF-1 and dehydroepiandrosterone sulphate (DHEA-S) have been observed in sarcopenic and frail patients.[42,51] Both age-related rapid decrease in estrogen in postmenopausal women and gradual decrease in testosterone in older men also led to a decline in muscle mass and strength. In CKD, abnormalities in vitamin D metabolites, parathyroid hormone and insulin resistance are highly prevalent, in addition to dysregulation of the hypothalamic−pituitary−gonadal and GH/IGF-1 axes.[52] Higher serum parathyroid hormone levels were also correlated with longer times in a timed up-and-go test in a cohort of patients with different stages of CKD, including dialysis-dependent patients.[53] These pronounced endocrine abnormalities, in combination with malnutrition, uremic toxin accumulation, metabolic acidosis, elevated angiotensin II levels, and low-grade inflammation,[54] might aggravate protein catabolism in CKD patients.

Skeletal muscle is continuously remodeled in response to workload, tension, and nutrition. Other factors that contribute to development of sarcopenia and frailty include low physical activity due to either sedentary lifestyle or disease-related immobility, and inadequate intake of energy or protein due to anorexia malabsorption, limited access to healthy foods, limited ability to eat, or high-nutrient requirements. Moreover, Chamberlain *et al*. performed a population-based cohort study involving 12,270 individuals and found that social and behavioral factors (education, marital status, living arrangements, smoking status, and alcohol use) were significantly associated with frailty trajectories in individuals aged 60 to 69 and 70 to 79 years after adjustment for age and sex. Following further adjustment for baseline frailty, less than a high school education, nonmarried marital status, smoking, and concerns from family or friends about one's alcohol intake remained strongly associated with high frailty trajectories.[55]

Clinical Significance of Sarcopenia and Frailty

Sarcopenia and frailty are closely related to detrimental outcomes in older adults, such as an increased risk of falls and fractures, impaired ability to perform activities of daily living, declined cognitive function, loss of independence, need for long-term care placement, and death.[56,57] Sarcopenia and frailty are dynamic processes that could be precipitated or exacerbated by acute illness or injury. Therefore, there is a need for periodic assessment to ascertain how quickly the condition is improving or worsening. Interestingly, Gill *et al*. reported, in a cohort of community-living older individuals, that the probability of transitioning to more severe frailty states was much higher than the opposite way[58] and will often lead to a spiral decline of increasing frailty and a higher risk of worsening disability, falls, hospital admissions, and death. Table 2[13,14,19,59] summarizes a total of 13 retrospective and prospective studies that investigated the adverse clinical outcomes (mortality and hospitalization) in CKD patients with sarcopenia and frailty, respectively, including both non-dialysis-dependent and dialysis-dependent patients. These data have consistently demonstrated that sarcopenia and frailty are common in CKD and are strongly associated with all-cause mortality.

In addition to the aforementioned findings, there is growing evidence to suggest that frail kidney transplant (KT) recipients are more susceptible to early post-transplantation complications than non-frail KT recipients. In a prospective cohort study of 183 KT recipients, Garonzik-Wang *et al*. found that frailty was independently associated with an approximately 2-fold greater risk of delayed graft function.[69] Frail KT recipients are also more likely to develop delirium (adjusted odds ratio [aOR] = 2.05, 95% confidence interval [CI] = 1.02−4.13)[70] and to experience early hospital readmission (adjusted relative risk [aRR] = 1.61, 95% CI = 1.18−2.19).[71] Similarly, sarcopenia, as determined by radiological measures (psoas muscle attenuation and paraspinous muscle lean volume), is associated with increased waitlist mortality among KT candidates.[72] Using CT imaging at the L3 vertebral level, low skeletal muscle mass was shown to correlate with greater hospital readmission within 30 days post−kidney transplantation discharge,[73] longer total hospitalization during the first year post kidney

Table 2. Studies that have evaluated the covariate-adjusted associations between sarcopenia/frailty and adverse health outcomes[a]

Authors, year, reference	Study population (no. of participants)	Instrumentation	Length of follow-up (yr)	Mortality (aHR ± 95% CI)	Hospitalization (aHR ± 95% CI)
Sarcopenia					
Chang *et al.* (2011)[59]	Stages 1–5 CKD (n = 128)	HGS	2.8	0.90 (0.84–0.97)[b]	—
Roshanravan *et al.* (2013)[60]	Stages 2–4 CKD (n = 385)	Gait speed (per 0.1m/s slower) TUAG (per 1-s slower) 6-min walk (per 50-m decrease) HGS (per 5-kg decrease)	3.0	1.26 (1.09–1.47) 1.08 (1.01–1.14) 1.15 (0.98–1.36) 1.07 (0.92–1.24)	—
Pereira *et al.* (2015)[61]	Stages 3–5 CKD (n = 287)	HGS and muscle mass (BIA)	3.3	3.02 (1.30–7.05)	—
Isoyama *et al.* (2014)[13]	Dialysis (n = 330)	HGS and muscle mass (DEXA)	2.4	1.93 (1.01–3.71)	—
Kittiskulnam *et al.* (2017)[14]	Dialysis (n = 645)	HGS and muscle mass (BIA) Gait speed and muscle mass (BIA)	1.9	2.83 (1.27–6.33) 3.31 (1.54–7.12)	—
Frailty					
Wilhelm-Leen *et al.* (2009)[19]	Stages 1–5 CKD (n = 10,256)	Modified Fried criteria	135 person months	2.00 (1.50–2.70)	—
Roshanravan *et al.* (2012)[62]	Stages 1–4 CKD (n = 336)	Fried criteria	2.6	2.50 (1.40–4.40)[c]	—
Delgado *et al.* (2015)[63]	Stages 3–5 CKD (n = 812)	Modified Fried criteria	17	1.48 (1.08–2.00)	—
Pugh *et al.* (2016)[64]	Stage 4 CKD (n = 283)	Clinical Frailty Scale	3	1.35 (1.16–1.57)	—
Johansen *et al.* (2007)[65]	Dialysis (n = 2,275)	Modified Fried criteria	1	2.24 (1.60–3.15)	1.56 (1.36–1.79)[d]
Bao *et al.* (2012)[66]	Dialysis (n = 1,576)	Modified Fried criteria	2.9	1.57 (1.25–1.97)	1.26 (1.09–1.45)[e]
McAdams De-Marco *et al.* (2013)[67]	Dialysis (n = 146)	Fried criteria	3	2.60 (1.04–6.49)	1.43 (1.00–2.03)
Alfaadhel *et al.* (2015)[68]	Dialysis (n = 390)	Clinical Frailty Scale	1.7	1.22 (1.04–1.13)	—

aHR, adjusted hazard ratio; BIA, bioelectrical impedance analysis; CI, confidence interval; CKD, chronic kidney disease; DEXA, dual-energy X-ray absorptiometry; HGS, handgrip strength; TUAG, timed up and go test.
[a]This table summarizes selected clinical studies that were published in recent years, and is not a systematic review.
[b]The primary outcome was composite renal end point of pre-dialysis mortality or reaching end-stage kidney disease (ESKD). A higher HGS was associated with lower risk of ESKD progression or death.
[c]The primary outcome was composite outcome for risk of death or progression to dialysis therapy.
[d]The primary outcome was composite outcome for time to first all-cause hospitalization or death.
[e]The median length of follow-up for hospitalization was 1.2 years.

transplantation, and a higher rate of wound complications.[74]

Given the association with poor clinical outcomes, sarcopenia and frailty assessments could be considered as useful risk stratification tools in the highly heterogeneous CKD population in a variety of care settings. For example, early identification of sarcopenia and frailty in CKD patients will enable prompt assessments of fall risk, nutritional status, and cognitive function to reduce injury risk and to improve quality of life. Moreover, it might assist shared decision-making processes in older patients with ESKD and multiple comorbidities in choosing treatment such as dialysis, which is potentially lifesaving but is associated with substantial physical and psychosocial burdens, or in opting for conservative management. In the pre-KT setting, sarcopenia, and frailty assessments during the KT evaluation and selection process, may help to identify patients at risk, allowing timely interventions to optimize overall health status before transplantation. However, concerns arise about the potential unintended consequences when integrating frailty assessment into the KT evaluation process, where frail candidates might be less likely to be listed,[28] and whether early intervention can improve post−kidney transplantation outcome in the short and long terms is yet to be determined.

In the clinical setting, sarcopenia and frailty are not routinely assessed, and patients are generally perceived as being "frail" based on a combination of age, sex, comorbidities, clinicians experience, and patient perception of their frailty. Notably, in a single-center study of 146 hemodialysis-dependent patients, the perceived frailty correlated poorly with measured frailty using the Fried criteria where less than half of frail patients were correctly identified by their nephrologists, nurse practitioners, or themselves.[75] Similarly, the Canadian Frailty Observation and Interventions Trial (CanFIT) reported that subjective measures of frailty (based on physician and nurse impressions) correlated poorly with objective measures using the Fried frailty criteria and Short Physical Performance Battery in a cohort of 603 patients with advanced CKD. Interestingly, subjective measures of frailty were more strongly associated with dialysis modality of choice (in-center dialysis), whereas objective measures were more strongly associated with all-cause mortality.[76]

One of the major challenges in kidney care is to develop a standardized definition and screening instruments that can be easily implemented to identify CKD patients with sarcopenia and frailty in a timely manner, which would help to enable targeted intervention development to improve patients' health and quality of life as well as optimizing the use of healthcare resources. In 2018, The American Society of Transplantation (AST) formed a frailty in solid organ transplantation working group to facilitate more

comprehensive discussion about frailty in the transplant community, exploring major barriers of integrating frailty assessment in the KT evaluation and organ allocation process, determining the best practices in clinical management (pre- and post-transplantation), and development of ideas for future research.[77] With an accelerated interest from physicians making the diagnosis of sarcopenia and frailty, it will be an impetus for pharmaceutical companies to hasten the development of pharmacological treatments.

Treatments for Sarcopenia and Frailty

There is considerable overlap between the management of sarcopenia and frailty. Therapeutic interventions often involve a multifaceted approach including exercise training, nutritional supplementation, and pharmaceutical agents to improve physical frailty, depression, and cognition (Table 3). It is also essential to recognize that most clinical studies have so far focused on outcomes such as muscle strength, gait speed, and health-related quality outcomes. The question still remains as to whether these interventions will improve the overall vulnerability among CKD and ESKD patients. Moving forward, other clinical outcome measures such as hospitalization, fracture rate, institutionalization, or death will be necessary measures to be addressed.

Exercise

Exercise is the intervention that has been consistently proved beneficial in treating frailty and its key component, sarcopenia. Exercise has physiological impacts on almost all organ systems, particularly the musculoskeletal, endocrine, and immune systems. A 2009 Cochrane review of progressive resistance training (in which participants exercised their muscle against an external force that was set at a specific intensity and adjusted throughout the training program) to improve physical function included a total of 121 randomized controlled trials (RCT) including 6700 participants with a mean age of $\geq$60 years, the majority of which were high-intensity programs performed 2 to 3 times per week in a home-based or gymnasium/clinic-based setting. More than half of the clinical trials (51.2%) recruited participants who had a health problem, had functional limitations, and/or resided in a hospital or residential care facility. Although the outcomes measured varied across different studies, there was evidence of a moderate-to-large beneficial effect on muscle strength in the lower limbs and a moderate effect on gait speed.[78]

Similarly, the 2011 Cochrane review of exercise training for adults with CKD included a total of 45 studies including 1863 patients with a mean participant age ranging from 36 to 71 years, although this review did not specifically focus on sarcopenic or frail CKD patients. The most common exercise training intervention was aerobic exercise training, followed by mixed aerobic and resistance training, resistance training, and yoga. The majority of studies included the performance of high-intensity exercise interventions 3 or 5 times per week, which were undertaken for 8 weeks or more. Significant improvement in physical fitness (as measured by aerobic capacity), cardiovascular parameters (resting systolic and diastolic blood pressure), serum albumin, and health-related quality outcomes were reported.[79] In addition, a systematic review of 29 clinical trials that evaluated the effectiveness of exercise training in adult patients receiving maintenance hemodialysis suggested that appropriately prescribed exercise involving both aerobic and/or resistance training during non-dialysis time or hemodialysis treatment is safe and beneficial for hemodialysis patients.[80] Despite the demonstrated benefits, the uptake and long-term participation in exercise training in HD patients remains low, primarily attributed to lack of time or clinical expertise, clinicians' concerns regarding safety issues, low patient motivation, inability to maintain the required exercise intensity, and scarce availability of equipment and appropriate training programs.[81]

Moreover, a recent pilot study involving 18 KT candidates showed that weekly physical therapy sessions with at-home exercises improved physical activity by 64% with high patient satisfaction, suggesting that prehabilitation (a process that augments preoperative functional capacity to increase tolerance for an anticipated stressor) might be a promising intervention for KT candidates with sarcopenia and frailty.[82] Several studies also investigated the role of a rehabilitation program post-kidney transplantation and demonstrated improvement in cardiopulmonary fitness (peak oxygen uptake), muscle strength, and self-reported physical functioning without significant change in body composition (body mass index, fat mass, lean mass, and percentage of body fat).[83,84]

Diet

Dietary intervention is a non-pharmacological modality that may correct nutritional deficits and address weight loss of the frailty syndrome. Older individuals are at higher risk for inadequate protein intake, and they may generate less muscle protein from the same amount of dietary protein intake as compared to younger individuals. Kerstetter *et al*. previously reported that 24% to 38% of men and 32% to 41% of women aged 60 years and above have dietary protein intakes less than the recommended daily allowance (0.8 g/kg per

Table 3. Potential interventions for sarcopenia and frailty

Intervention	Pros	Cons
Exercise	Resistance or aerobic exercise training with demonstrated benefits including improvement in physical fitness, muscle strength, and cardiovascular parameters	Low uptake and long-term participation in patients Lack of time or clinical expertise Scarce availability of equipment or appropriate training programs
Nutritional supplementation	The association between nutrition and muscle health underpins the importance of maintaining an optimal nutritional status in the prevention of sarcopenia/frailty Correct nutritional deficits and address weight loss of frailty syndrome High-quality, protein-enriched, oral nutritional supplements have been shown to be beneficial	Up to 40% of older adults do not meet the recommended target Inconsistent adherence
Pharmacological treatment • Vitamin D supplement • Angiotensin-converting enzyme inhibitors • Oral alkali supplements to correct metabolic acidosis • Testosterone	Existing pharmacological agents with favorable safety profiles including vitamin D, angiotensin-converting enzyme inhibitors, and oral alkali supplements	Small number of participants in clinical studies and questionable utility in the prevention and treatment of sarcopenia and frailty Undesirable adverse events (e.g., testosterone is associated with cardiovascular adverse effects)
Psychosocial support / health education / multidisciplinary intervention	Modifiable risk factors including alcohol and smoking cessation, increase physical activity and psychosocial support	Patient choice (poor adherence) Scarce resources or lack of access to psychosocial support

day).[85] It has been suggested that a balanced protein and energy supplement may be useful in preventing and reversing sarcopenia.[86] Nevertheless, a Cochrane review in 2009 did not identify any evidence of functional improvement relevant to sarcopenia with protein and energy supplementations in older adults.[87]

In the CKD population, the need to achieve optimal caloric intake is often compounded by the conflicting need to limit excess protein intake due to several potentially harmful elements such as high nitrogenous waste products, phosphorus, and acid loads, resulting in the need for energy supplementation to avoid protein energy wasting, which is a state of nutritional and metabolic derangement in patients with chronic disease, characterized by concurrent loss of systemic body protein and energy stores.[88] The recommended energy and protein intakes in different stages of CKD and KT patients with adequate renal function are summarized in Table 4.[89,90] Low dietary protein and calorie intakes have been recommended for patients with Stage 3b-5 CKD, as these have been suggested to slow the progression of kidney failure and possibly to alleviate uremia.[91] Although there is concern about the risk of protein energy wasting with protein-restriction diets, studies using stable isotope amino acid (AA) kinetics demonstrated that body adaptation to low protein intake led to more proficient use of dietary amino acids and a decrease in ureagenesis.[91,92] Furthermore, a recent randomized controlled trial comparing low dietary protein with and without non-protein calorie supplements in 109 CKD patients suggested that non-protein calorie supplements could improve patient adherence to a low-protein diet with beneficial effects on kidney function and proteinuria.[93] On the contrary, the recommended daily protein intake requirement for HD and peritoneal dialysis patients is 2-fold higher as compared to that in individuals who are non−dialysis dependent,[89] due to additional protein catabolic stimuli such as loss of amino acids and albumin through dialysis and uremia no longer of concern while on maintenance dialysis.

Pharmacological Treatment

Despite advances in our understanding of the pathogenesis of sarcopenia and frailty over the past 2 decades, there is no recommended pharmacological therapy for these conditions. Hormonal therapy such as testosterone, while improving muscle mass and strength, is associated with cardiovascular side effects.[94] Therapy with IGF-1 was found to have no

Table 4. Recommended protein and energy intakes in patients with chronic kidney disease

Patient population	Protein intake	Energy Intake
Stages 3b-5 CKD (eGFR <45 ml/min per 1.73 m^2)[89]	0.6–0.8 g/kg per day 1.0 g/kg per day (in the presence of illness)	30–35 kcal/kg per day (30 kcal/kg per day in sedentary individuals)
Hemodialysis[89]	>1.2 g/kg per day	30–35 kcal/kg per day (30 kcal/kg per day in sedentary individuals)
Peritoneal dialysis[89]	>1.2 g/kg per day >1.5 g/kg per day (in the presence of peritonitis)	30–35 kcal/kg per day (30 kcal/kg per day in sedentary individuals, including kcal from dialysate)
Kidney transplant recipients with good renal function[90]	1.3–1.5 g/kg per day (with first month post transplantation) 0.8–1.0 g/kg per day (as per general population)	30–35 kcal/kg per day (30 kcal/kg per day in sedentary individuals)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

beneficial impact on bone density, muscle strength, muscle mass, or psychological function in older women.[95] It has been recommended that 25(OH)vitamin D levels be measured in all sarcopenic patients and replaced if deficient, as adequate replacement of vitamin D in individuals with low levels reduces the risk of falls, possibly through improvement in muscle strength and function.[96] Furthermore, angiotensin-converting enzyme inhibitors were found to correlate with improved muscle strength and performance in older patients without heart failure.[97,98] Although vitamin D and angiotensin-converting enzyme inhibitors have favorable pharmacological and safety profiles, their clinical utility in the prevention and treatment of sarcopenia and frailty has yet to be investigated.

Chronic metabolic acidosis causes muscle catabolism in CKD patients, yet its treatment is often limited by the lack of approved drugs, undesirable adverse effects from the currently available oral alkali supplements (typically containing sodium, resulting in fluid retention), or poor adherence to diets low in animal protein and high in fruits and vegetables. Veverimer is a new oral, nonabsorbed polymer that selectively binds and eliminates hydrochloric acid from the gastrointestinal tract, leading to an increased serum bicarbonate. Patients with CKD (estimated glomerular filtration rate of 20−40 ml/min per 1.73 m^2) showed a normalized or increased serum bicarbonate level of ≥4 mmol/L when treated with veverimer as compared to placebo at week 52. Veverimer therapy was also associated with better patient-reported physical functioning and an improved timing in the chair stand test.[99]

More recently, new therapeutic agents such as LY2495655 (a humanized myostatin antibody that binds and neutralizes myostatin)[100] and bimagrumab (a humanized monoclonal antibody that binds to type II activin receptors and prevents the binding of its ligand)[101] were found to increase lean body mass and to improve muscle performance including gait speed and handgrip strength in phase II clinical trials. Future studies are required to confirm these findings and to explore whether myostatin-targeted therapy could reduce fall risk and physical dependency.

Conclusion

Many aspects of the epidemiology and pathophysiology of sarcopenia and frailty are better understood today than 20 years ago. The development of consensus definitions for sarcopenia and frailty has facilitated the conformity of clinical diagnoses and patient recruitment into clinical trials as well as the expedition of drug discovery. To this end, we hope that this review will increase the awareness of health care professionals who treat patients at risk for sarcopenia and frailty and lead to taking action to promote early detection and management.

DISCLOSURE

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