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Wasting in chronic kidney disease

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Abstract Wasting/cachexia is prevalent among patients with chronic kidney disease (CKD). It is to be distinguished from malnutrition, which is defined as the consequence of insufficient food intake or an improper diet. Malnutrition is

characterized by hunger, which is an adaptive response, whereas anorexia is prevalent in patients with wasting/cachexia. Energy expenditure decreases as a protective mechanism in malnutrition whereas it remains inappropri-

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ately high in cachexia/wasting. In malnutrition, fat mass is preferentially lost and lean body mass and muscle mass is preserved. In cachexia/wasting, muscle is wasted and fat is relatively underutilized. Restoring adequate food intake or altering the composition of the diet reverses malnutrition. Nutrition supplementation does not totally reverse cachexia/wasting. The diagnostic criteria of cachexia/protein–energy wasting in CKD are considered. The association of wasting surrogates, such as serum albumin and prealbumin, with mortality is strong making them robust outcome predictors. At the patient level, longevity has consistently been observed in patients with CKD who have more muscle and/or fat, who report better appetite and who eat more. Although inadequate nutritional intake may contribute to wasting or cachexia, recent evidence indicates that other factors, including systemic inflammation, perturbations of appetite-controlling hormones from reduced renal clearance, aberrant neuropeptide signaling, insulin and insulin-like growth factor resistance, and metabolic acidosis, may be important in the pathogenesis of CKD-associated wasting. A number of novel therapeutic approaches, such as ghrelin agonists and melanocortin receptor antagonists are currently at the experimental level and await confirmation by randomized controlled clinical trials in patients with CKD-associated cachexia/wasting syndrome.

Keywords Wasting · Chronic · Kidney disease

1 Introduction

Wasting is prevalent among patients with chronic kidney disease (CKD). Eighteen to 75% of adults with end-stage renal disease (ESRD) undergoing maintenance dialysis showed some evidence of wasting [1, 2]. The differences in prevalence of wasting may be due to the different ESRD patient population mix reported, in the context of race, age, and prevalence of comorbid conditions such as congestive heart failure, diabetes mellitus, and liver disease. Wasting, defined by the World Health Organization as low weight for height [3], was thought to be the direct consequence of inadequate nutrition intake or malnutrition. As a result, the terms, “wasting”, “cachexia”, and “malnutrition” were used interchangeably. Although inadequate nutrition may contribute to wasting or cachexia, other factors including systemic inflammation, perturbations of appetite-controlling hormones from reduced renal clearance, aberrant neuropeptide signaling, insulin and insulin-like growth factor resistance, and metabolic acidosis, may be important in the pathogenesis of CKD-associated wasting [4–12]. The wasting/cachexia syndrome in CKD patients consists of anorexia, increased energy expenditure, decreased protein stores characterized by a low serum albumin, and loss of

body weight and loss of muscle mass. Importantly, the individual components of this syndrome all represent risk factors for mortality in patients with CKD [13–16], which is 100–200 times higher than the general population [17, 18]. The wasting/cachexia syndrome should be distinguished from malnutrition, which is defined as the consequence of insufficient food or an improper diet. Responses in malnutrition are adaptive whereas those in wasting/cachexia are maladaptive. Hunger, which is an adaptive response, characterizes malnutrition whereas anorexia is prevalent in patients with wasting/cachexia [13]. Energy expenditure decreases as a protective mechanism in malnutrition whereas it remains inappropriately high in cachexia/wasting [14]. In malnutrition, such as in simple starvation, fat tissues are preferentially lost and lean body mass (LBM) and muscle mass is preserved until the advanced stages, whereas in cachexia/wasting, muscle is wasted and fat is relatively underutilized [5, 10, 12]. Restoring adequate food intake or altering the composition of the diet reverses malnutrition. Nutrition supplementation does not totally reverse the cachexia/wasting syndrome [19, 20].

2 Diagnostic criteria of cachexia/protein–energy wasting in CKD

Cachexia was recently defined as “a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle, with or without loss of fat” by a group of scientists and clinicians participating in a consensus conference on cachexia [21]. This group, which later formed the Society for Cachexia and Wasting Disorders (SCWD), and included participants with diverse backgrounds encompassing many of the diseases states that result in cachexia (such as cancer, HIV infection, congestive heart failure (CHF), CKD, and chronic obstructive pulmonary disease), identified weight loss and growth failure as the most important clinical features of cachexia in adults and children, respectively. In the context of CKD, the term protein–energy wasting (PEW) has been proposed by The International Society of Renal Nutrition and Metabolism (ISRNM) to describe a “state of decreased body stores of protein and energy fuels (body protein and fat masses)” [22]. The ISRNM suggested that the term cachexia be reserved for only the most severe forms of PEW. However, there is no obvious distinction between PEW and cachexia from a pathophysiology standpoint. Limiting the term cachexia to the extreme forms of PEW could be considered too restrictive. The term pre-cachexia has been proposed to include the milder forms of wasting in cancer patients [23].

The diagnostic criteria for cachexia (proposed by the SCWD) and for PEW (proposed by the ISRNM) are

similar, but not identical. Weight loss of at least 5% over 12 months or fewer, or a BMI <20 kg/m², is necessary for the diagnosis of cachexia; three of the following five additional criteria are also required: decreased muscle strength, fatigue, anorexia, low fat-free muscle mass, and abnormal biochemistry (including elevated inflammatory markers such as C-reactive protein (CRP) or interleukin (IL)-6, anemia [Hb <12 g/dL] and hypoalbuminemia; Fig. 1). The proposed criteria for a diagnosis of PEW fall into four distinct categories: (1) biochemical indicators, (2) low body weight, reduced body fat or weight loss, (3) decreased muscle mass, and (4) low protein or energy intake (Table 1). In contrast to those for PEW, the diagnostic criteria for cachexia emphasize lean mass deficits and functional measures (such as muscle strength and fatigue); in addition, anemia is considered a feature of cachexia, but not of PEW.

Evidence of low body weight, reduced body fat or weight loss are important indicators of cachexia/PEW. Body mass index (BMI) is proposed as a method of

assessing appropriateness of body weight. Although BMI gives little information about body composition, BMI is a useful means of assessing PEW. BMI is strongly correlated with LBM at the low end of the BMI spectrum [24], and low BMI is a consistent predictor of mortality in both adults [25, 26] and children [27] on maintenance dialysis. However, BMI is not a very precise parameter of nutritional status in patients in whom gross imbalances in fluid homeostasis are commonly observed, such as in patients with ESRD, CHF, and liver disease. Furthermore, in patients with significant muscle wasting with relatively well-preserved fat mass, small changes in BMI may well be obscured by imbalances in fluid homeostasis. In this respect, some investigators have preferred to use subjective global assessment (SGA) as a surrogate marker in assessing the nutritional status of patients with ESRD. Stenvinkel et al. analyzed 268 patients with ESRD according to their BMI and SGA. They found that 38% of their patients in the low BMI group had a normal SGA, whereas 45% of the patients in the normal BMI group and 17% in the high BMI

Fig. 1 Conceptual representation of the definition: cachexia results from adaptation to an underlying illness such as cancer or CKD. The illness creates an environment that may be characterized by inflammation, loss of appetite (anorexia), low levels of anabolic hormones, and anemia. Decreased food intake and anorexia result in loss of body and muscle mass. In addition, inflammation, insulin resistance, and low levels of anabolic hormones result in muscle wasting. Reproduced with permission from [21]

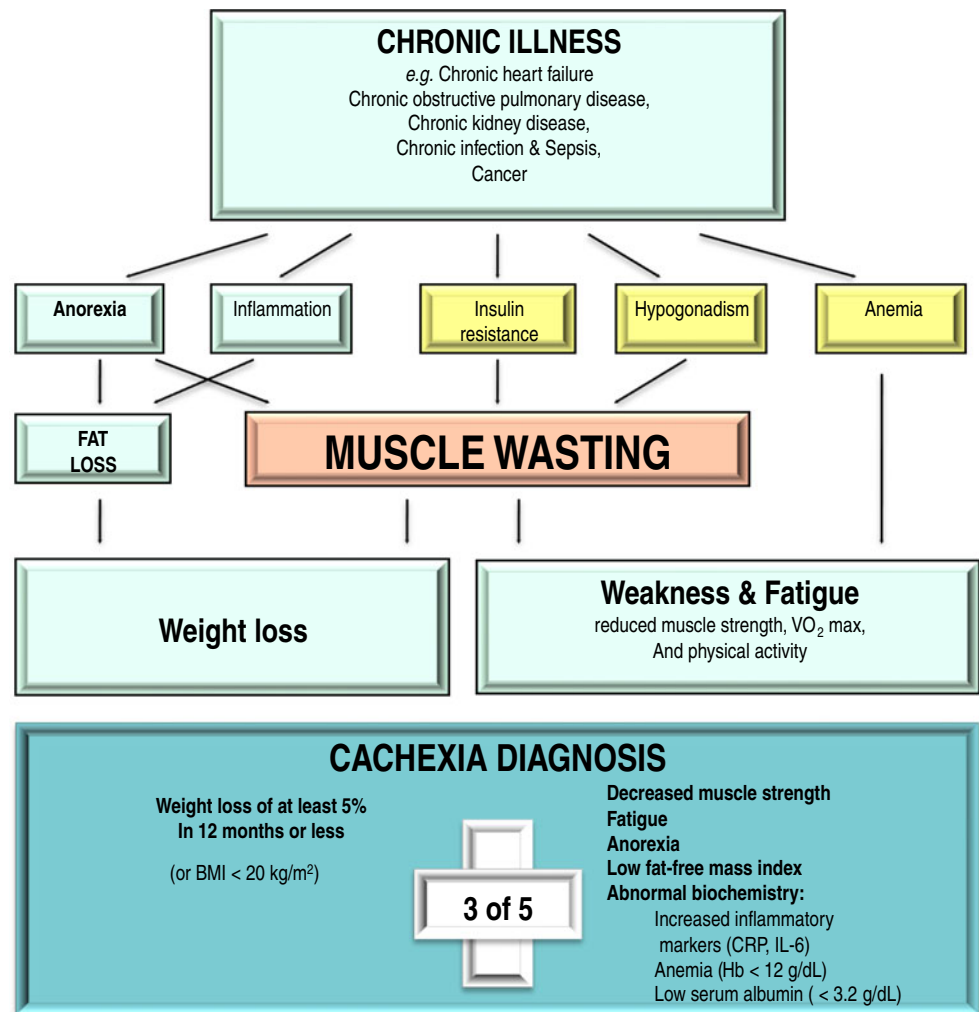


Table 1 Readily utilizable criteria for the clinical diagnosis of protein energy wasting in CKD

| Criteria |
|---|
| Serum chemistry |
| Serum albumin <3.8 g 100 ml ⁻¹ (Bromocresol Green) ^a |
| Serum prealbumin (transthyretin) <30 mg 100 ml ⁻¹ (for maintenance dialysis patients only; levels may vary according to GFR level for patients with CKD stages 2–5) ^a |
| Serum cholesterol <100 mg 100 ml ^{-1a} |
| Body mass |
| BMI <23 ^b |
| Unintentional weight loss over time: 5% over 3 months or 10% over 6 months |
| Total body fat percentage <10% |
| Muscle mass |
| Muscle wasting: reduced muscle mass 5% over 3 months or 10% over 6 months |
| Reduced mid-arm muscle circumference area ^c (reduction >10% in relation to 50th percentile of reference population) |
| Creatinine appearance ^d |
| Dietary intake |
| Unintentional low DPI <0.80 g kg ⁻¹ day ⁻¹ for at least 2 months ^e for dialysis patients or <0.6 g kg ⁻¹ day ⁻¹ for patients with CKD stages 2–5 |
| Unintentional low DEI <25 kcal kg ⁻¹ day ⁻¹ for at least 2 months ^e |

At least three out of the four listed categories (and at least one test in each of the selected category) must be satisfied for the diagnosis of kidney disease-related PEW. Optimally, each criterion should be documented on at least three occasions, preferably 2–4 weeks apart

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DEI dietary energy intake, *DPI* dietary protein intake, *nPCR* normalized protein catabolic rate, *nPNA* normalized protein nitrogen appearance

^a Not valid if low concentrations are due to abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines

^b A lower BMI might be desirable for certain Asian populations; weight must be edema-free mass, for example, post-dialysis dry weight. See text for the discussion about the BMI of the healthy population

^c Measurement must be performed by a trained anthropometrist

^d Creatinine appearance is influenced by both muscle mass and meat intake

^e Can be assessed by dietary diaries and interviews, or for protein intake by calculation of normalized protein equivalent of total nitrogen appearance (nPNA or nPCR) as determined by urea kinetic measurements

group were considered to have PEW by SGA. They further showed that low BMI has no impact on cardiovascular mortality whereas an SGA ≥ 2 was associated with a marked increase in cardiovascular mortality by Kaplan–Meier survival analysis [28]. Unintentional weight loss or reduction in weight of 5% or more over 3 months, or 10% or more over 6 months are suggested as indicators of cachexia/PEW, independent of absolute BMI [21]. Linear growth failure in children with CKD was highlighted as central to the diagnosis of cachexia [21], and has been associated with a greater mortality risk in children on maintenance dialysis [27]. However, the etiology of growth retardation in CKD is multifactorial, including other factors such as delayed sexual maturation, bone disease, acidosis, and growth hormone/insulin growth factor resistance. Growth failure may emerge as a necessary, but insufficient criterion, for PEW in children with CKD.

Reduced muscle mass appears to be the most valid criterion for the presence of PEW in CKD [22], and is also emphasized in the diagnostic criteria for cachexia [21].

Mid-arm circumference has been shown to correlate with quality of life and survival in adult patients on maintenance hemodialysis (HD) [29]. Accurate assessment of the adequacy of muscle mass is even more challenging. Dual X-ray absorptiometry, near-infrared interactance, and bio-electrical impedance have been used in investigations of ESRD patients [30] but these techniques have limitations in ESRD and are not currently accepted as clinically useful tools. Indirect measures, such as creatinine appearance (estimated by quantification of creatinine in a 24-h urine collection and in the collected spent dialysate) have been proposed as an index of muscle mass in patients with CKD and ESRD [22]. Body fat mass lower than 10% of body weight is considered an additional criterion for PEW in adults with CKD [22] due to the known association between total body fat below 10% and increased mortality risk in adult maintenance dialysis patients [31]. A more recent study showed that higher fat mass in dialysis patients might actually be protective in survival predictability [32]. On the other hand, Cordeiro et al. [33] recently showed that

abdominal fat deposition is linked to inflammation and PEW, resulting in an increased mortality risk in maintenance HD patients.

Anorexia is one of the suggested criteria for cachexia [21], while low protein and/or energy intake is a criterion for PEW [22]. Both subjectively reported anorexia [13, 34] as well as measured low protein or energy intake has been associated with increased mortality in adult ESRD patients [35]. Anorexia is prevalent, in 30–40% in adult maintenance HD patients, and is associated with higher concentrations of pro-inflammatory cytokines and higher levels of erythropoietin hypo-responsiveness as well as poor clinical outcome, including a fourfold increase in mortality, greater hospitalization rates, and poor quality of life [13]. As male ESRD patients seem to be more prone to inflammation-associated anorexia than female patients, sex hormones may play an important role in this context [34]. Anorexia is prevalent in children with fairly mild CKD can be the primary reason for growth failure [36]. Poor growth due to inadequate intake has been observed in children with glomerular filtration rate as high as 70 ml/min/1.73m² [37]. Growth of children with CKD is compromised when energy intake fall below 80% of recommended daily allowance [36].

Among biochemical indicators of PEW, low serum albumin stands out as a consistent predictor of mortality in epidemiological studies of both adult [38–42] and pediatric [43] ESRD patients. A low serum albumin concentration is by far the strongest predictor of mortality and poor outcomes in adult ESRD patients on maintenance dialysis when compared to any other risk factors [38, 39], including traditional risk factors (hypertension, smoking, hypercholesterolemia, diabetes, and obesity) and non-conventional ones (anemia measures, oxidative stress, minerals and bone surrogates, dialysis treatment and technique) [44]. The sensitivity of serum albumin to predict CKD patient outcomes is relatively high with such a granularity of as little as 0.2 g/dL or even smaller [39, 40]. Dialysis patients with baseline serum albumin of even 0.2 g/dL higher or lower than other dialysis patients with similar demographic and comorbidity constellations have significantly lower or higher death risk, respectively. The albumin–death association is highly incremental and linear, and the mortality–predictability of serum albumin below 4.0 g/dL has virtually no cutoff level, below which the association with death would cease or reverse [39, 40]. This is in sharp contrast to most other outcome predictors in CKD, which demonstrate U- or J-shape survival associations. Changes in serum albumin over time are associated with proportional and reciprocal alterations in subsequent death risk, in that a rise or drop in serum albumin by as little as 0.1 g/dL over a few months period is associated with improving or worsening survival, respectively [40].

Approximately two thirds of all maintenance dialysis patients in the USA exhibit “relative hypoalbuminemia”, i.e., a serum albumin <4.0 g/dL, as suggested by the National Kidney Foundation *Kidney Disease Quality Outcome Initiative* for the diagnosis of PEW [45]. In the USA, and most other countries, serum albumin is measured at least monthly to quarterly in all maintenance dialysis patients, making it the most readily available PEW biomarker. Dialysis clinics with superior patient care and performance also exhibit higher serum albumin levels and better survival rates, whereas those with inferior performance have lower albumin levels [46, 47].

Relatively low serum prealbumin (e.g., <30 mg/dL) is another indicator of PEW and a strong predictor of outcomes in maintenance dialysis patients [48]. Two recent studies showed that change in serum prealbumin over time is associated with corresponding changes in survival of ESRD patients [20, 48]. Even though baseline serum prealbumin may not be superior to albumin in predicting mortality in maintenance HD patients, prealbumin concentrations <20 mg/dL are associated with death risk even in normoalbuminemic patients, and a fall in serum prealbumin over 6 months is independently associated with increased death risk [48]. An interesting observation is that there is an inverse association between prealbumin and percentage total fat. Dialysis patients with high serum prealbumin have lower proportion of body fat as well as higher proportion of muscle mass, which suggest that normal serum prealbumin is associated with reversal of the abnormal body composition in cachexia. Furthermore, serum prealbumin strongly correlated with serum IL-6 independently in dialysis patients. Further analysis showed that in dialysis patients with a baseline serum prealbumin between 20 and 40 mg/dl, a drop of 10 mg/dl was associated with 37% increase in death risk independent of baseline markers of malnutrition inflammation score (MIS), serum albumin, and inflammatory markers [48].

Other nutritional indicators that predict survival in maintenance dialysis patients include serum transferrin level [49, 50] and nutritional scoring systems such as the SGA [51] and MIS which also correlate with quality of life [16]. Table 1 includes the list of potential PEW markers, from a recent consensus paper about the definition of PEW [2]. Low serum cholesterol has also been proposed as a biochemical indicator of PEW. Circulating inflammatory markers such as CRP, and proinflammatory cytokines such as IL-6 may also be persistently elevated in PEW but were not included as part of the criteria for diagnosis of PEW. This is however evident that the concurrent presence of PEW, inflammation, and CVD have additive interaction in the association with mortality in patients with ESRD on maintenance dialysis [52]

3 Pathophysiology of cachexia/PEW syndrome in advanced CKD

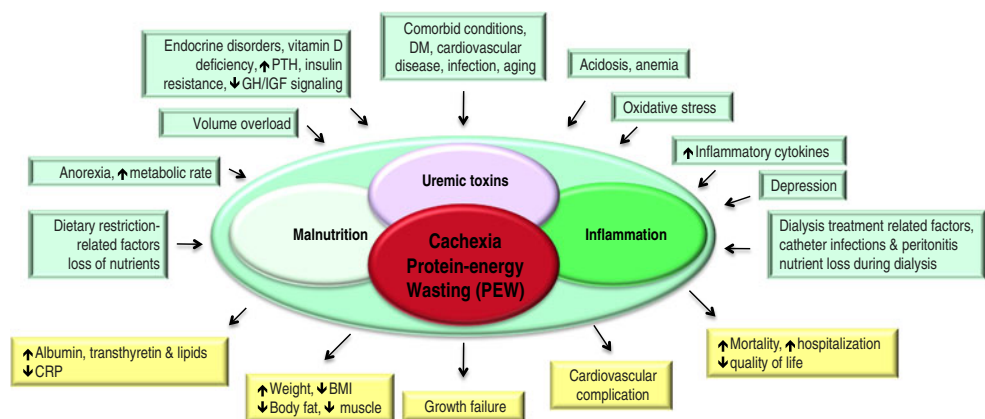
The pathophysiology of cachexia/PEW syndrome in CKD is multifactorial. An overview is summarized in Fig. 2 [22].

3.1 Anorexia

Anorexia is caused by a combination of factors including altered taste [53], gastroesophageal reflux, delayed gastric emptying, and elevated levels of numerous cytokines, including IL-1, IL-6, and tumor necrosis factor (TNF)- α [9]. Infants with high urine volumes may consume water in volumes large enough to diminish their appetite for milk or food. Furthermore, depression is common in ESRD patients and may be important in the pathogenesis of anorexia and PEW. Hung et al. [54] recently showed strong associations between depression, inflammation, and serum albumin in maintenance dialysis patients.

Furthermore, perturbations in appetite-regulating hormones such as leptin [6] and ghrelin [55] may contribute to anorexia in CKD (Fig. 3). As the kidney degrades leptin, CKD is independently associated with a peripheral increase in circulating leptin concentrations that are strongly and inversely correlated with GFR in children [56]. Experimental uremic anorexia can be ameliorated by blockade of leptin signaling through the hypothalamic melanocortin-4 receptor by the addition of agouti-related peptide (AgRP), a melanocortin reverse agonist, suggesting a possible future therapeutic strategy for PEW in CKD [4, 57]. Human data on leptin and CKD–PEW are so far inconclusive. Hyperleptinemia has not been associated with worse appetite in adult maintenance dialysis patients [58], and normalization to body weight resulted in an obliteration of differences between patients with different degrees of anorexia or different caloric intake [59]. It has consequently been suggested that because anorectic patients are subjected to an increased body fat mass loss, leptin will primarily reflect these fat stores thus obscuring any links to appetite [60].

Fig. 2 Schematic representation of the causes and manifestations of the protein–energy wasting syndrome in chronic kidney disease. Reprinted with permission from [22]

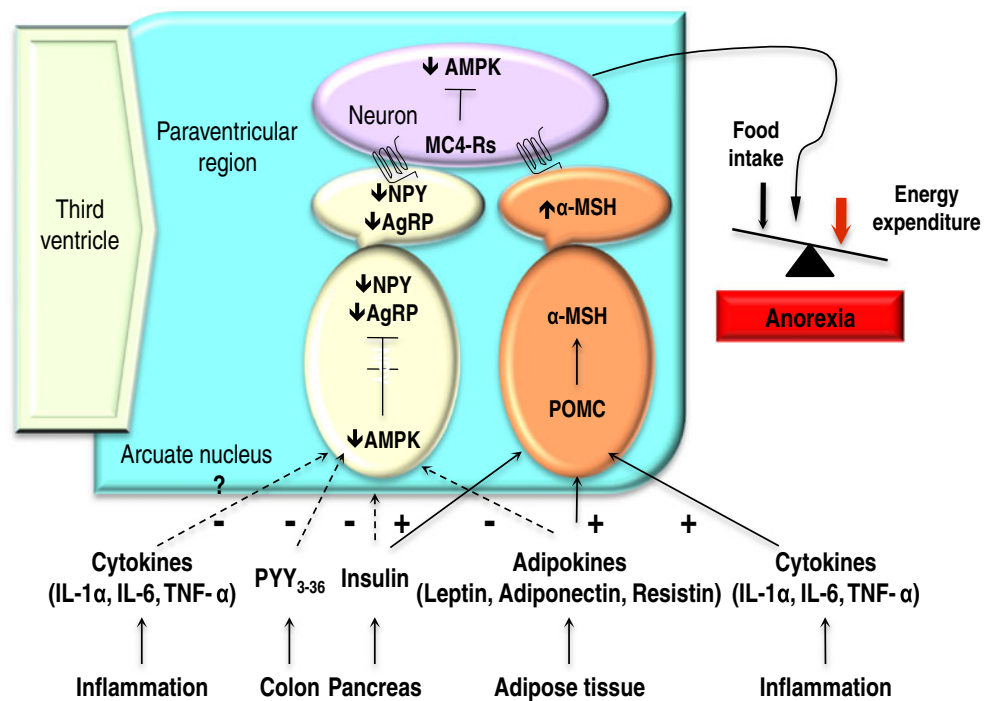


Increased total ghrelin levels in CKD are primarily due to the decreased degradation of ghrelin in the kidney [55, 61]. Whereas some studies found elevated ghrelin levels in dialysis patients, levels were normal or even low in other studies [62–64]. Multiple confounding factors may contribute to these seemingly contradicting findings. The two major forms of circulating ghrelin are acylated (<10%) and des-acyl ghrelin [61, 65, 66]. Acylated ghrelin promotes food intake while des-acyl ghrelin induces negative energy balance. Most of the investigators have used the traditional radioimmunoassay method to analyze the sum of both acylated and des-acyl ghrelin. However, only plasma des-acyl ghrelin levels were elevated in CKD patients compared with those patients with normal renal functions. Recent studies have suggested that elevated des-acyl ghrelin levels could be involved in the anorexia on CKD patients [61]. Variations in residual renal function affect ghrelin metabolism. Nutritional status of CKD patients may also influence the metabolism of ghrelin [61]. Assessment of nutritional status has not been performed in most studies in which chronic energy deficiency is evident in CKD patients. In addition, nutrients may be introduced during peritoneal dialysis in CKD patients. The absorption of glucose may influence plasma ghrelin levels [67]. Longitudinal studies, by following the same patients cohort in terms of their serum ghrelin and nutritional status [68], and by applying the discriminating ELISA assays to differentiate acylated versus des-acyl ghrelin levels, are more likely to reveal the pathophysiologic role of ghrelin in CKD [69].

3.2 Increased energy expenditure

Increased energy expenditure despite calorie insufficiency is an important feature of cachexia often observed in CKD. Wang et al. [14] reported elevated resting energy expenditure (REE) in adult peritoneal dialysis (PD) patients and that a higher REE was associated with increased mortality in PD patients, which was partly explained by its close correlations with residual kidney function, CVD, inflam-

Fig. 3 Orexigenic and anorexi-
genic mechanisms controlling
energy homeostasis in CKD.
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from [7]



mation, and poor nutrition in these patients [14]. Utaka et al. [70] also reported that the treatment of infection and subsequent resolution of elevated CRP is associated with the normalization of elevated resting energy expenditure in CKD patients, which is expected based on the known hypermetabolic effects of inflammation. In addition to inflammation, increased resting metabolic rate in CKD may be due to increased activity of mitochondrial uncoupling proteins (UCPs). UCPs, a family of the mitochondrial anion transporters, regulate ATP synthesis and the production of reactive oxygen species. Uncoupling of mitochondrial electron transporter chain activity from the phosphorylation of ADP results in thermogenesis [71]. UCP-1 and UCP-3 are key regulators of energy expenditure in rodents [72] and humans [73]. Cheung et al. have shown that UCP-1 mRNA and protein of brown adipose tissue was increased in uremic mice. Brown adipose tissue UCP-3 protein content was higher in uremic mice than in pair-fed control mice. This was associated with an elevation of basal metabolic rate in uremic mice compared with controls [57].

3.3 Inflammation

There is evidence that inflammation is an important cause of muscle wasting in CKD. Infusion of cytokines such as TNF- α , IL-6, IL-1 β , interferon (IFN)- γ enhanced muscle protein degradation via the NF κ B pathway whereas neutralization of these factors by genetic or pharmacological approaches attenuates muscle wasting [9]. Raj et al. [74] observed ineffective utilization of exogenous amino

acid for muscle protein synthesis in patients with ESRD. These investigators hypothesized that increased expression of IL-6 in the skeletal muscle augments muscle protein catabolism and the amino acid released is used for acute phase protein synthesis [75]. Inflammation activates the ubiquitin-proteasome system, leading to cleavage of a characteristic 14 kDa actin fragment in the soluble fragment of muscle which is the hallmark of increased muscle proteolysis in CKD [76]. Boivin et al. observed increased caspase-3 activity in the skeletal muscle of ESRD patients leading to increased generation of 14 kDa actin as well as ubiquitinated carboxy-terminal actin fragment. They also noted that the skeletal muscle of ESRD patients exhibited augmented apoptosis [77]. Furthermore, this increased muscle breakdown is not counterbalanced by a corresponding increase of the anabolic pathways [78] (Fig. 4).

NF κ B is a central integration site for pro-inflammatory signals and a regulator of related target genes. TNF- α enhances muscle wasting via NF κ B pathway [79]. NF κ B activation is required for cytokine-induced loss of skeletal muscle proteins [80] and is controlled by the I κ B kinase complex (IKK). Treatment with TNF- α , which induces NF κ B activation, attenuates insulin-stimulated protein synthesis [81]. TNF- α inhibits myocyte differentiation through NF κ B activation, further enhancing muscle wasting [82]. Activation of NF κ B signaling is sufficient to induce significant muscle atrophy, as measured by increases of amino acid excretion and tyrosine turnover in isolated muscles via the upregulation of muscle Ring-finger protein-

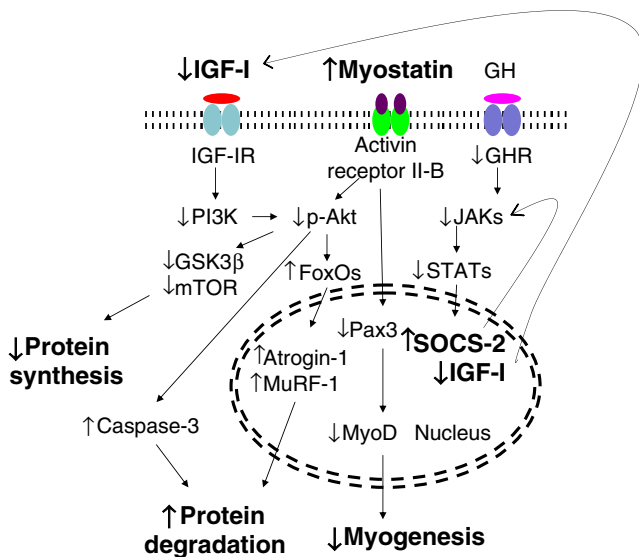


Fig. 4 Pathophysiology of muscle wasting in CKD. Reprinted with permission from [78]

1. Thus, the $\text{IKK}\beta/\text{NF}\kappa\beta/\text{MuRF1}$ signaling pathway is important in the pathogenesis muscle wasting associated with pro-inflammatory cytokines such as $\text{TNF-}\alpha$ [83].

Furthermore, inflammation may affect muscle wasting by multiple other mechanisms. Inflammation may suppress insulin signaling and increases production of glucocorticoids [84]. Furthermore, myostatin signaling pathway is recognized to functional counter to PI3k/Akt in mediating muscle wasting. Myostatin regulates skeletal muscle mass [85]. Myostatin-deficient mice display a marked increase in muscle mass, due to muscle fiber hyperplasia and hypertrophy [86]. IGF-I is essential for development of skeletal muscle and other tissues. IGF-I or the IGF-I receptor knockout mice were significantly smaller than their control littermates and had reduced muscle tissue, whereas over-expressed *IGF-I* transgenic mice showed increased muscle mass [87]. It has been proposed that the balance between local expression of myostatin and IGF-I represents a yin-and-yang system regulating muscle mass in CKD [88]. Sun et al. [89] showed that uremia and exercise have opposing effects in affecting this balance of myostatin and IGF-I in the pathogenesis of uremic wasting. Signaling of myostatin, IGF-I and SOCS-2 are important factors in the pathogenesis of muscle wasting in CKD [78].

3.4 Insulin resistance

Resistance to actions of insulin on carbohydrate, protein, and lipid metabolism has become an increasingly recognized complication of CKD. An important consequence of insulin resistance is its role in the pathogenesis of PEW in CKD [90]. Pupim et al. [91] reported that maintenance

hemodialysis patients with diabetes mellitus have a higher incidence of protein energy wasting as compared with CHD patients who are not diabetic [91]. The same investigators subsequently examined whether this unfavorable metabolic state could lead to accelerated loss of lean body mass over a period of 12 months [91, 92] and showed that chronic dialysis patients with DM had significantly accelerated loss of lean body mass compared to nondiabetic chronic dialysis patients during the first year of maintenance HD. Multivariate linear regression analysis revealed that the presence of diabetes mellitus was the strongest predictor of lean body loss independently of several clinically relevant variables such as age, gender, serum albumin, presence of malnutrition, presence of inflammation, baseline LBM, and renal replacement therapy modality. Furthermore, even in the absence of diabetes mellitus or severe obesity, insulin resistance is detectable in maintenance dialysis patients and is strongly associated with increased muscle protein breakdown, primarily mediated by the ubiquitin–proteasome pathway [93]. The underlying proteolytic mechanism, elegantly demonstrated by Mitch et al. [76] in animal models of insulin-deficiency and insulin resistance, appears to involve a decrease in the activity of PI3K leading to enhanced activation of the ubiquitin–proteasome pathway. They also reported that a decrease in muscle PI3K activity will activate Bax leading to stimulation of caspase-3 activity and increased protein degradation, which can be reversed by administration of rosiglitazone, a peroxisome proliferator-activated receptor (PPAR) agonist with profound insulin-sensitizing capabilities [94]. Recent epidemiological data indicate a survival advantage and better nutritional status in insulin-free type II DM patients treated with PPAR agonist thiazolidinediones [95].

3.5 Vitamin D deficiency

The complex metabolic abnormalities observed in CKD such as vitamin D deficiency, obesity, metabolic acidosis, inflammation, and accumulation of “uremic toxins” are believed to contribute to the etiology of insulin resistance and acquired defects in the insulin-receptor signaling pathway in this patient population. Intriguing data have begun to emerge linking the known vitamin D deficiency observed with CKD and insulin resistance. A recent large cross-sectional analysis of 14,679 subjects, also from NHANES III, revealed that serum $25(\text{OH})\text{D}_3$ levels and loss of renal function have an independent and inverse relationship with insulin resistance [96]. Active vitamin D compounds are distinguished by their ability to bind with high affinity to vitamin D receptors not only in the parathyroid glands, but in cells throughout the body indicating a role for significant systemic effects. One important nonclassical function of $1,25(\text{OH})_2\text{D}_3$ is as an important modulator of insulin release from pancreatic islets

[97]. Intravenous vitamin D₃ corrects glucose intolerance and stimulates insulin secretion in response to a glucose challenge in 1,25(OH)₂D₃ deficient animals [98]. Intravenous 1,25(OH)₂D₃ administration corrected glucose intolerance, insulin resistance, hypoinsulinemia as well as hypertriglyceridemia in ESRD patients, in the absence of parathyroid hormone suppression [99]. Metabolic acidosis is a common complication of advanced CKD and may represent yet another factor associated with increased insulin resistance. Correction of metabolic acidosis with bicarbonate supplementation has been demonstrated to improve insulin resistance in animal models of uremia as well as in humans. Oral bicarbonate replacement significantly improved insulin resistance observed in ESRD patients with metabolic acidosis. The mechanism may be mediated through upregulation of 1,25(OH)₂D₃ levels potentially via enhanced renal 1- α hydroxylase activity [100].

4 Therapeutic strategies for prevention and/or treatment of cachexia/PEW in CKD

4.1 Nutritional supplementation

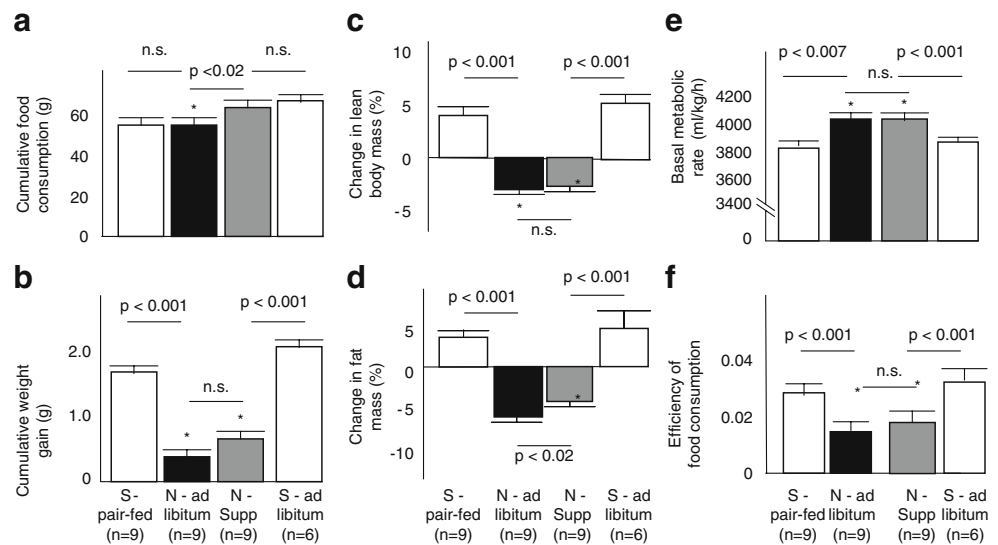
Cheung et al. [4, 57] investigated impact of nutritional supplementation on cachexia/wasting or malnutrition with a mouse model of CKD by 5/6 nephrectomy. CKD mice was fed ad libitum and compared with control sham-operated pair-fed mice fed with CKD mice as well as sham-operated mice fed ad libitum. CKD mice manifested anorexia; their average food intake is 80% or less of control mice. CKD mice gained significant less weight and lost both lean body mass and fat mass compared to both control pair-fed mice as well as control mice which are fed ad libitum. CKD mice also had a higher basal metabolic rate and were energy inefficient compared with both groups of control mice. CKD mice fed ad libitum were also compared with CKD mice forced-fed to bring their energy intake back to the level of control mice fed ad libitum. Despite the increased energy intake back to control levels, CKD mice still gained significantly less weight and their lean body mass and fat mass gains were significantly less than control values, which might explain by the elevated metabolic rate and resultant energy inefficiency. This experimental evidence clearly shows that the nutritional status in CKD is more compatible with cachexia/wasting than malnutrition and that nutritional supplements may improve but will not fully correct the wasting and elevated metabolic rate in CKD (Fig. 5).

There is evidence that nutritional therapy will improve PEW in adult ESRD patients. Caglar et al. [101] studied 55 HD patients with PEW, who received conventional nutrition counseling for 3 months, followed by 6 months of thrice-weekly in-center intake of an 8-oz oral nutritional

supplement specifically designed for dialysis patients [102] (Nepro™, Abbott Nutrition, Columbus, OH, USA), which was provided during the dialysis treatment in the dialysis clinics to ensure adherence. There were significant increases in concentrations of serum albumin and prealbumin levels [101]. In another in-center, prospective and controlled trial by Kalantar-Zadeh et al. [103] in 40 HD patients with hypoalbuminemia (≤ 3.8 g/dL), 20 HD patients received the same 8-oz can of the dialysis patient-specific oral supplement [96] accompanied by an additional 8-oz can of a liquid anti-inflammatory and anti-oxidative oral supplements that included borage oil and fish oil (Oxepa™, Abbott Nutrition, Columbus, OH, USA). After 4 weeks of thrice-weekly nutritional intervention during the HD treatment, the pre-trial serum albumin level of 3.45 ± 0.31 g/dl increased to 3.68 ± 0.34 g/dL ($p=0.02$) [103]. To the best of our knowledge, there are 13 randomized controlled trials [104–112] of nutritional therapy in ESRD patients. In eight out of the nine randomized trials with serum albumin as a surrogate outcome measure, significant improvement in hypoalbuminemia was reported [104–112]. Serum albumin did not increase significantly in the study by Fouque et al. [113] but even in this study higher serum albumin and prealbumin levels were observed in those who achieved higher dietary protein intake. In the trial by Cano et al. [20], 186 malnourished HD patients were randomized to intradialytic parenteral nutrition (IDPN) vs. no IDPN, while both arms received oral supplements. Despite apparently negative results for the IDPN, serum albumin and prealbumin levels increased in both groups under oral supplement therapy, and greater survival was observed in those whose serum prealbumin increased by more than 3 mg/dL after 3 months [20]. These data underline the importance of serum prealbumin in the follow-up of patients during nutritional support. Leon et al. [112] randomized 180 HD patients to compare usual care with targeting specific nutritional barriers, including poor nutritional knowledge, poor appetite, help needed with shopping or cooking, low fluid intake, inadequate dialysis dose, depression, difficulty chewing, difficulty swallowing, gastrointestinal symptoms, and acidosis. As part of the intervention, patients with poor appetite or low fluid intake as nutritional barriers were given limited amounts of oral nutritional supplements, such as commercially available enteral nutrition drinks and cookies. After 12 months, intervention patients had greater increases in serum albumin levels, energy intake, and protein intake compared to the control patients.

Poor growth due to inadequate intake has been observed in infants with GFR as high as 70 ml/min/1.73m². Growth of children with CKD is compromised when energy intake fall below 80% of recommended daily allowance (RDA) [36]. Increasing energy intake to 100% of the RDA can increase weight gain and stabilize growth rates. However,

Fig. 5 Impact of nutritional supplementation on energy homeostasis in experimental CKD. $N=5/6$ nephrectomized, *S* sham-operated controls, *Supp* mice given nutritional supplements by gavage. Modified from data published in [4, 57]



there is no evidence that children will grow better if their intake exceeds recommended amounts for healthy children. Gastrostomy tube feeding leads to improvement in weight and BMI-for-age z scores but not height-for-age z scores in children with advanced CKD [37, 114, 115].

4.2 Exercise and physical activity

Several studies have been performed examining the effect of exercise on nutritional status and functional status in ESRD patients. Most of the studies have assessed the effects of cardiopulmonary fitness training, whereas a few have examined the role of resistance or strength training on LBM in ESRD patients. Despite the proven efficiency of resistance exercise as an anabolic intervention in the otherwise healthy elderly population and certain chronic disease states, recent studies in patients on maintenance hemodialysis have not been encouraging in terms of long-term improvements in markers of muscle mass. In the most extensive study, Johansen et al. [116] studied whether anabolic steroid administration and resistance exercise training induce anabolic effects among patients who receive maintenance hemodialysis. Exercise did not result in a significant increase in LBM. Quadriceps muscle cross-sectional area increased in patients who were assigned to exercise and to nandrolone in an additive manner. On the other hand, patients who exercised increased their strength in a training-specific fashion, and exercise was associated with an improvement in self-reported physical functioning. Nandrolone deaconate and resistance exercise produced anabolic effects among patients who were on hemodialysis. Further studies are needed to determine whether these interventions improve survival. Most recently, Cheema et al. [117] studied whether 12 weeks of high-intensity, progressive resistance training (PRT) administered during

routine hemodialysis treatment could improve skeletal muscle quantity and quality versus usual care. While there were no statistically significant improvements in LBM, there were statistically significant improvements in muscle attenuation, muscle strength, and mid-thigh and mid-arm circumference in the PRT group relative to the nonexercising control group. Kopple et al. also studied resistance and endurance exercise over a 6-month period in maintenance dialysis patients and showed that while individuals assigned to individual treatment groups did not show significant improvement in their LBM, the overall group that exercised showed a small but significant increase in total LBM by dual-energy X-ray absorptiometry. These positive effects were accompanied by upregulation in skeletal muscle of mRNA and protein of insulin-like growth factor-I [118]. In addition to exercise alone, preliminary studies indicated that a combination of simultaneous exercise and nutritional supplementation could augment the anabolic effects of exercise, at least in the acute setting [119, 120]. However, a recent randomized clinical trial failed to show further benefits of additional resistance exercise training on long-term somatic protein accretion above and beyond nutritional alone [121]. These findings suggest that while that is evidence that patients with ESRD can improve skeletal muscle quality by exercise, longer training durations or more sensitive analysis techniques are required before this regimen can be recommended as therapy for cachexia/PEW in CKD. Furthermore, there is no data on whether exercises capacity tests can predict outcome in ESRD.

4.3 Appetite stimulant

Megestrol acetate is a synthetic derivative of progesterone. Megestrol acetate may induce appetite via stimulation of hypothalamic neuropeptide Y, modulation of

calcium channels in hypothalamic appetite centers or inhibition of inflammatory cytokines such as IL-1, IL-6, and TNF. Administration of megestrol acetate to ESRD patients resulted in improvements in appetite as well as increases in fat mass but decreases in fat-free mass. In the only double-blinded, crossover study [122], 24 maintenance hemodialysis patients with anorexia were studied. Four patients withdrew because of diarrhea and two died of comorbid conditions. Of the 18 who completed the study, no significant increase in albumin or LBM was observed. A large number of side-effects were reported, including headaches, dizziness, confusion, diarrhea, hyperglycemia, thrombo-embolism, uterine bleeding, peripheral edema, hypertension, and adrenal insufficiency [123]. Thus, the current experience in ESRD patients does not support the use of megestrol acetate in clinical practice. Large randomized control trials are needed to clarify the therapeutic role of megestrol acetate in uremic anorexia.

4.4 Correction of acidosis

There is evidence that acidosis can induce muscle protein catabolism and it could therefore be an important factor contributing to loss of muscle protein in these conditions [124]. Acidosis is associated with negative nitrogen balance and degradation of branched-chain amino acids and protein in patients with CKD. Stein et al. randomly assigned 200 PD patients with metabolic acidosis to treatment with a dialysate solution of 35 mmol/l lactate or to a dialysate of 40 mmol/l lactate. After 1 year, both groups of patients had a higher serum HCO_3^- , had gained weight, and had an increase in mid-arm muscle circumference compatible with an increase in muscle mass [125]. Pickering et al. determined if increasing the serum bicarbonate concentration of CAPD patients would improve their nutritional status, increase plasma branched-chain amino acids (BCAA) levels, and reduce ubiquitin mRNA in their muscle as an index of suppressed activity of the ubiquitin–proteasome system (UPS). Eight stable long-term PD patients underwent vastus lateralis muscle biopsy before being randomized to continue 35 mmol/l lactate dialysate or convert to a 40 mmol/l lactate dialysate. After 4 weeks, measurements were repeated. Increasing the serum bicarbonate level in CAPD patients leads to a downregulation of proteolysis via the UPS pathway in muscle. There was also an increase in plasma BCAA consistent with a decrease in their degradation. The number of patients studied was small, but the agreement between the results from both human and animal studies provide compelling evidence that muscle wasting in dialysis patients occurs via stimulation of these catabolic pathways [126]. There are, however, few treatments available for correcting metabolic acidosis apart from alkali supplements such as NaHCO_3 which, in CKD

patients, carry the risk of sodium loading and fluid overload. Despite these theoretical risks, a recent study using NaHCO_3 supplementation in patients with CKD actually led to a slower decline in their renal function as well as improvement in their nutritional status. Following correction of acidosis in these predialysis CKD patients, dietary protein and calorie intake increased, accompanied by improvements in serum albumin and LBM as assessed by mid-arm muscle circumference [127].

4.5 Growth hormone

Acquired resistance to the anabolic actions of growth hormone (GH) is a potential cause of the increased net protein catabolism and wasting in patients with advanced CKD. Several studies have shown that the administration of recombinant human growth hormone (rhGH) at pharmacologic doses induces a net anabolic action and improves food utilization in uremic animal models. Similar findings were reported in studies that used different methods to assess protein homeostasis in patients with ESRD. Thus, pharmacologic doses of rhGH constitute another potential anabolic therapy in maintenance dialysis patients. Pupim et al. showed that short-term GH therapy (for three consecutive days) led to a 22% improvement in pre-HD whole-body protein homeostasis. Essential amino acid muscle loss was also significantly less during the pre-HD period when rhGH was administered. The whole body anabolic effects of rhGH observed during the pre-HD period persisted throughout the entire study, as evidenced by a lack of significant interaction or main effect of treatment during HD and in the post-HD period [128]. Using stable isotope techniques to assess skeletal muscle protein homeostasis, Garibotto et al. [129] showed significant improvement in net muscle protein balance over a 6-week administration of 50 μg rhGH in cachectic ESRD patients on HD. Feldt-Rasmussen et al. [130] showed GH treatment in ESRD patients increased lean body mass and quality of life with no significant side-effects. Thus, rhGH improves whole body protein homeostasis in chronic HD patients in the short-term. A recent large multicenter randomized controlled study designed to look at the effects of daily rhGH administration on mortality was terminated due to lack of recruitment [131]. Interestingly, the preliminary results of this trial indicated a beneficial effect on the cardiovascular outcomes in maintenance hemodialysis patients [Kopple et al., personal communication]. Thus, more studies are needed to evaluate its long-term effect of rhGH on outcomes in patients with advanced CKD.

4.6 Ghrelin agonists

The salutary effects of ghrelin on food intake and meal appreciation suggest that it could be an effective treatment

for anorexic ESRD patients. Wynne et al. [132] reported that a single subcutaneous injection of ghrelin enhances short-term (3 days) food intake in PD patients, as evidenced by a twofold increase in short-term energy intake. Subcutaneous ghrelin administration resulted in a twofold increase in short-term energy intake in a cohort of nine anorexic PD patients. Although these results are encouraging, it is possible that the initial short-term increase in food intake may be followed by subsequent decline, negating any long-term beneficial effect of ghrelin administration. Ashby et al. [133] evaluated the nutritional and cardiovascular effect of daily subcutaneous ghrelin injection over a period of 7 days in 12 anorexic PD patients. Their results suggest that subcutaneous administration of synthetic ghrelin stimulates food intake among dialysis patients over the intermediate term. Energy expenditure, measured with free-living pulse and motion monitors, is unchanged. Importantly, there was no subsequent compensatory reduction in energy intake in these patients; this suggests potential long-term beneficial effects. No significant adverse effects were observed during the study. Tolerance in appetite-regulating centers and/or other factors may override the long-term appetite-stimulating effects of ghrelin. Potential side effects of ghrelin therapy have to be considered. Ghrelin infusion acutely induces lipolysis and insulin resistance independently of GH and cortisol [124]. Thus, it will be important to follow subjects for the risk of diabetes while on long-term ghrelin treatment. Finally, a major limitation of treatment based on natural hormones is the need for parenteral administration, because of the large size of the molecule. The long-term therapeutic potential of GHS-R agonists will likely rest with orally bioavailable compounds. DeBoer et al. [134] recently showed that ghrelin and small-molecule GHS-R agonist administration, over a 2-week period, increased food intake and lean body mass retention and decreased systemic inflammation and muscle catabolism in rats with cachexia associated with CKD. However, despite reports of the short- and intermediate-term success of ghrelin administration in treating anorexia and cachexia in ESRD patients, we must await results of studies on its long-term efficacy in improving appetite, weight gain, and lean body mass as well as quality of life.

4.7 Leptin and melanocortin signaling modulation

Cheung et al. [4] demonstrated that uremia-associated cachexia in mice could be ameliorated by genetic or pharmacological blockade of leptin and central melanocortin signaling via the MC4-R. The potential clinical utility of this approach, however, is limited by the need to deliver AgRP intracerebroventricularly. NBI-12i, a small molecule MC4-R antagonist with high affinity, selectivity, and central nervous

system penetration after peripheral administration, has been recently developed. Cheung et al. [57] examined the effects of NBI-12i in a mouse model of uremic cachexia. Intraperitoneal administration of NBI-12i effectively stimulated food intake and weight gain in uremic mice. Furthermore, NBI-12i exhibited additional desirable metabolic effects beyond the nutritional effects of stimulating appetite. NBI-12i-treated uremic mice gained LBM and fat mass and had a lower basal metabolic rate, while vehicle-treated and diet-supplemented uremic mice with the same caloric intake lost both LBM and fat mass and had an increased basal metabolic rate. The protective effects of NBI-12i may be due to the normalization of the upregulation in uncoupling protein expression seen in uremic mice. These data underscore the importance of melanocortin signaling in the pathogenesis of uremia-associated cachexia and demonstrate the potential of peripheral administration of MC4-R antagonists as a novel therapeutic approach. Recently, orally active MC4-R antagonists have been introduced and hold the promise of potential therapy for cachexia/PEW [135].

4.8 Ubiquitin–proteasome inhibitors

Cachexia/PEW in CKD is characterized by protein catabolism. Protein synthesis is unchanged while protein degradation is increased in CKD. The daily rate of protein turnover in cells is so high that even a small increase in protein degradation will cause marked protein depletion over time. The mechanism of increased protein degradation in CKD is through the activation of the UPS. Complications of CKD, including acidosis, insulin resistance, inflammation, and increased glucocorticoid and angiotensin II production, all activate the UPS to degrade muscle protein [136]. Recognition of the role of the UPS in the pathogenesis of cachexia/wasting has led to the therapeutic use of bortezomib—a proteasome inhibitor—in cancer patients. Inhibition of the proteasome will block activation of NF- κ B, which is a common final pathway for signal transduction of many cytokines, thought to be a central mechanism of cachexia/wasting in many chronic disease states including CKD [137].

4.9 Dose and frequency of dialysis

Rocco et al. found no significant effect of HD dose or HD membrane flux on longitudinal nutritional status in maintenance HD patients as measured by appetite, serum albumin, and anthropometric measures [138]. Galland et al. converted eight patients from standard maintenance hemodialysis of 4–5 h three times a week to daily maintenance HD of 2–21/2 h six times a week and observed significant improvements in appetite and in nutritional status as reflected by increases in serum albumin, serum prealbumin, cholesterol, dry weight, and lean body mass after 6-month and 1-year

intervals [139]. However, a recent randomized controlled trial failed to confirm the beneficial effects of daily HD on nutritional status in maintenance HD patients, as measured by serum albumin [140].

5 Conclusion

Many questions remain about the description, classification, and treatment of PEW or cachexia in children and adults with CKD. Can a PEW scoring system effectively predict morbidity and mortality? Can nutritional intervention improve the biochemical and clinical disorders related to PEW? If therapeutic interventions are effective at improving indicators of PEW, will these interventions improve clinical outcomes? New understanding of the pathophysiology of PEW in CKD has the promise of novel therapeutic strategies. Targeted anti-inflammatory agents, already in clinical trials for autoimmune disorders, including anti-TNF- α , anti-IL-1 and anti-IL-6 may hold the potential of improving cachexia/PEW in CKD patients. Other novel therapies such as ghrelin agonists, melanocortin antagonists and ubiquitin–proteasome inhibitors are also potentially exciting alternative strategies. On the other hand, the basic question whether nutritional supplementation can improve nutritional status and hence morbidity and mortality in ESRD patients remains to be tested with appropriately designed randomized controlled trials. Most of the information on the novel strategies is currently at the experimental level and awaits confirmation, again by randomized controlled clinical trials in patients with CKD-associated cachexia/PEW syndrome.

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