REVIEW ARTICLE

CPE Etiology of the Protein-Energy Wasting Syndrome in Chronic Kidney Disease: A Consensus Statement From the International Society of Renal Nutrition and Metabolism (ISRNM)

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Protein-energy wasting (PEW), a term proposed by the International Society of Renal Nutrition and Metabolism (ISRNM), refers to the multiple nutritional and catabolic alterations that occur in chronic kidney disease (CKD) and associate with morbidity and mortality. To increase awareness, identify research needs, and provide the basis for future work to understand therapies and consequences of PEW, ISRNM provides this consensus statement of current knowledge on the etiology of PEW syndrome in CKD. Although insufficient food intake (true undernutrition) due to poor appetite and dietary restrictions contribute, other highly prevalent factors are required for the full syndrome to develop. These include uremia-induced alterations such as increased energy expenditure, persistent inflammation, acidosis, and multiple endocrine disorders that render a state of hypermetabolism leading to excess catabolism of muscle and fat. In addition, comorbid conditions associated with CKD, poor physical activity, frailty, and the dialysis procedure per se further contribute to PEW.

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Introduction

A SYNDROME OF adverse changes in nutrition and body composition is highly prevalent in patients with chronic kidney disease (CKD), especially in those undergoing dialysis, and it is associated with high morbidity and mortality. A summary of the mechanisms involved in these alterations is provided in Figure 1. Although insufficient food intake (true undernutrition) due to poor appetite and dietary restrictions contributes to these problems, there are features of the syndrome that cannot be explained by undernutrition alone. Many contributing causes are directly related to kidney

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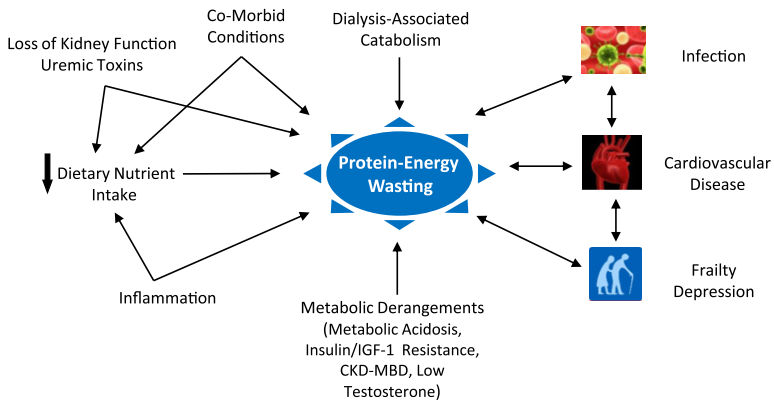

Figure 1. A conceptual model for etiology of PEW in CKD and direct clinical implications. PEW is the result of multiple mechanisms inherent to CKD, including undernutrition, systemic inflammation, comorbidities, hormonal derangements, the dialysis procedure, and other consequences of uremic toxicity. PEW may cause infection, CVD, frailty, and depression, but these complications may also increase the extent of PEW.

disease, including increased resting energy expenditure (REE), persistent inflammation, acidosis, multiple endocrine disorders, and the dialysis procedure itself. However, this syndrome shares etiologic factors that contribute to cachexia in non-CKD populations, including comorbid conditions associated with cachexia, decreased physical activity, frailty, and aging. The CKD and end-stage renal disease (ESRD) populations are unique in the constant surveillance that facilitates the diagnosis of wasting before frank cachexia begins. Given the unique features of the syndrome, the International Society of Renal Nutrition and Metabolism (ISRNM) proposed a common nomenclature and diagnostic criteria for these alterations in the context of CKD.[1] Protein-energy wasting (PEW) was proposed to denote concurrent losses in protein and energy stores, with cachexia being regarded as only the end stage. ISRNM's intention was to begin creating a framework to identify and understand disorders that promote PEW.[2] To further this process, the ISRNM now provides a consensus review of current knowledge on the etiology of PEW in kidney disease (Table 1) to provide a basis for future advances in diagnosis and therapy and to identify gaps in knowledge for future research.

Table 1. Causes of PEW in CKD Patients

1. Decreased protein and energy intake
   a. Anorexia
      i. Dysregulation in circulating appetite mediators
      ii. Hypothalamic amino acid sensing
      iii. Nitrogen-based uremic toxins
   b. Dietary restrictions
   c. Alterations in organs involved in nutrient intake
   d. Depression
   e. Inability to obtain or prepare food
2. Hypermetabolism
   a. Increased energy expenditure
      i. Inflammation
      ii. Increased circulating proinflammatory cytokines
      iii. Insulin resistance secondary to obesity
      iv. Altered adiponectin and resistin metabolism
   b. Hormonal disorders
      i. Insulin resistance of CKD
      ii. Increased glucocorticoid activity
3. Metabolic acidosis
4. Decreased physical activity
5. Decreased anabolism
   a. Decreased nutrient intake
   b. Resistance to GH/IGF-1
   c. Testosterone deficiency
   d. Low thyroid hormone levels
6. Comorbidities and lifestyle
   a. Comorbidities (diabetes mellitus, CHF, depression, coronary artery disease, peripheral vascular disease)
7. Dialysis
   a. Nutrient losses into dialysate
   b. Dialysis-related inflammation
   c. Dialysis-related hypermetabolism
   d. Loss of residual renal function

Undernutrition and Anorexia

Low energy and/or protein intake associates with a significant decline of nutritional parameters (including hypoalbuminemia) and increased risk of morbidity and mortality in patients with advanced CKD.[3,4] In most of these studies, dietary energy and protein intakes are lower than recommended for patients undergoing either hemodialysis (HD)[3,5,6] or peritoneal dialysis (PD).[7,8] However, dietary recalls underestimate dietary intake,[9–11] and improving accuracy of dietary monitoring is needed. There is presently limited information correlating dietary composition, including micro/macronutrient intake, with outcomes.[12–14] In one study that was based on food-frequency questionnaires, HD patients consume significantly lower amounts of potassium, dietary fiber, vitamin C, and certain cardioprotective carotenoids.[15] Data from the Third National Health and Nutrition Examination Survey showed that high dietary total fiber intake was associated with lower risk of inflammation and mortality in CKD patients.[16] Many of the restrictions in renal diets contradict current recommendations for healthy eating. Although limiting dietary sodium, phosphate, potassium, and fluid intake prevents important patient complications, problems arise when these restrictions are not accompanied

with appropriate counseling on alternative food choices and/or strategies to ensure adequate nutrient intake.[17,18]

Anorexia often drives inadequate protein and energy intake and directly contributes to poor quality of life.[6,19-21] The prevalence of anorexia has been reported at 35% to 50% of ESRD patients.[22,23] Although few studies exist in CKD stages 1-3, a progressive, spontaneous decrease in food intake occurs with greater loss of kidney function, which correlates with accumulation of nitrogen-derived uremic toxins.[24-26] The factors influencing food intake involve not only metabolic signals but also anomalies in the digestive system and psychological and acquired aspects, including a desire for pleasure, social behavior, and customs.[27] Anorexia may be mediated by circulating appetite regulators, such as gastric mediators (such as cholecystokinin,[28] peptide YY,[29] ghrelin,[30,31] or obestatin), adipokines (such as leptin[32] and visfatin[33]), or cytokines (such as tumor necrosis factor [TNF], interleukin [IL]-6, and IL-1β[19,20]), but these mediators need additional research in the uremic milieu.[34] Signaling by hypothalamic neurons that sense the ratio of essential to nonessential amino acids[35] may be influenced by the fall in branched-chain amino acid levels with uremia or dialysis, creating the so-called brain hyperserotoninergic-like syndrome. The role of other complications of uremia on anorexia need to be further explored, including dental and oral problems (such as palatability problems or incidence of periodontitis[36]), gastric alterations[37] (motility disorders,[38] dyspepsia,[39] or bacterial infections in the intestine[40]), and depression.[21,41]

Although reduced intake of food or poor absorption of nutrients plays a critical role in most cases of PEW,[42,43] the science of starvation suggests that additional mechanisms are needed for PEW to occur (Fig. 2). Decreased

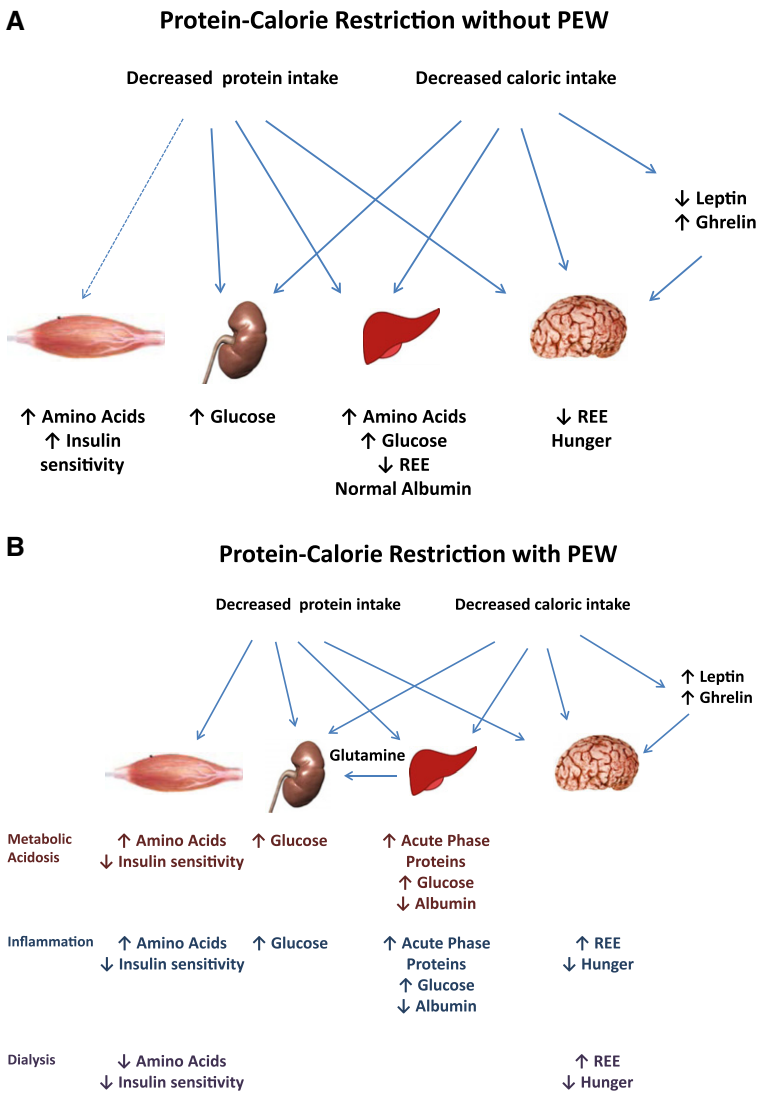

Figure 2. Response to reduced dietary protein and energy intake. (A) Normal response. Reduced dietary protein and energy drive an increase in hunger and a fall in REE, loss of protein preferentially from the visceral organs, and increased insulin sensitivity of muscle. The liver and kidney provide glucose, and serum albumin is maintained at a normal level. (B) Response with PEW. During PEW, the adaptations to increase hunger and lower REE are blunted in part by an increased half-life of leptin and ghrelin and in part by inflammation and dialysis. The loss of protein occurs preferentially from muscle because of the effects of metabolic acidosis, glucocorticoids, and inflammation, leading to increased insulin resistance. Dialysis results in the loss of amino acids, stimulating muscle protein breakdown. Under the influence of inflammation and metabolic acidosis, the liver makes glutamine for deamination in the kidney, increases acute-phase reactants, and reduces serum albumin. The kidney increases glucose production from glutamine under the influence of metabolic acidosis.

energy intake reduces insulin secretion and stimulates the production of sugar from glycogen and increased mobilization of fatty acids.[44] Activation of these systems contributes to a reduction in basal metabolic rate and mobilization of free fatty acids and amino acids.[44,45] Muscle proteolysis only transiently increases in early starvation, but muscle release of amino acids declines over the first 2 weeks of starvation and visceral organ proteins are used preferentially to muscle.[46] Muscle and visceral proteins can be preserved to some extent because of heightened insulin sensitivity, and diets with as little as 0.55 g/kg/day of balanced protein may be well tolerated.[47] Below that level, the loss of visceral protein and increases in lipolysis lead to fatty infiltration of the liver and decreased plasma protein synthesis.[48] However, plasma proteins, particularly prealbumin and S-albumin, have increased half-life and do not change in concentration with moderate calorie or protein restriction alone.[49,50] Generally, other factors in addition to starvation (especially inflammation and acidosis) are required for accelerated muscle loss and hypoalbuminemia. However, depletion of visceral protein stores caused by prolonged decreased energy intake or frequent intermittent starvation causes disruption of certain protective mechanisms. Heavy ketone body formation marks a transition in metabolism to more severe starvation and causes a loss of the adaptation that prevented hypoalbuminemia and limited muscle wasting earlier in starvation.[44,51] The acid and the ketone bodies in severe starvation appear to be critical in making protein loss from muscle greater than from other organs and making amino acids a critical source of glucose.[46]

Hypermetabolism

Increased Energy Expenditure

In simple starvation, the body reduces energy expenditure to conserve energy needs. REE is usually normal in stable maintenance dialysis or CKD patients. In contrast, REE increases from 12% to 20% in CKD patients during the HD procedure[52] or in the presence of comorbidities such as cardiovascular disease (CVD),[53] severe hyperparathyroidism,[54] poorly controlled diabetes,[55] inflammation, PEW,[53,56,57] and loss of residual kidney function.[53] In PD patients, PEW was more frequent among patients in the highest tertile of REE when compared with those in the lower tertile.[53] Because protein catabolism and inflammation result in elevated energy expenditure,[58] higher energy intake alone should not correct increased REE under these circumstances (although this has not been rigorously tested). Increased REE is frequently mitigated by decreased physical activity, leading to a reduction, rather than an increase, in total energy expenditure in some studies.[59,60]

Persistent Inflammation

Inflammation overcomes the adaptive responses protecting muscle and reducing REE during decreased protein and energy intake. Inflammation activates intracellular NADPH oxidases, creating signals that induce muscle insulin resistance.[61] The inflammatory response is associated with a rise in REE, which can be so severe that starvation responses are activated in well-fed individuals.[44,61] Inflammation is associated with a decline in albumin concentration and reduces the synthesis and half-life of albumin.[62] Inflammation explains the requirement for infection to promote edema and hypoalbuminemia in kwashiorkor.[48] Protein, DNA, and lipid oxidation occur in severe starvation as a result of depletion of dietary antioxidants, exhaustion of autophagy, depletion of protein stores, and/or from inflammation.[50,63] It is interesting to note that increased oxidative signaling is associated with muscle insulin resistance, muscle wasting, and atherosclerotic disease.[51,64] Thus, inflammation causes increased REE, preferential muscle loss, and oxidation.

Inflammatory markers are increased in most conditions associated with loss of muscle mass, including CKD,[65–68] cancer, congestive heart failure (CHF), chronic pulmonary disease, acquired immune deficiency syndrome, and aging.[69] Muscle loss due to inflammation has been ascribed to inflammatory cytokines.[65,70] Animal studies show that infusion of TNF, IL-1, and IL-6 causes an increase in muscle protein breakdown, resulting in muscle atrophy.[69] Proinflammatory cytokines also act on the central nervous system to decrease appetite[71] and increase REE.[72] Proinflammatory cytokines impair insulin/insulin-like growth factor (IGF)-1 signaling by augmenting the level of glucocorticoids (see *Impairment of Insulin/IGF-1*) and by directly inducing insulin and IGF-1 resistance in skeletal muscle.[73] Multiple studies show that high circulating levels of IL-6, a prominent biomarker of inflammation, contribute to inflammatory muscle protein losses.[74] In part, these losses are triggered by alteration of IL-6 signaling due to interaction with acute-phase proteins, including serum amyloid A, to impair insulin/IGF-1 signaling via the activator of transcription 3 and suppressor of cytokine signaling 3.[74] Ineffective utilization of exogenous amino acids for muscle protein synthesis during HD has been linked to increased skeletal muscle expression of IL-6.[75] In uremic skeletal muscle, IL-6 has also been linked to increased caspase-3 activity (an initial step resulting in loss of muscle protein).[76]

Myostatin, a member of the transforming growth factor (TGF)-β superfamily of proteins, is induced by CKD in mouse models via cytokine-activated pathways, and downregulating the myostatin receptor improved IGF-1 signaling, enhanced satellite cell function, and suppressed inflammatory cytokines.[77] Significantly, inflammation-induced increase in muscle protein degradation in CKD can be blocked by a humanized antibody inhibiting the function of myostatin, leading to increased muscle growth, suppression of the levels of inflammatory cytokines, and improvement in insulin/IGF-1 resistance.[78] Consistent with a role of myostatin in PEW, its endogenous inhibitor,

follistatin, is induced by exercise,[79] one of the few interventions that increases muscle strength and mass in CKD.[80] However, in CKD patients, follistatin is positively correlated with inflammation and PEW resistance to its action.[81] Thus, it is possible that inflammation or CKD alters the balance between follistatin, and myostatin to regulate muscle mass in uremia and that intervening in myostatin signaling might preserve muscle and/or reduce inflammation.[82-84]

TNF-related weak inducer of apoptosis (TWEAK), a member of the TNF superfamily[85] binds to its receptor (Fn14) linked to signaling pathways involved in the regulation of nuclear factor kappa light-chain enhancer of activated B cells (NF-κB), myogenesis, and apoptotic cascades.[86] TWEAK-Fn14 expression is induced in animal models of tissue injury and inflammation, and biomarker studies show a significant interaction between soluble TWEAK and IL-6 in the prediction of mortality and reduced muscle strength in HD patients.[85] Recently, alternative pathways of NF-κB activation have been identified that regulate distinct forms of NF-κB and its effectors.[87] Finally, complex regulation of IL-15, an immunoregulatory cytokine with proinflammatory activity but also paradoxical anabolic functions, may play a role in insulin/IGF-1 resistance.[88]

Abdominal Obesity and Adipokines

Observational studies indicate improved survival in obese patients undergoing HD. Thus, it is hypothesized that dialysis patients at high risk of PEW are protected by excess weight. However, obesity does not necessarily imply good nutritional status, and muscle wasting occurring despite fat accumulation in the general population has been termed "obese sarcopenia".[89] Furthermore, the regional fat distribution has metabolic implications. Abdominal subcutaneous tissue in otherwise healthy subjects is proinflammatory and CKD patients have increased expression of proinflammatory cytokines and adipokines in abdominal subcutaneous tissue compared with healthy controls.[90-92] Observational studies in CKD patients link abdominal fat with inflammation, insulin resistance, hyperadipokinemia, dyslipidemia and oxidative stress,[91,93-98] and cardiovascular events.[99] In a large cohort of prevalent HD patients, each kilogram of body mass index (BMI) increase reduced the risk of dying whereas, concomitantly, each centimeter increase of waist circumference raised mortality risk.[100] Thus, although a high BMI in the setting of CKD may signal health and better nutritional status, abnormal deposition of abdominal fat may be detrimental because of metabolic derangements. This concept was demonstrated in a study of disproportional fat mass accumulation in HD patients by modeling the body as a bicone centered on the waist.[101] In addition, the recent observations that waist circumference modifies the mortality risk associated with circulating triglycerides,[102] leptin, and adiponectin[103] underscores the overall effect that abdominal obesity has on PEW.

Although leptin inhibits food intake and increases energy consumption via the hypothalamic melanocortin system,[32] evidence is lacking that the markedly elevated circulating leptin level in uremia contributes clinically to anorexia and PEW.[90] In fact, the positive association between circulating leptin levels and improved nutrition in CKD suggests that uremia is a state of leptin resistance.[27,104,105] Although early reports in CKD showed that higher adiponectin levels are linked to better outcomes,[106] recent studies showed the opposite.[107] Lower fat mass in PEW increases circulating adiponectin, causing adiponectin to lose its association with mortality after adjustment for BMI in diseases such as CHF.[108] Adiponectin has anti-inflammatory, antiatherogenic, and insulin sensitizing actions, and increased adiponectin has been suggested to be a "reparatory response" to the microvascular insults in uremia,[109] but experimental data suggest that adiponectin also promotes weight loss via increased energy expenditure.[110] Therefore, although adiponectin is a biomarker of PEW, its role in pathogenesis remains to be determined.

Visfatin is expressed in human atherosclerotic plaques and is associated with plaque destabilization, independently predicting coronary artery disease in humans.[111] Although studies are limited, visfatin in CKD is positively associated with endothelial dysfunction and inflammation and negatively associated with HDL cholesterol.[90,112] Visfatin may also be involved in appetite regulation and nutrient homeostasis,[90] and elevated visfatin levels were associated with loss of appetite and low fasting serum amino acids in dialysis patients.[33] The inconsistency in PEW is that plasma visfatin in normal individuals is related positively to fat mass. However, Hallschmid et al.[113] found that visfatin in human cerebrospinal fluid was negatively correlated with fat mass, suggesting that central nervous system visfatin insufficiency and/or resistance drives higher plasma levels.

Hormonal Disorders

Impairment of Insulin/IGF-1

As a direct consequence of the kidneys' role as modulator of endocrine function, kidney disease causes abnormalities in the excretion, synthesis, and action of many hormones. Resistance to insulin, growth hormone (GH), and IGF-1 are implicated in loss of muscle mass in adult CKD patients. Insulin or IGF-1 bind distinct cell surface receptors to activate similar downstream signaling pathways, which act to prevent loss of muscle protein.[114] When muscle is lost, large multinucleated myofibers decrease in size rather than decrease in number. Regenerative systems that involve the fusion of muscle cell precursor cells (i.e., satellite or stem cells) with myofibers are also inhibited. Although current evidence suggests that myofiber shrinkage due to accelerated protein degradation is the predominant mechanism for loss of muscle mass, myofiber shrinkage and satellite cell

fusion are regulated by insulin and IGFs. This has led to the hypothesis that the integrated outputs of these insulin/IGF-activated signaling pathways determine the balance between protein accretion and loss, determining overall changes in muscle mass.

The effect of low insulin on muscle is clear: Uncontrolled type 1 diabetes mellitus leads to negative nitrogen balance, lean tissue atrophy, and hyperaminoacidemia easily reversed through the provision of insulin.[115] The net protein anabolic effect of insulin involves a blunting of proteolysis rather than enhanced protein synthesis. Alterations in insulin function in uremia were reported as early as 1951,[116] and the alterations in glucose metabolism in the face of hyperinsulinemia and diminished tissue sensitivity to insulin are partially correctable by HD.[117,118] In insulin-deprived animals, muscle protein breakdown is significantly increased, a process that is mediated by the proteasome-ubiquitin pathway.[110,111] Enhanced protein catabolism applies to insulin-deficient and insulin-resistant states. HD patients with suboptimally controlled type 2 diabetes have a higher rate of muscle protein loss than HD patients without diabetes.[119] Altered insulin sensitivity is primarily due to a postreceptor defect altering primarily skeletal muscle, rather than hepatic glucose uptake. Furthermore, the extent of insulin resistance correlates with muscle protein breakdown in HD patients who are not diagnosed with diabetes mellitus.[120] Individual uremic toxins removed by dialysis (such as P-cresol, the byproduct of tyrosine metabolism) have been shown to induce insulin resistance.[121] Insulin resistance represents a major target for intervention in PEW. For example, treatment with an insulin sensitizer (PPARγ agonist, rosiglitazone) suppressed muscle proteolysis in insulin-resistant mice.[122] It is not surprising that the use of rosiglitazone treatment was associated with significantly lower all-cause mortality and higher *S*-albumin among insulin-free, but not insulin-requiring, diabetic HD patients.[123]

Uremia, inflammatory cytokines, acidosis, glucocorticoids, and angiotensin (ANG) II share a common mechanism of muscle wasting: impairment of insulin/IGF-1 actions by altering signaling through the phosphatidylinositol 3-kinase (PI3-kinase)/Akt pathway.[124,125] Although the precise signals causing insulin/IGF-1 resistance in CKD are unknown, several steps in PI3-kinase/Akt signaling contribute to the impairment, including activation of the FoxO family transcription factors that induce the expression of several atrophy-inducing genes involved in the ubiquitin-proteasome and autophagic proteolytic systems.[126] Dysfunctional PI3-kinase/Akt activity can also result in activation of caspase-3, an apoptotic protease that also degrades actin in actomyosin complexes.[127] A byproduct of this proteolytic reaction is a characteristic actin fragment that was shown to serve as a biomarker of muscle wasting in HD patients and others with conditions associated with muscle wasting.[76]

Testosterone Deficiency and Low Thyroid Hormone Levels

Prolactin retention in CKD impairs the production of gonadotropic hormones in men and women.[128] In men, this translates into a high prevalence of testosterone deficiency (hypogonadism).[129–132] Testosterone levels are also abnormally low among women. Testosterone is an anabolic hormone that induces skeletal muscle hypertrophy by promoting nitrogen retention, stimulating fractional muscle protein synthesis, inducing myoblast differentiation, and augmenting the efficiency of amino acid reuse by skeletal muscle. Testosterone suppresses myostatin expression, inhibits apoptosis, induces muscle IGF-I mRNA expression, and affects the differentiation of mesenchymal-derived pluripotent stem cells into myocytes.[133] In dialysis and predialysis patients, low testosterone levels were associated with increased mortality risk,[134–136] and the observation that adjustment for serum creatinine levels (a surrogate marker of muscle mass) abrogated this mortality prediction[134] may indirectly support this pathophysiological mechanism. In CKD stage 2-4, endogenous testosterone was an independent determinant of bioelectrical impedance analysis-estimated muscle mass and muscle strength (handgrip).[137] Randomized intervention studies with androgen therapy in CKD patients (alone or in combination with resistance training) have shown significant improvement of muscle mass and nutritional status.[138,139]

Available data cannot distinguish if low thyroid hormone levels in CKD patients with PEW are an adaptation that reduces energy expenditure and minimizes protein catabolism or a maladaptation participating in the wasting syndrome.[140] Low triiodothyronine levels in CKD stage 5 patients correlate with systemic inflammatory markers, endothelial dysfunction, and all-cause as well as cardiovascular mortality.[141–144] Correction of metabolic acidosis in dialysis patients improves these hormonal derangements.[145,146] The correlation of triiodothyronine with mortality prediction was abrogated after adjustment for C-reactive protein and albumin as surrogates of PEW.[147] Thus, even if low thyroid hormone participates in the PEW process and is not adaptive, then changes in thyroid hormones may act as an intermediate link among inflammation, acidosis, PEW, and mortality and not a primary cause.

Metabolic Acidosis and Glucocorticoids

Metabolic acidosis is a key mechanism in the starvation response, inducing release of branched-chain amino acids from muscle during ketosis. It also causes insulin resistance leading to loss of muscle mass. Acidosis does not alter insulin/IGF-1 receptor binding, but rather it inhibits intracellular signaling. In a rat model of CKD-induced acidosis, intracellular pH of myofibers was not changed,[148] but an acidic extracellular pH is sufficient to reduce postreceptor signaling through insulin/IGF-1 pathways in cultured muscle cells.[149] However, a decline in extracellular pH

by itself is not sufficient to induce muscle wasting in a rat CKD model.[73,114,122,148,150,151] Metabolic acidosis induces increased adrenal glucocorticoid production, and adrenalectomized rats have markedly reduced muscle wasting that is restored by replacement of glucocorticoids. Glucocorticoids induce insulin/IGF-1 resistance in skeletal muscle by altering the same signaling pathways that are affected by acidosis, but they act on slightly different signaling molecules within the pathway.[126] Notably, prevailing evidence from other comorbidities of CKD, including ANG II and inflammation, indicates that insulin/IGF-1 resistance and elevated glucocorticoids are the common physiological responses that are causative for the increase in protein and amino acid catabolism as well as the suppression of protein synthesis.[74,152,153] Understanding this coordinated response may provide additional clues in how insulin/IGF1 signaling controls muscle wasting.

Correction of acidosis has salutary effects on nutritional parameters. For example, sodium bicarbonate stimulates the growth of premature infants and that of children with renal tubular acidosis.[138,154] Likewise, treatment with sodium bicarbonate and potassium bicarbonate improves the nitrogen balance of elderly women with mild metabolic acidosis.[155,156] In normal adults, induction of metabolic acidosis not only decreases serum albumin concentration but also stimulates nitrogen losses due to accelerated degradation of protein and essential amino acids.[157,158] Similar adverse consequences occur in CKD patients who develop metabolic acidosis: Acidosis decreases serum levels of essential branched-chain amino acids in muscle although muscle protein degradation is accelerated. Both abnormalities correct when metabolic acidosis is treated.[159] Likewise, in patients being treated by HD or PD, treatment of metabolic acidosis reduced the excessive rate of protein degradation.[160,161] Long-term clinical trials show similar results in PD and CKD.[162,163] Thus, acidosis contributes to PEW, and correction of acidosis ameliorates it.

Comorbidities and Lifestyle

Comorbidities

Typical comorbidities associated with CKD or ESRD contribute to a catabolic milieu and the development of PEW. As Table 2 demonstrates, these factors share common etiologic mechanisms with PEW. Given its high prevalence in CKD patients, diabetes may be the most important single comorbidity. Pupim et al.[164] showed that diabetes mellitus is an important predictor of lean body mass loss in dialysis patients, and reduced insulin signaling by insulin absence or resistance results in increased muscle protein breakdown.[119] Diabetes also causes CVD and neuropathy that contribute to infection, muscle atrophy, and diabetic gastroparesis (with resultant food intake impairment). One out of three long-term diabetic dialysis patients no longer require hypoglycemic therapy. The poor outcomes in this subgroup with "burnt-out diabetes" may be the result of PEW.[165]

Another common comorbid state in CKD patients is CVD, in particular CHF.[166] Cardiac cachexia is in many ways indistinguishable from uremic PEW and shares important mechanisms. Inadequate cardiac output drives neurohumeral responses associated with PEW including glucocorticoids, increased ANG II, and sympathetic nerve activity. Right ventricular heart failure with passive

Table 2. Typical Comorbidities in CKD Patients that Contribute to PEW

Comorbitiy	Possible Effects Related to Etiology of PEW
Diabetes/metabolic syndrome	Gastroparesis, inflammation/oxidation, insulin deprivation (type I), insulin resistance, pain
CVD/heart failure	Cachexia, inflammation, glucocorticoid release, sympathetic nerve overactivity, increased circulating ANG II, insulin resistance, decreased activity, pain
Peripheral vascular disease	Reduced activity, ulcers, inflammation, pain
Fluid overload	Inflammatory cytokine release, gut edema, leg ulcers, decreased physical activity, pain
Hyperparathyrodism, CKD-MBD	Increased energy expenditure, glucose intolerance, hypovitaminosis D, muscle wasting, gastric ulcers, heart disease
Anemia	Frailty, decreased activity, iron-deficiency, high output heart failure
Autoimmune/rheumatologic disorders	Inflammation, intercurrent infections, joint involvement reduces activity, glucocorticoids, pain
Gastrointestinal disorders	Anorexia, swallowing disorders, nutrient malabsorption, acidosis (diarrhea, drains, and ostomies), inflammation, infections, pain
Chronic lung diseases	Increased work of breathing (raises REE), decreased activity, intercurrent infections, inflammation, glucocorticoids, fluid overload, ANG II
Liver disease	Hypoalbuminemia, volume overload, ANG II, infections, inflammation, acidosis (bowel therapies), anorexia, pain
Infections	Inflammation, reduced appetite, increased REE, pain
Pain	Anorexia, constipation (narcotics), inflammation
Psychiatric disorders/depression/dementia	Unwillingness to eat, anorexia, inability to obtain/prepare food, inflammation, decreased activity
Neurologic disorders	Reduced activity, anorexia, swallowing disorders, pain
Malignant diseases	Cancer cachexia, inflammation, increased REE, decreased activity, pain

congestion of the liver and gut wall edema can be associated with alterations in nutrient absorption, anorexia, and gut mucosal barrier function.[166,167]

CKD-metabolic bone disease (CKD-MBD) is a comorbid condition associated with PEW. PEW can contribute to CKD-MBD because loss of body weight, inflammation, and physical inactivity lead to bone loss. Certain conditions associated with CKD such as protein losses and anorexia can predispose these patients to hypovitaminosis D. What is more controversial is the extent to which CKD-MBD contributes to the etiology of PEW. Low circulating levels of vitamin D, a decrease in klotho, and a rise in fibroblast growth factor-23 can increase parathyroid hormone synthesis, thereby contributing to the development of secondary hyperparathyroidism.[168] Vitamin D and/or parathyroid hormone have long been considered contributors to PEW, and vitamin D appears to be involved in some key molecular pathways for PEW and muscle regulation.[169] Experimental animal models of kidney failure and humans show improvements in muscle size and strength, markers of muscle metabolism, and/or serum albumin with replacement of 1,25-dihydroxyvitamin D.[170,171] Finally, there is a positive association between 25-hydroxyvitamin D and testosterone levels, suggesting an additional mechanism in which vitamin D may regulate muscle mass.[172]

Symptoms of depression are more frequent with reduction in kidney function and relate to poor outcome and mortality.[173-175] Cytokines are thought to be important mediators of brain immune connection and may play an important role in the pathogenesis of depression because of their effect on neurotransmitters and neurohormones.[173,176] In dialysis patients, symptoms of depression are associated with increased IL-6 levels,[177,178] and 8 weeks of fluoxetine treatment resulted in decreased serum IL-1β levels.[179] Depression may also lead to fatigue[180] and unwillingness to eat,[23] contributing in a vicious circle to anorexia, physical inactivity, and overall PEW.

Poor Physical Activity, Frailty

Decreased physical activity likely plays a major role in the etiology of PEW and the associated cardiovascular mortality. This is in part because individuals with low physical activity have increased risk of CKD secondary to obesity, diabetes, hypertension, and heart disease, and common comorbidities in CKD patients, especially heart disease and aging, are partly associated with decreased ability to exercise. Furthermore, complications of CKD including anemia, volume overload, and muscle wasting limit exercise ability. Subjects with stages 3-5 CKD have lower median peak oxygen consumption, and in some individuals this limits exercise enough to prevent activities of daily living.[181] Muscle weakness is common in stage 5 CKD by measures including grip strength, rising from a chair, and maximum gait speed.[181] In the geriatric population, IL-6 level is associated with current physical performance and predicts a future decline in physical activity.[182] Lack of exercise can increase inflammatory markers, and this change, rather than the decreased muscle mass, may dominate the association with mortality.[183]

In CKD, just as in the diabetic patients, exercise-induced benefits in muscle are likely due to improvement in insulin/IGF-1 sensitivity of skeletal muscle.[184] Endurance exercise decreased the rate of protein degradation in the muscle of CKD rats,[185] and aerobic exercise reduced the amount of caspase-3-generated 14-kDa actin biomarker in muscle from HD patients.[185] Resistance exercise also has beneficial effects on muscle in CKD patients by increasing mitochondrial biogenesis.[186] Because these anabolic actions are attributed to insulin/IGF-1 signaling, it is possible that so called "exercise mimetics" (e.g., resveratrol) will prove equally effective at slowing muscle loss in CKD patients.[187] Regardless of mechanism, a Cochrane review of trials to improve physical activity in CKD concluded that the interventions improved markers of PEW and traditional cardiovascular risk factors.[188]

Dialysis Procedure

As discussed above, dialysis may contribute to PEW through infectious, inflammatory, and volume-related complications. Recent studies have improved our understanding of how dialysis treatment per se affects protein and energy homeostasis. Amino acid and protein losses during the dialysis session, together with low nutrient intake, promote low nutrient availability for muscle synthesis.[189-192] In a study comparing high (1.4 g/kg/day) and low (0.5 g/kg/day) protein diets, Borah et al.[193] found negative nitrogen balance on every day on the low-protein diet, but only on HD days with high protein intake. Several more recent studies show that the catabolic effects of HD, especially on the protein homeostasis, are profound, affecting whole-body and skeletal muscle protein homeostasis. All of these careful metabolic studies consistently show a decrease in protein synthesis at the whole-body level whereas one specific study showed an additional increase in whole-body protein breakdown.[194] Moreover, two separate studies showed a significant increase in net skeletal muscle protein breakdown; in one study, these undesirable effects persisted for at least 2 hours after the completion of HD.[58,195] Mechanistically, the net protein breakdown has been related to (1) an absolute decline in amino acid levels due to dialysis losses—a study in normal swine showed that a reduction in plasma amino acid concentrations similar to the extent seen during dialysis signals an inhibition of muscle protein synthesis and that corresponding changes in eIF2B activity suggest a possible role in mediating the response[196]; (2) imbalances in amino acid levels; and (3) activation of the inflammatory cascade.[58,197,198] Fortunately, in HD and PD patients, concurrent amino acid supplementation can prevent

or reverse these adverse effects,[199-201] providing an opportunity for treatment of PEW.

Inadequate dialysis is well known to cause PEW,[4,5] and it has been shown in PD patients that loss of residual kidney function contributes to PEW.[202] Loss of residual kidney function is independently associated with reduced dietary energy, protein,[203] and micronutrient intake.[204] It was also associated with increased inflammation[205] and increased resting energy metabolism.[53]

Conclusion

This ISRNM working group concludes that advances in understanding how inflammation, insulin resistance, oxidative stress, glucocorticoids, and acidosis modify the response to reduced protein and energy intake provide a strong model framework to understand the pathophysiology of PEW. PEW naturally develops with the progression of CKD and is an inherent component of advanced disease. Although dialysis reverses uremia, residual metabolic derangements, inflammation, comorbid conditions, and the dialysis procedure itself may allow PEW to develop or worsen. As new mediators are discovered, integration of those mediators into the model and refinement of hypotheses are needed. Regarding clinical outcomes, the ability to separate the effects of nutrition, aging, and comorbidities is critical for understanding etiology, and, perhaps more importantly, for the design of future therapeutic clinical trials including anti-inflammatory and anabolic treatment strategies.

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