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Frailty and Protein-Energy Wasting in Elderly Patients with End Stage Kidney Disease

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ABSTRACT

Older people constitute an increasingly greater proportion of patients with advanced CKD, including those patients undergoing maintenance dialysis treatment. Frailty is a biologic syndrome of decreased reserve and resistance to stressors that results from cumulative declines across multiple physiologic systems and causes vulnerability to adverse outcomes. Frailty is common in elderly CKD patients, and it may be associated with protein-energy wasting (PEW), sarcopenia, dynapenia, and other complications of CKD. Causes of frailty with or without PEW in the elderly with CKD can be classified into three categories: causes primarily caused by aging *per se*, advanced CKD *per se*, or a combination of both conditions. Frailty and PEW in elderly CKD patients are associated with impaired physical performance, disability, poorer quality of life, and reduced survival. Prevention and treatment of these conditions in the elderly CKD patients often require a multifaceted approach. Here, we examine the causes and consequences of these conditions and examine the interplay between frailty and PEW in elderly CKD patients.

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Older patients comprise an increasing proportion of people with stage 5 CKD and those patients undergoing maintenance hemodialysis (MHD) or chronic peritoneal dialysis (CPD).[1–4] Frailty and protein-energy wasting (PEW) are common complications in elderly patients with ESRD undergoing MHD or CPD.[2,5–9] This phenomenon is clinically relevant, because many manifestations of frailty and PEW are strong risk factors for low quality of life (QOL), morbidity, and mortality.[3,5,10,11] Frailty and PEW may be caused by aging, advanced kidney failure, or both conditions combined. Here, we review causes, consequences, and potential therapies for frailty and PEW in elderly ESRD patients.

DEFINITIONS

The US National Library of Medicine defines aged in humans as ages 65–79 years old. Individuals >79 years old are categorized as aged 80 years and over. Frailty can be defined as a biologic syndrome of decreased reserve and resistance to stressors that results from cumulative declines across multiple physiologic systems and causes vulnerability to adverse outcomes.[11] Frailty implies decreased body energy and protein reserves and reduced strength. There are several excellent discussions of frailty in CKD patients.[2,6,12,13] A simple criterion for frailty can be the presence of three or more of the following abnormalities: unintentional weight loss, self-reported exhaustion, measured weakness, slow walking speed, and low physical activity.[11–13]

PEW is defined as the loss of somatic and circulating body protein and energy reserves.[14] The term PEW is used rather than protein-energy malnutrition, because some causes of PEW are unrelated to inadequate nutrient intake.[9,14,15] Causes of PEW in ESRD patients include inadequate nutrient intake, losses of nutrients during dialysis, superimposed catabolic illnesses, nonspecific inflammation, acidemia, catabolic stress from the dialysis procedure, low levels of or resistance to such anabolic hormones as insulin, growth hormone, and IGF-1, increased levels of such catabolic hormones as parathyroid hormone and glucagon, blood losses from blood drawing or gastrointestinal bleeding,[9,15] and possibly, oxidative and carbonyl stress.[16–20]

Two related concepts are sarcopenia and dynapenia. Sarcopenia is derived from the Greek words sarx (flesh) and penia (loss).[21] Two common definitions for sarcopenia are progressive decline in

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muscle mass caused by aging, which results in decreased functional capacity of muscles,[22] or simply, decreased muscle mass in the elderly.[23] Dynapenia, derived from the Greek words dyn (power) and penia (loss), is defined as loss of strength with aging.[23,24] These definitions may not be optimal, because reduced muscle mass and strength are not always present in people≥65 years old, and morbidity, malnutrition, or just physical inactivity can reduce muscle mass and strength in younger people.[24] Skeletal muscle (SKM) mass size seems to be the most important predictor of muscle strength or physical performance[25] and in maintenance dialysis patients, survival.[26,27] However, SKM mass and strength can be disassociated.[28] As normal people age, the rate of decline in muscle strength is greater than the rate of loss of muscle mass,[29] and strength can diminish even while muscle mass is maintained or increases.[30]

Physical performance is defined as the capability to conduct normal daily physical activities. Physical performance is often measured by such activities as the time required to climb a defined number of stairs or the distance walked or number of rises from a chair during a given time period.[31] Physical performance and mortality may be associated more with muscle strength than muscle mass.[32–34] Another age-related change in body composition, sarcopenic obesity,[35] refers to low muscle mass (sarcopenia) combined with increased body fat (obesity).[36] Sarcopenic obesity may develop without weight changes if the decrease in muscle mass is similar to the gain in body fat.[37]

INCREASED PREVALENCE OF FRAILTY AND PEW IN ELDERLY ESRD PATIENTS

Frailty and PEW are well described in adult ESRD patients independent of age. PEW is found in 18%–75% of maintenance dialysis patients in different reports.[9,13,38] There is less information concerning the prevalence and magnitude of these abnormalities in elderly ESRD patients. However, PEW (low serum albumin and subjective global assessment), sarcopenia (reduced mid-arm muscle circumference [MAMC]), and dynapenia (decreased hand grip strength) seem to be more common in older (>65 years) than younger maintenance dialysis patients.[39] In MHD patients, decreased lean body mass[40] and thigh muscle area[41] are associated with aging. The prevalence of sarcopenia also increases with aging in CKD patients without ESRD.[8] However, muscle wasting tends to be more severe in maintenance dialysis patients than dialysis-independent CKD patients.[42] Sarcopenic obesity is more pronounced in aging nondiabetic MHD patients than aging controls.[43] The volume of visceral fat, standardized by body mass index, is greater in nondiabetic MHD patients (mean age=57.5±1.3 years) compared with people with normal kidney function of similar age.[44]

Compared with the prevalence of frailty in elderly community-dwelling people (6.9% in the Cardiovascular Health Study[11] and 16.3% in the Women's Health Initiative[45]), frailty is substantially greater in elderly and near-elderly ESRD patients (67.7% in 2275 maintenance dialysis patients ages 58.2±15.5 years in the Dialysis Morbidity and Mortality Wave 2 Study).[6] The prevalence of frailty increases with age in MHD patients.[6] Moreover, elderly nondialyzed patients with primarily stage 3 CKD (mean age=76 years) had a greater prevalence of frailty (15% versus 6%; $P<0.001$) than elderly persons (mean age=72 years) with normal or mildly reduced kidney function.[14]

CAUSES OF FRAILTY AND PEW IN ELDERLY ESRD PATIENTS

Current thinking and scientific evidence regarding the many causes of frailty and PEW are well reviewed, and they are illustrated in Figure 1 and listed in Table 1 according to whether, in the authors' opinion, the causes are kidney failure, aging, or both factors.[9,46] The relative contributions of aging and ESRD to frailty and PEW may also be heavily influenced by such individual characteristics as the person's genotype, phenotype, medical history, duration and severity of renal failure, psychosocial condition, and lifestyle.

The causes of the aging process and its potential contributions to frailty are the foci of much research. These causes can be categorized into genetic and environmental exposure, including epigenetic factors.[16,47,48] Hundreds of genetic variations have been identified that are associated with longevity in various species.[16,47] Interestingly, a number of these genetic variations involve the insulin pathways including insulin, IGF, their receptors, and the signal transduction system that they induce.[47,49,50] Alterations that suppress activity of this pathway seem to be particularly associated with increased longevity. The finding that, in many species, reducing intake of calories or other nutrients increases longevity might be related to the fact that carbohydrates and some amino acids stimulate release of insulin, IGF-1, or the major IGF binding protein in serum. The elderly may be growth hormone (GH)-deficient.[51] IGF-1 exerts anabolic, anticatabolic, and antiapoptotic actions on SKM, and it helps to maintain SKM mass and enhance physical performance.[52,53] There is an age-related decline in IGF-1 activity that stems from the decline of GH; this decline may result in loss of muscle mass and strength and reduced exercise capacity.[54] Whether this decline promotes longevity is unknown.

Other environmental disorders that might contribute to aging include mitochondrial dysfunction and oxidative stress.[55,56] The accumulation of free radicals[48,57] may play a particular role in inducing age-related sarcopenia[16] and DNA damage, protein crosslinking, nonenzymatic glycation or other carbonyl reactions with proteins, accumulation of partially or completely denatured proteins, and cellular inflammation, which is commonly present in the aged.[58,59] Cellular apoptosis[48] and autophagy,[60,61] leading to loss of functional parenchymal cells, may increase along with failure of normal replacement by stem cells.[62] In addition,

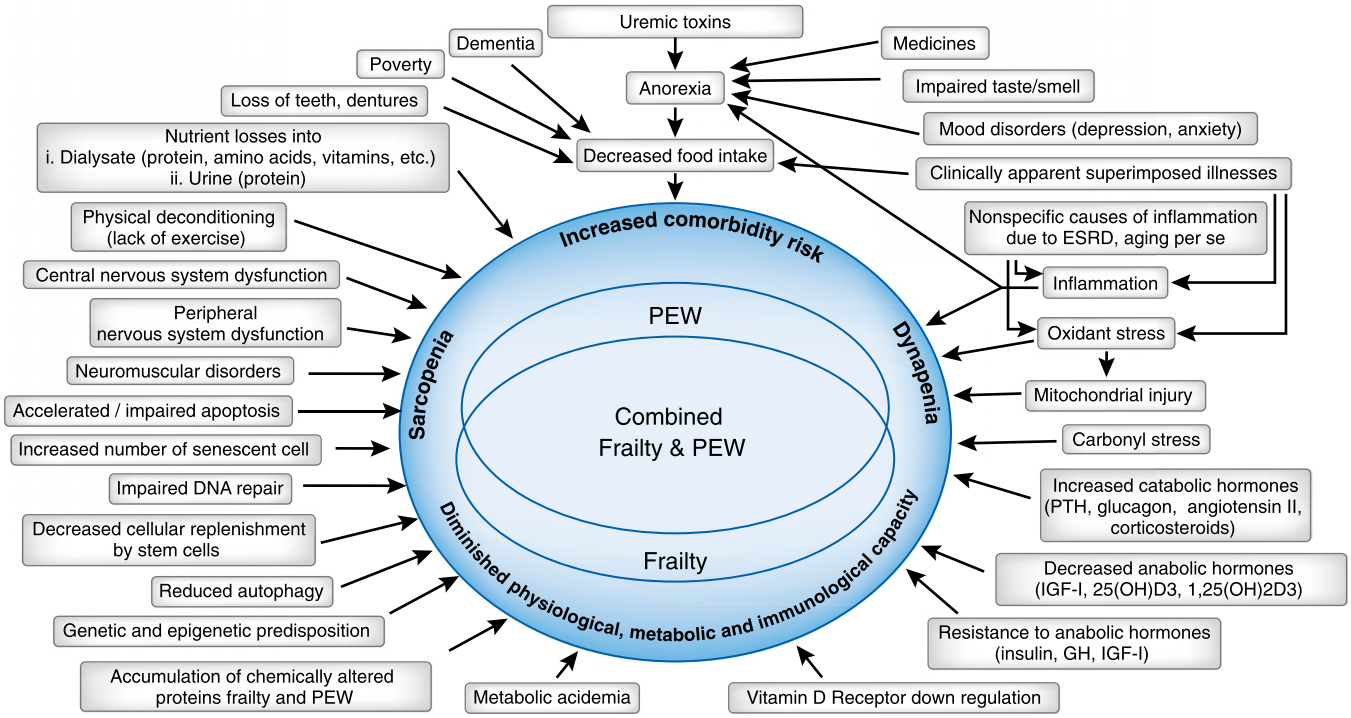

Figure 1. Potential causes of frailty and protein-energy wasting in elderly patients with end stage kidney disease. $1,25(OH)_2D_3$, 1,25-dihydroxycholecalciferol; ESKD, end stage kidney disease; PTH, parathyroid hormone; VDR, vitamin D receptor.

the limits of cellular replication cycles because of telomere shortening[48,63,64] as well as DNA damage and oncogene expression in aging lead to the accumulation of dysfunctional senescent cells, which may contribute to dysfunctional tissues and organ systems.[48,65] Immune function also declines with aging.[48,66] Chronic inflammation also plays an important role in the aging process.[48,66–68]

Hormonal dysfunction with low levels or resistance to many hormones, including sex hormones, testosterone, insulin, IGF-1, and thyroid hormone, may occur. Deficiency of 25-hydroxyvitamin D [25(OH)D] has become common in industrialized societies because of reduced time spent in sunlight and the frequent use of sunscreen or clothing that covers the skin.[69] Increasing age does not alter intestinal absorption of dietary vitamin D, but it is associated with lower 25(OH)D levels, regardless of season.[69] Decreased dietary vitamin D intake and reduced cutaneous synthesis of vitamin D, possibly related to decreased skin thickness, may contribute to lower serum 25(OH)D in the elderly.[70] The normal elderly with low (<25 nmol/L) serum 25(OH)D levels are at higher risk for sarcopenia (assessed by dual-energy X-ray photon absorptiometry [DEXA]; odds ratio=2.14) and dynapenia (assessed by grip strength; odds ratio=2.57) compared with elderly persons with high serum levels (>50 nmol/L).[71] Vitamin D supplementation in the elderly improves lower extremity muscle performance[72] and increases the number and diameter of type II muscle fibers.[73] ESRD patients are also likely to develop deficiency of both serum 1,25-dihydroxycholecalciferol, which is primarily synthesized in the kidney, and 25(OH)D. MHD patients receiving calcitriol (1,25-dihydroxyvitamin D) or paricalcitol (a 1,25-dihydroxyvitamin D analog) showed larger thigh muscle cross-sectional area measured by magnetic resonance imaging ($P<0.05$) and greater lower limb muscle strength ($P<0.05$) compared with MHD patients without either treatment.[74] Because vitamin D deficiency has a direct association with type II muscle fiber atrophy and physical performance,[75,76] vitamin D deficiency, particularly if advanced, may cause severe dynapenia, which may improve dramatically with supplements of 1,25-dihydroxyvitamin D.

Aging is associated with changes in central and peripheral nervous system activity, which affect SKM structure and function.[77–79] Loss of lower motor neurons in the lumbospinal segments (L1–L3) is observed in people>60 years old.[80] Doublet discharges from motor neuron axons are considered to increase both the rate and amount of force production in SKM and slow muscle fatigue development. The frequency of doublet discharges is lower in older individuals (74.1±8.8 years) than young subjects (21.9±3.6 years).[81] The number and diameter of motor axons,[80] peroneal nerve conduction velocity (a measure of nerve myelination), and compound muscle action potentials (a measure of axonal degeneration)[82] all decrease with age. Compound muscle action potential is positively correlated with calf muscle density (a measure of fatty degeneration in muscle) assessed by computerized tomography.[82]

Table 1. Clinical causes promoting frailty and PEW in elderly CKD patients

Clinical Causes
1. Reduced food intake
Anorexia caused by uremic toxins (RF), other anorexigens (TNF-α, cholecystokinin, or leptin; RF), impaired sense of taste/smell (RF,A), inflammation (RF,A), emotional depression (RF,A), or medications (RF,A)
Dementia (A)
Poverty (RF,A)
Loss of teeth or loss of dentures (A)
2. Dialysate and urine nutrient losses (RF)
Losses of protein into dialysate (~1 g/HD with MHD; ~9 g/d with CPD)
Losses of amino acids into dialysate (~10–12 g/HD with MHD; ~2.0–3.5 g/d with CPD)
Losses of protein into urine and nephrotic range proteinuria
3. Catabolic effects
Nonspecific inflammation (RF,A)
Oxidant stress (increased oxidants, including advanced glycation end products and advanced lipid end products, and decreased levels or activities of antioxidants: vitamins E, C, selenium, or glutathione; RF,A)
4. Inflammation associated with clinically apparent diseases
Medical illnesses (*e.g.*, diabetes, infection, heart failure, or cancer) and surgical illnesses (RF,A)
5. Increased levels or activities of catabolic hormones
Parathyroid hormone (RF), glucagon (RF), corticosteroids (RF), or angiotensin II (RF)
6. Deficiency or resistance to anabolic hormones
Insulin (RF,A), growth hormone (RF, A), IGF-1 (RF,A), testosterone (RF,A), 25(OH)D_3 (RF,A), or 1,25-dihydroxycholecalciferol (RF)
7. Metabolic acidemia (RF)
Activates the caspase-3 and the ubiquitin–proteasome system in skeletal muscle, promoting protein catabolism
Suppress protein synthesis
8. Primary neuromuscular disorders
Central nervous system dysfunction
Specific neuronal changes (RF,A)
Dementia (A)
Peripheral nervous system dysfunction (RF,A)
Muscular changes
Loss of myocytes (A)
Reduced numbers of satellite cells and myogenic factors (RF,A)
Tendon stiffness (RF,A)
9. Physical inactivity and deconditioning (RF,A)
10. Accelerated/impaired apoptosis (A)
11. Increased number of senescent cells (A)
12. Decreased cellular replenishment by stem cells (A)
13. Reduced autophagy (A)
14. Accumulation of chemically altered proteins (RF,A)
15. Impaired DNA repair (RF,A)
16. Epigenetic alterations (RF,A)
17. Genetic predisposition (A)

The disorder was estimated to be caused by RF (chronic kidney failure), A (aging), or RF,A (both chronic kidney failure and aging).

With aging, the loss of fast motor units (type II fibers) because of denervation is more pronounced than the loss of slow motor units (type I fibers).[46] Denervated muscle fibers are recruited by surviving motor units and change their fiber type to the type of the surviving motor unit. Hence, there is a net conversion of type II fibers to type I fibers.[46] Type II fiber-specific TNF-α signaling is another pathway that may account for the preferential loss and atrophy of type II muscle fibers with advancing age.[83] Predominant atrophy of type II fibers is also observed in MHD patients (ages 44.1±17.2 years).[84]

Satellite cells (muscle stem cells) from older mice show reduced number and impaired myoblast generation and differentiation.[85] In SKM of elderly men (76±1 years) compared with young men (20±1 years), the percent of type II fibers was lower (47±3% versus 57±3%; $P<0.05$), and the total cross-sectional area of the type II fibers was significantly reduced ($P<0.05$).[86] The number of satellite cell per millimeter squared of type II muscle fibers was reduced in the elderly men compared with young men (9.7±1.0 versus 12.6±0.9, respectively; $P<0.05$).[86] Aging is associated with decreased or delayed expression of myogenic regulatory factors, which regulate satellite cell proliferation and differentiation. These factors include myogenic determination factor, myogenic regulatory factor 5, and myogenin.[87] The number of fibers in the vastus lateralis muscle and the motor units in the extensor digitorum brevis muscles begin to decline at approximately 50 and 60 years of age, respectively, in the general population.[88,89] Possibly because of some of the foregoing neuromuscular disorders, muscle protein synthesis in the elderly in the general population (70±6 years) shows decreased sensitivity and responsiveness to essential amino acids compared with young men (28±6 years).[90] Formerly, when access to dialysis was often delayed or not possible, severe neuropathy was often observed in patients with advanced CKD and ESRD. This uremic neuropathy, which often presents clinically with impaired sensation, could progress to hypoesthesia, reduced deep tendon reflexes, paresis, and ultimately, frank paralysis.

Tendons from older people (ages 69–80 years) are ~15% more compliant than tendons from younger people (ages 20–26 years). This compliance may lead to force reduction and slower contractile force transmission from muscles to bones.[91] In ESRD patients, calcium deposits may accumulate in tendons.[92,93] Tendons in both elderly people and ESRD patients have an increased

likelihood of rupturing or separating from their bony insertion when subjected to increased contractile force.[93,94] ESRD patients may also fracture bones with intense muscle contraction.[95,96] Scarring and loss of parenchymal function may occur from physical trauma, acute illnesses, and high prevalence of chronic diseases and other disorders, including hypertension, obesity, diabetes mellitus, atherosclerosis, osteoarthritis, physical deconditioning, and depression. Skeletal muscle mass within the lower 10th percentile of normal is observed in up to 62% of dialysis patients.[97]

Physical activity, in general, is decreased in dialysis patients and tends to decrease with age in both the general population[98] and MHD patients.[99] Decline in physical activity with advancing age, measured by accelerometry, is much greater for MHD patients than sedentary people without kidney disease.[99] Dialysis patients are likely to describe a greater reduction in moderate or vigorous physical activity with aging.[100] Physical inactivity in dialysis patients (ages 60±14 years) is associated with lower serum albumin and serum creatinine levels, which are indicative of PEW and small SKM mass.[101] In contrast, increased levels of physical activity, measured by accelerometry, are associated with higher lean body mass, assessed by DEXA, in MHD patients (ages 47±2 years).[102] In MHD patients (ages 64±11 years), physical activity for ≥50 min/d is associated with faster normal ($P<0.001$) and maximum ($P<0.001$) walking speed, greater leg strength ($P=0.04$), and better functional reach ($P=0.02$) compared with MHD patients with physical activity <50 min/d.[103] In elderly dialysis patients, reduced frequency of daily physical activity is correlated with higher mortality risk ($P<0.05$).[104]

Reduced food intake in advanced CKD is often caused by anorexia, which may be caused by uremic toxins, inflammation, superimposed illnesses and depression, or other psychiatric disorders. In support of an anorexia-causing role for uremic toxicity in patients treated with conventional maintenance dialysis, quotidian MHD seems to be associated with increased energy and protein intake.[105,106] Dietary protein intake is lower in normal elderly men (68.5±4.7 years) than normal younger men (25.6±3.7 years).[107] The median age of incident ESRD patients was 64.2 years in 2008[4] in the United States; hence, aging *per se* may contribute to their reduced nutrient intake. Dementia is not uncommon in elderly ESRD patients and may reduce food intake. People with ESRD commonly are less affluent and may have inadequate funds to purchase food. Even an edentulous state may impair the ability of ESRD patients to eat. Vintage (duration) of MHD is negatively associated with intake of energy ($r=-0.89$, $P<0.01$) and protein ($r=-0.05$, $P<0.05$).[108] Losses of amino acids, peptides, and water-soluble vitamins into dialysate may contribute to PEW and frailty.

Kidney failure intensifies and adds to many of the processes associated with aging. Kidney failure *per se*, like aging, engenders inflammation. In advanced CKD, there is impaired removal of proinflammatory cytokines (*e.g.*, increased serum C-reactive protein, TNF-α, and IL-6) and exposure to inflammatory stimulants (*e.g.*, uremic toxins), including those toxins engendered by the dialysis procedure itself (dialysis catheters, tubing, dialyzer membranes, and impure dialysate).[9] Inflammation also may result from clinically apparent superimposed illnesses (Table 1). Inflammation not only stimulates protein degradation and SKM wasting[109] but also suppresses appetite,[110,111] stimulates resistance to insulin and GH,[112] and enhances energy expenditure.[113] Aging *per se* predisposes to chronic inflammation.[114] A higher inflammatory state is associated with parenchymal fibrosis, less muscle mass and strength, and lower physical performance and functionality in the elderly.[114]

In chronic kidney failure as well as aging, there is also increased oxidant stress with enhanced generation of reactive oxygen species (ROSs), elevated serum oxidants, and reduced levels of antioxidants (Table 1).[115,116] ROS-induced mitochondrial injury, where the ROSs are primarily generated, has been invoked as a key cause of the aging process, although this theory has recently been challenged.[117,118] Both inflammatory cytokines and ROSs stimulate the ubiquitin–proteasome system. Oxidative stress caused by aging may cause atrophy and loss of muscle fibers[17]; oxidative stress may not be associated with muscle fiber atrophy in MHD patients.[18] There are increased levels of protein carbonyls, such as[58,119] advanced glycation endproducts[120,121] and advanced lipid endproducts,[121] which cause damage by reaction with endogenous proteins. Protein carbonyls, an indicator of oxidative damage to proteins, are directly associated with grip strength ($\beta=-6.77$, $P<0.01$) and decline in walking speed ($P=0.002$) in normal women≥65 years old.[19,20]

Genetic and epigenetic factors influence the propensity of individuals to develop CKD and the manifestations of the ESRD syndrome.[122–124] As with aging, kidney failure engenders a cascade of changes in gene function, cell signaling, and metabolism that, ultimately, leads to expression of many of the phenotypic characteristics of the aged person.[60,61,117,118,125]

Serum levels of gluconeogenic hormones (glucagon and parathyroid hormone) are increased, and there is resistance to anabolic hormones (insulin, growth hormone, and IGF-1) in ESRD.[126] Vitamin D deficiency, obesity, metabolic acidemia, inflammation, and accumulation of uremic toxins contribute to insulin resistance in advanced CKD.[127] Insulin resistance in ESRD may activate caspase-3 and the ubiquitin–proteasome system, thereby enhancing muscle protein degradation.[128,129] Insulin also stimulates protein synthesis. In nondiabetic MHD patients, insulin resistance is closely associated with SKM protein breakdown ($R^2=0.49$, $P=0.006$).[128] In diabetic compared with nondiabetic MHD and CPD patients, insulin resistance may contribute to greater loss of SKM during the first year of dialysis treatment[130,131]; diabetes mellitus was the strongest predictor of lean body mass loss in this study.[130] Older adults, ages 70–79 years, with type 2 diabetes and without ESRD also show

greater declines in leg muscle mass compared with nondiabetes.[132] SKM from chronic renal failure rats shows reduced IGF-1 mRNA levels and IGF-1 protein, resistance to the IGF-1–induced suppression of protein degradation and stimulation of protein synthesis, increased IGF-1 receptor mRNA and IGF-1 receptor number, and impaired receptor tyrosine kinase activity. These findings suggest abnormal IGF-1 physiology and reduced sensitivity to IGF-1 in chronic renal failure.[133] This pattern of skeletal muscle mRNA for IGF-1 and IGF-1 receptor is also observed in MHD patients.[134,135]

Male MHD patients not uncommonly have low serum testosterone.[136] A progressive decline in serum testosterone occurs with aging in normal men.[137] Low serum free testosterone is associated with frailty in elderly men.[138] Treatment with supraphysiological doses of testosterone may increase muscle size and strength in otherwise normal men.[139]

Metabolic acidemia, which is common in CKD because of impaired ability of the kidney to excrete acid, promotes frailty and PEW in many ways. Acidemia enhances intracellular protein degradation by activating caspase-3 and the ubiquitin–proteasome system,[129,140,141] reduces protein synthesis,[142] causes growth hormone and insulin insensitivity, and engenders negative protein balance.[143] Metabolic acidemia causes bone loss, more rapid progression of kidney failure in CKD patients, other endocrine disorders, systemic inflammation with increased proinflammatory cytokines, enhanced β2-microglobulin formation, and hypertriglyceridemia.[143–145] Severe metabolic acidemia (*e.g.*, arterial blood pH$\leq$7.25) may be associated with anorexia, reduced food intake, malaise, and hypotension.

CLINICAL CONSEQUENCES OF FRAILTY AND PEW IN ELDERLY ESRD PATIENTS

Frailty and PEW are associated with impaired physical performance, poorer quality of life, and reduced survival in elderly ESRD patients (Figure 2).[7,27,146] In MHD patients ages 63$\pm$14 years, age-related decreases in SKM mass and increases in fat mass (intramuscular and intermuscular adipocytes) are associated with decreased isometric strength and impaired physical performance (6-minute walk test and gait speed).[147] Reduced anterior tibialis muscle mass, which is more common in MHD patients than age- and sex-matched sedentary controls without advanced CKD, is significantly associated with reduced gait speed and isometric ankle dorsiflexor strength.[148] MHD patients (ages 53$\pm$15 years) with lower MAMC had worse mental health scores, which was assessed by the Short Form 36-item health survey (SF-36) questionnaire, and poorer survival.[26]

ESRD in adults of any age is associated with decreased physical performance. Scores of the Short Physical Performance Battery, an indicator of physical performance, are significantly lower in MHD patients compared with normal values for the elderly population in the Established Populations for Epidemiology Research in the Elderly, although the age of the MHD patients averaged 20 years younger than the elderly normals.[149] The physical functioning subscale of the SF-36 questionnaire in these MHD patients was also reduced.[149] In MHD patients$>$60 years (median age=75 years), both sit-to-stand scores and staircase climbing scores showed 50% and 54% fewer cycles, respectively, compared with age- and sex-matched control subjects without CKD.[150]

The foregoing findings mirror the effects of aging in the general population. In the elderly, the rate of decline in cognitive activity is positively correlated with increasing frailty[151] and decreasing muscle strength.[79] Moreover, the National Health and Nutrition Examination Survey Study indicates that normal adults$\geq$55 years old (mean=70.1 years) with obesity and dynapenia have poorer physical function (walking speed) than adults without these two disorders.[152] Increased fat mass rather than decreased fat-free mass is associated ($P<0.01$) with reduced physical capacity (walking speed) in normal people ages 68–82 years.[153]

Frailty and dynapenia are also associated with adverse clinical consequences. In adult maintenance dialysis patients in the Dialysis Morbidity and Mortality Wave 2 Study, frailty compared with no frailty is associated with greater hospitalization risk (adjusted hazard ratio [HR]=1.56, 95% confidence interval [CI]=1.36–1.79) and higher mortality (adjusted HR=2.24, 95% CI=1.60–3.15).[6] In the general population, decreased whole-leg extension strength exposes the elderly to more falls.[154] MHD patients$\geq$65 years old commonly fall; in one study, 27% of patients fell in the previous 12 months, and another 16% of patients fell before the past year.[155] Fall rates in elderly MHD patients ($\geq$65 years) were higher than rates in community-dwelling elderly people without CKD (1.6 versus 0.6–0.8 falls/person-year).[156] Impaired physical performance (10-m walking test) increases the risk of falls and fall-related fractures in elderly MHD patients.[157] Falls are independently associated with increased mortality (adjusted HR=1.78, 95% CI=1.07–2.98, P=0.03) in elderly MHD patients.[158]

Impaired neuromuscular function, which was indicated by increased get-up-and-go time, reduced functional reach, and slower 6-minute walk test, is associated with an increased risk of bone fracture in MHD patients,[146] roughly one-half of whom were elderly (mean age=66$\pm$9 years). The Dialysis Outcomes and Practice Patterns Study of MHD patients (mean age$\sim$60 years), sampled from 12 countries, indicated that their yearly incidence of hip fracture was much higher than the general population (age$\sim$60–65 years; 0.89% versus 0.07%–0.22%).[95,96] Among maintenance dialysis patients from the Dialysis Morbidity and Mortality Study (age=61.7$\pm$15.5 years), those patients who sustained a hip, vertebral, or pelvic fracture had a 2.7 times greater mortality than those patients who did not sustain such fractures.[159]

In direct contrast to the general population, body mass index is inversely related to mortality in MHD and CPD patients.[160–162] One hypothesis advanced to explain this observation is that obese MHD patients and CPD patients often have greater muscle mass than nonobese

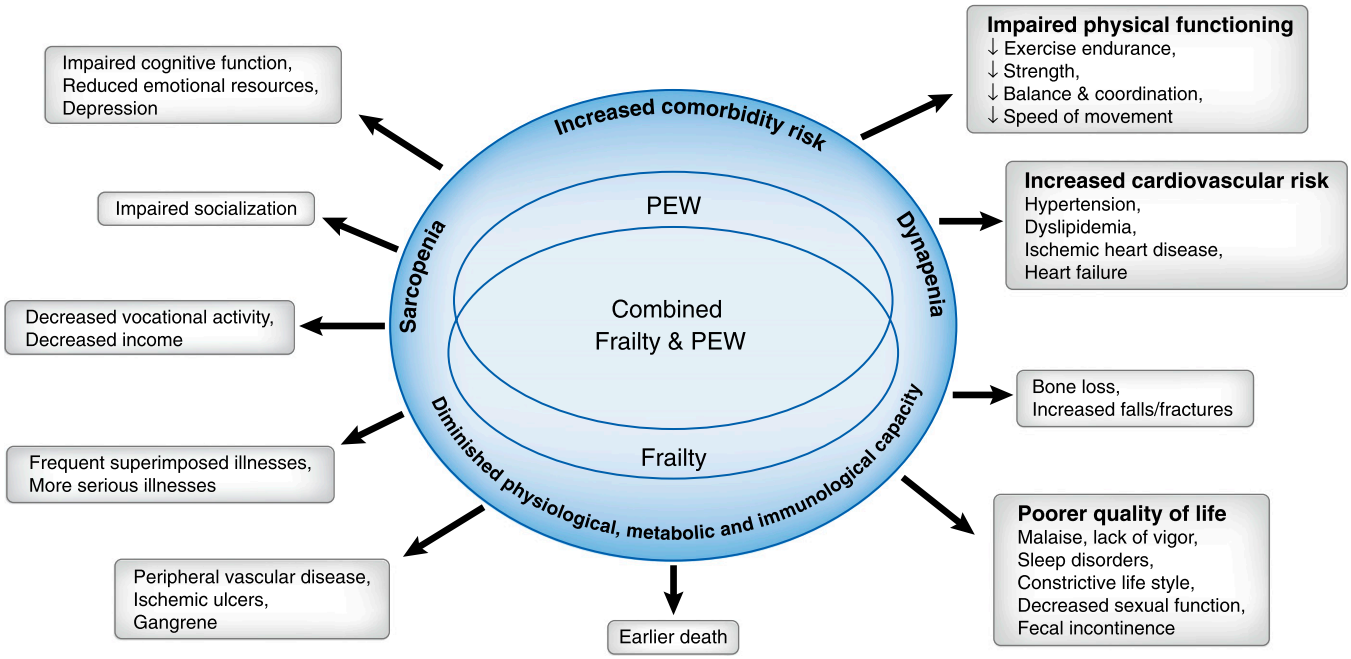

Figure 2. Clinical consequences of frailty and protein-energy wasting in elderly patients with end stage kidney disease.

patients.[163–166] Larger SKM mass, indicated by higher serum creatinine or MAMC, increased body fat mass, and gain in SKM mass or body fat are each independently associated with increased survival in nonelderly and elderly MHD and CPD patients,[27,167,168] although it is still unclear why SKM mass or obesity should promote longer lifespan. Muscle mass may be more important than fat mass for survival.[27] Obesity combined with sarcopenia may be considered a form of PEW, and it is associated with inflammation and increased mortality in MHD and CPD patients.[169] In MHD patients, the location of the increased fat mass influences mortality. In MHD patients with a mean age of 65 years (range=51–74 years), such as in the general population, excess abdominal fat seems to be associated with higher mortality rate.[170]

MANAGEMENT STRATEGIES FOR FRAILTY AND PEW IN ELDERLY ESRD PATIENTS

Because frailty and PEW usually have multiple causes in elderly dialysis patients, prevention and treatment generally require a multifaceted approach. This subject is the focus of many studies and reviews.[9,13,46,129] This section and Table 2 briefly summarize potential strategies for prevention and treatment.

Good Medical/Nephrology Care

We are unaware of any randomized prospective interventional trials that have assessed the effects of preventing or improving frailty or PEW on clinical outcomes of elderly ESRD patients. However, observational data indicate that, in general, the better the clinical status of the patient commencing dialysis, the better the prognosis for survival.[171,172] PEW at the onset of dialysis is associated with poorer survival.[171,172] Starting dialysis before patients develop PEW is associated with better long-term nutritional status and lower mortality.[15,171,172] Indeed, commencement of dialysis is often associated with improvement in protein-energy status.[173,174] Better control of uremia may lead to less frailty and PEW. Experience with quotidian hemodialysis suggests that more than two times per week MHD treatments and larger doses of dialysis may improve patients' appetite, food intake, nutritional status, and QOL and reduce frailty and PEW.[106,175]

Intuitively, it would seem that advanced CKD and ESRD patients who have inflammatory catabolic illnesses and are treated promptly and aggressively with attention to their nutritional needs should have better clinical outcomes with less frailty and PEW. Moreover, given the high prevalence of oxidative, carbonyl, and inflammatory stress in ESRD patients, there should be a role for agents that correct these disorders. Anti-inflammatory and antioxidant drugs have been used in many trials of dialysis patients, most without apparent success.[176–178] However, rather small-scale studies indicate that the antioxidants α-tocopherol and *N*-acetylcysteine may reduce adverse cardiovascular events in MHD patients.[179,180] Hopefully, with further development, anti-inflammatory, antioxidant, or anticarbonyl drugs will be shown to reduce frailty and PEW and improve morbidity and mortality.

Nutrient Intake

Clearly, prevention and treatment of frailty and PEW require adequate intake

Table 2. Potential preventive and therapeutic strategies for frailty and PEW in elderly ESRD patients

Strategies
1. Start maintenance dialysis in a timely manner
2. Treat comorbid conditions aggressively; timely institution of increased protein/amino acid intake, enteral tube feedings, and iv nutrition
3. Consider optimal frequency/duration/dose of dialysis
4. Anti-inflammatory agents, antioxidants, anticarbonyl compounds? (several clinical trials are in progress)
5. Prescription of optimal dietary energy and protein intakes
6. Dietary counseling and monitoring as needed
7. Use of food supplements, enteral tube feeding, intradialytic nutrition, nutritional peritoneal dialysis, and nutritional hemodialysis
8. Prevent and treat acidemia; optimal arterial blood pH=7.40–7.45?
9. Use of anabolic hormones and other compounds
Insulin
Growth hormone
IGF-1
Carnitine
Anabolic steroids testosterone, nandrolone decanoate, decadurabolin, etc.
10. Exercise training

Many of these interventions have not yet been proven to be effective and safe in large-scale clinical trials.

of nutrients. Space does not allow for a detailed discussion of nutritional requirements in clinically stable and stressed ESRD patients, and reference is made to published reviews.[38,181,182] Multivitamin and trace element supplements are commonly needed.[181,183] Most expert groups recommend similar amounts of dietary protein intake (DPI) for adult MHD and CPD patients, ranging from 1.0 to 1.3 g/kg per day with at least 50% of the DPI of high biologic value.[182] It has been suggested that a safe protein intake that maximizes the probability of good protein nutrition for clinically stable MHD and CPD patients is 1.2 g/kg per day and 1.2–1.3 g/kg per day, respectively.[181] Current recommendations for DPI do not vary with age in adult MD patients, but this question has not been examined. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for energy intake in MHD and CPD patients recommend 35 kcal/kg per day for patients$<$60 years and 30 kcal/kg per day for MHD patients$\geq$60 years old.[181] Energy prescription can be increased for patients who are underweight, have PEW, or engage in chronic heavy physical activity, and it can be reduced in patients who are very obese.

Most people undergoing standard maintenance dialysis treatment will not be able to ingest these quantities of protein and energy, and their food intake may need to be augmented to meet these goals. In these circumstances, oral nutritional supplements can be used. Oral supplements of protein or primarily essential amino acids, usually including additional calories, may improve protein balance and PEW, promote protein accrual in SKM of people with ESRD, or prevent or retard the development of sarcopenia in elderly persons without CKD.[184–187] Tube feeding, intradialytic parenteral nutrition, or if necessary, total parenteral nutrition may be used for patients who are unable to take oral supplements.[188,189] Tube feeding, intradialytic parenteral nutrition, and provision of amino acids through peritoneal dialysate may increase protein balance.[182,190,191] Amino acids with or without glucose may be given through hemodialysate. The long-term nutritional or clinical benefits of all of these forms of nutritional support have not been well studied.[191] Nutritional support for elderly ESRD patients apparently has not been examined.

Metabolic Acidemia

Although the KDOQI Nutrition and KDOQI Bone Mineral Disease Clinical Practice Guidelines recommended serum bicarbonate$\geq$22 mEq/L,[181,192] recent evidence suggests that higher pH values may be more anabolic. An arterial blood pH of 7.45–7.45 compared with 7.36–7.38 may engender more positive protein balance in CPD patients.[142] CPD patients with plasma bicarbonate of 27.8$\pm$2.6 compared with 24.7$\pm$3.9 mmol/L (P=0.002) because of oral sodium bicarbonate treatment have a healthier higher subjective global assessment, increased nPNA (normalized total nitrogen appearance), and shorter hospitalizations.[193] MHD patients with mean arterial pH=7.44 and predialysis plasma bicarbonate=26.1 mEq/L showed greater growth hormone sensitivity compared with MHD patients with arterial pH=7.32 and plasma bicarbonate=20.4 mEq/L.[144] Moreover, a serum bicarbonate of about $<$23 mEq/L is associated with more rapid progression of CKD.[143,194–197] We suggest that, pending additional information, serum bicarbonate should probably be maintained above 24 mEq/L, and arterial blood pH should probably be maintained above 7.38 and possibly closer to 7.44 in CKD and ESRD patients.

Anabolic Agents

Publications dating back $>$50 years indicate that testosterone and other androgenic steroids may increase nitrogen balance and/or decrease serum urea or net protein breakdown in advanced CKD or dialysis patients.[198–201] More recent studies indicate that testosterone or other androgenic compounds may engender muscle hypertrophy and strength in dialysis patients.[202–204] Nandrolone decanoate increases lean body mass (LBM), and it improves walking, stair-climbing,[202] and quadriceps muscle cross-sectional area in maintenance dialysis patients.[205] Androgens may increase anabolism and strength in the elderly without CKD. A meta-analysis of 11 randomized, double-blind trials in elderly men without known CKD ages 69.1$\pm$3.3 years reported that testosterone replacement significantly increased muscle strength.[204] Carnitine also increases nitrogen balance in CPD patients (J.D. Kopple, unpublished observations).[206]

In MHD patients, GH increases muscle protein synthesis, reduces net protein catabolism,[207] lowers serum urea and urea nitrogen appearance,[208,209] induces positive protein balance,[210,211] reduces fat mass, increases LBM,[212–214] increases serum transferrin,[212,214] decreases serum high-sensitivity C-reactive protein,[214] improves SF-36 QOL,[212] and seems to be safe.[215] Not all studies report all of these positive results.[216] In a small, randomized study focused on older MHD patients (mean age=73 years, range=53–92 years), GH increased muscle cross-sectional area, LBM, serum albumin, hand grip strength, and walking speed and reduced fat mass.[217] Thus, GH also seems to be anabolic for elderly ESRD patients.

GH induces its anabolic effects primarily by stimulating IGF-1 production and release.[218] IGF-1 may ameliorate some of the age-related derangements in neuromuscular innervation and changes in muscle fiber types,[219] and it may improve excitation–contraction coupling in SKM.[220] Administration of IGF-1 also reduces serum urea and urea nitrogen appearance, and it increases nitrogen balance in CPD patients.[221] The side effect profile of IGF-1 is not as safe as GH, and IGF-1 has not been used in large clinical trials in CKD patients.[222,223] A cautionary note in this regard, as indicated above, some genes associated with longevity may attenuate the insulin/IGF pathways.[47,49,50] Whether chronic treatment with these anabolic hormones will reduce survival must be examined.

Exercise

Although many benefits are ascribed to exercise training of CKD and dialysis patients,[224] the most universally observed improvement is in endurance exercise capacity. Increased strength and physical performance are probably the next most commonly reported improvements.[31,205,225] Occasionally, exercise in nonelderly CKD or ESRD patients is reported to reduce inflammatory cytokines.[226,227] Increased muscle mass with exercise training is described less commonly. This finding may caused by less frequent or lower intensity strength training regimens for dialysis patients or their antianabolic status.[134] Muscle intracellular protein remodeling without hypertrophy seems to be common with exercise training.[134] Several studies have examined exercise training in elderly CKD patients. Twelve weeks of strength training of the thigh in elderly (76±7 years) stage 4–5 CKD patients significantly increased ($P<0.004$) muscular strength and walking capacity to a similar extent as in elderly healthy subjects.[228] MHD patients, ages 71±13 years, underwent low-intensity training of the leg and pelvic muscles.[229] Patients, compared with nonexercising controls, displayed increased lower extremity strength and leg and whole-body lean mass (DEXA), reduced body fat mass, and increased activities of daily living scores.

CONCLUSIONS

This review suggests that many causes may contribute to frailty and PEW in ESRD patients, and many potential strategies may prevent or reduce the severity of these disorders. Few, if any, of these methods have been tested in large randomized clinical trials in elderly ESRD patients. Many of the mechanisms engendering these disorders (and on which prevention and treatment strategies must be based) are still not well defined. The importance of some preventive and therapeutic approaches is intuitively obvious, such as inauguratation of dialysis therapy in a timely manner before frailty or PEW develop, aggressive evidence-based treatment of superimposed illnesses, and assurance of adequate nutrient intake. However, the optimal methods for such treatments often are not well defined. For example, the indications for starting dialysis are still imprecise. Similarly, the optimal nutrient intakes for the various clinical disorders encountered by a dialysis patient are not conclusively defined. Even more relevant, the clinical benefits of most preventative and therapeutic approaches listed in the text and Table 2 have not been shown in large-scale clinical trials in which QOL, morbidity, and mortality are used as key outcomes. The large and growing numbers of elderly ESRD patients coupled with the strong association of frailty and PEW with poor QOL and high morbidity and mortality provide a strong justification for directing more research effort and resources into investigating these questions.

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