HHS Public Access

Author manuscript

Curr Opin Clin Nutr Metab Care. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

Curr Opin Clin Nutr Metab Care. 2015 May ; 18(3): 254–262. doi:10.1097/MCO.0000000000000171.

Latest Consensus and Update on Protein Energy-Wasting in Chronic Kidney Disease

Yoshitsugu Obi[a,b], **Hemn Qader**[a,b], **Csaba P. Kovesdy**[c], and **Kamyar Kalantar-Zadeh**[a,b]

[a]Division of Nephrology and Hypertension, University of California Irvine, Orange, California, USA

[b]Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, Orange, California, USA

[c]University of Tennessee Health Science Center, Memphis, TN

Abstract

Purpose of review—Protein-energy wasting (PEW) is a state of metabolic and nutritional derangements in chronic disease states including chronic kidney disease (CKD). Cumulative evidence suggests that PEW, muscle wasting and cachexia are common and strongly associated with mortality in CKD, which is reviewed here.

Recent findings—The malnutrition-inflammation score (KALANTAR Score) is among the comprehensive and outcome-predicting nutritional scoring tools. The association of obesity with poor outcomes is attenuated across more advanced CKD stages and eventually reverses in form of obesity paradox. Frailty is closely associated with PEW, muscle wasting and cachexia. Muscle loss shows stronger associations with unfavorable outcomes than fat loss. Adequate energy supplementation combined with low-protein diet (LPD) for the management of CKD may prevent the development of PEW and can improve adherence to LPD, but dietary protein requirement may increase with aging and is higher under dialysis therapy. Phosphorous burden may lead to poor outcomes. The target serum bicarbonate concentration is normal range and ≥23 mEq/L for non-dialysis-dependent and dialysis-dependent CKD patients, respectively. A benefit of exercise is suggested but not yet conclusively proven.

Summary—Prevention and treatment of PEW should involve individualized and integrated approaches to modulate identified risk factors and contributing comorbidities.

Keywords

Chronic kidney disease; end-stage renal disease; protein-energy wasting; malnutrition; cachexia

Correspondence: Kamyar Kalantar-Zadeh, MD, MPH, PhD, Harold Simmons Center for Kidney Disease Research and Epidemiology, University of California Irvine, 101 The City Drive South, City Tower, Suite 400 – ZOT: 4088, Orange, CA 92868, USA, Tel: +1 310-222-2346; Fax: +1 310-222-3839; kkz@uci.edu.

Conflict of interest

KKZ has received honoraria from Abbott, Abbvie, Aveo and Fresenius. CPK has received honoraria from Sanofi-Aventis.

Introduction

The concept of protein energy wasting (PEW) was proposed in 2007 by the *International Society of Renal Nutrition and Metabolism* (ISRNM) as a state of nutritional and metabolic derangements in patients with chronic kidney disease (CKD) characterized by simultaneous loss of systematic body protein and energy stores, leading ultimately to loss of muscle and fat mass and cachexia [1]. Suggested diagnostic criteria are listed in Table 1. The PEW is caused by hypercatabolic status, uremic toxins, mulnutrition, and inflammation, and exceptionally common and closely associated with mortality and morbidity in patients with CKD, particularly in those with CKD stage G3b, G4 and G5 (eGFR<45 ml/min/1.73 m^2 BSA) and end-stage renal disease (ESRD) requiring maintenance dialysis treatment (Figure 1). The concept of PEW should be discriminated from malnutrition because CKD-related factors may contribute to the development of PEW, which are in addition to or independent from inadequate nutrient intake due to anorexia and/or dietary restrictions. (Table 2 and Figure 2) [2*,3*]. Pathophysiological mechanisms involved in PEW have been reviewed elsewhere [3*,4*].

Multiple treatment strategies against those etiologies may be required to prevent or reverse PEW [5*]. Individualized, continuous nutritional counseling, optimizing the dialysis regimen, preventing or correcting muscle wasting, and management of comorbidities (e.g. metabolic acidosis, diabetes, infection, congestive heart failure, and depression) are the most essential preventive measures. Oral or parenteral nutrition supplements along with appetite stimulators and muscle enhancing agents should be prescribed if the patients are unable to sustain protein and energy stores despite those efforts.

In the current review, we present a summary of recent advances in understanding and management of PEW from related clinical aspects: its consequences, assessment tools, the obesity paradox, frailty, muscle wasting, and potential therapeutic interventions.

PEW and clinical outcomes in CKD

Among ESRD patients who undergo maintenance hemodialysis treatment, there is a significant longitudinal decline in anthropometric nutritional parameters such as weight, muscle mass, and fat mass;[6] while inflammatory markers including C-reactive protein and pro-inflammatory cytokines such as interleukin-6 (IL-6) increase over time [7]. The decline in serum albumin concentration, the strongest mortality predictor, is affected by both nutritional derangements and heightened inflammatory status [8], and progresses with time on dialysis, known as dialysis vintage [7]. These changes associated with PEW are significant risk factors for weakness [9], poor responsiveness to erythropoiesis-stimulating agents, low quality of life, hospitalization, and mortality [6,7,10]. Therefore, serial assessment of nutritional status for detection and management of PEW is encouraged using scoring tools, including the subjective global assessment (SGA), the malnutrition inflammation score (MIS), and PEW definition criteria [11]. Among them, the MIS, also known as the Kalantar Score [12,13], may have better association with hospitalization and mortality as well as nutritional and inflammatory parameters in ESRD patients.

Recently, the geriatric nutritional risk index (GNRI), originally developed as a modified nutritional risk index for the elderly, has attracted attention for assessment of PEW. While SGA and MIS require multiple components including subjective assessments, GNRI is a simple objective nutritional tool which requires only 2 components (serum albumin concentration and actual-to-ideal weight ratio), and it has been validated as an effective tool in Asian prevalent ESRD patients [11,14–16]. Beberashvili et al. compared MIS and GNRI in prevalent hemodialysis patients and found that MIS had lower inter-observer agreement than GNRI [17*]. Longitudinal changes in both scores correlated well with several body composition parameters and serum concentrations of transferrin, creatinine, cholesterol, and IL-6. Nevertheless, changes in daily energy and protein intakes were associated with MIS but not with GNRI. Furthermore, only MIS was a significant risk factor of death in this study. Thus, MIS may be a more comprehensive tool than GNRI.

Obesity paradox in chronic kidney disease

Contrary to those in the general population, many studies in ESRD patients have consistently reported an “obesity paradox” or “reverse epidemiology” where higher body mass index (BMI) is paradoxically associated with better survival. In addition to obesity itself, gaining solid (edema free) weight is also associated with better survival in hemodialysis patients irrespective of age, gender, diabetes, and the severity of obesity [18]. This phenomenon known as obesity paradox or “reverse epidemiology” – to encompass other cardiovascular paradoxes in CKD such as lipid paradox [19] – is at least partly explained by PEW; hence, the obesity paradox has important clinical implications in the weight-management approach tailored to patients with CKD [20] and in particular in transplant wait-listed dialysis patients [21]. The results of recent observational studies have several implications for this concept.

In a cohort of prevalent hemodialysis patients treated in the Unites States, the benefit of high BMI on survival was more pronounced in incident hemodialysis patients and in relatively younger hemodialysis patients (aged <65 years) [22]. This result is apparently inconsistent with the previous report from Netherland (NECOSAD-2) where there was a U-shaped association between BMI and mortality in incident hemodialysis patients aged <65 years but no association in those aged ≥65 years [23]. The differences between these 2 studies may be due to a longer follow-up period in the latter study (7 years versus 3 years). Given a high short-term mortality in incident hemodialysis patients, obesity – or high BMI to be more accurate – may be associated with better survival due to better nutritional status or larger muscle mass particularly in a short period while it may exert deleterious effects over longer follow-up. The NECOSAD-2 cohort also included a significant number of peritoneal dialysis patients (50% and 22% in those aged <65 and ≥65 years, respectively). Published results have shown that the obesity paradox is less consistent in this population than in hemodialysis populations [20].

Additionally, using a nationwide cohort of US veterans with stage G3-5 CKD, Lu et al. have shown how the association of BMI with mortality and renal outcomes changes according to kidney function [24*]. Similar to the general population, BMI showed a U-shaped association with both of these outcomes in earlier stage of CKD, with the best outcomes

observed in overweight and mildly obese patients. However, while lower BMI was consistently associated with worse outcomes, the associations of high BMI with both outcomes were substantially attenuated and lost significance in advanced CKD (estimated GFR <30 ml/min per 1.73 m^2 BSA). A previous study also showed that the mortality risk of high BMI was diminished even in patients with preserved kidney function if they had positive proteinuria [25].

Frailty and muscle wasting in chronic kidney disease

Frailty is common, closely related with PEW and muscle wasting, and associated with morbidities and mortality in patients with CKD, especially those requiring maintenance dialysis therapy (see Table 3 for the suggested criteria for frailty) [9,26–30]. Among incident hemodialysis patients in the U.S., the prevalence of frailty was reported to be as high as 30% [31*]. Furthermore, muscle loss and frailty, as with PEW, may develop and progress during the course of CKD. The Chronic Renal Insufficiency Cohort (CRIC) study revealed that the prevalence of frailty and pre-frailty in stage G2–4 CKD was 7% and 43%, respectively, and that lower kidney function was associated with frailty [32]. Another study showed that muscle mass, evaluated by multi-slice CT, longitudinally declined with time especially in nondialysis-dependent patients and incident hemodialysis patients [33].

Given the high prevalence and progressive course of frailty in CKD, investigating the relationship between body composition and clinical outcomes is needed for further understanding of the obesity paradox in CKD. Dual-energy X-ray absorptiometry (DEXA) and MRI are the current gold standard methods for assessing lean body mass and muscle mass, respectively. However, those tools are not commonly used in routine clinical practice because of low accessibility and high cost.

Traditionally, 24-hour urine creatinine excretion is considered a reliable index of muscle mass in non-dialysis dependent patients. A Canadian cohort study including 525 patients with stage G3–5 CKD also showed that 24-hour urinary creatinine excretion declined at a rate of 16 mg/year, and that faster decline in urine creatinine, suggesting more rapidly progressive muscle wasting, was associated with death and initiating dialysis independent of BMI and estimated GFR [34*]. In hemodialysis population, serum creatinine concentration is suggested as a reliable biomarker of muscle mass if appropriate adjustments are done for residual kidney function and dietary meat intake as well as delivered dialysis dose [35,36]. Using 2 nationally representative cohorts of Korean hemodialysis patients and matched US Caucasian and African American hemodialysis patients, Park et al. found a significant association of higher serum creatinine concentrations and BMI with better survival in all three races [37]. Kalantar-Zadeh et al. also examined changes in dry weight and changes in serum creatinine concentration in prevalent hemodialysis patients in the U.S., and reported that a decline in serum creatinine appeared to be a stronger predictor of mortality than weight loss [38,39]. Furthermore, patients whose weight declined but whose serum creatinine concentrations increased had lower mortality than those whose weight increased but whose serum creatinine concentrations declined (Figure 3), suggesting the obesity paradox in hemodialysis patients might be at least partly explained by the impact of muscle mass.

Recently, bioelectrical impedance spectroscopy (BIS) has attracted attention as a novel tool for evaluating body composition such as muscle, fat, and extracellular fluid. Indeed, BIS-guided fluid management in hemodialysis patients improves fluid overload and survival [40]. The above-mentioned study of prevalent hemodialysis patients in the U.S. also evaluated the association between frailty and body composition using BIS, and reported that higher BIS-derived estimates of intracellular water (an index for muscle mass) were associated with lower odds of frailty while higher fat mass and higher estimates of extracellular water were associated with higher odds of frailty [31*]. Additionally, adding BIS data improved the predictability of frailty while adding BMI data did not.

The role of body fat on the clinical outcomes in CKD has been discussed elsewhere [20].

Dietary interventions

Dietary protein and energy intakes of 0.6–0.8 g/kg/day and 30–35 kcal/kg/day has been recommended for patients with stage G3b-5 CKD (estimated GFR <45 ml/min/1,73m^2 BSA) because low protein diet (LPD) has been suggested to slow the progression of advanced CKD to ESRD and because it may mitigate uremia [2*,5*]. However, it is difficult to implement proper protein restriction for patients with CKD, and inadequate energy intake is considered a common reason for why protein restriction fails and potentially leads to PEW [2*]. Partly because of this concern, LPD has not been widely used in clinical settings in the United States, Europe and some other industrialized nations. To address this issue, Wu et al. conducted an open-label randomized controlled study of energy supplement in patients with stage G3-4 CKD on LPD [41*]. A supplement packet contained 40 g of maltodextrin and 5 g of oil creamer at breakfast significantly decreased protein intake estimated by 24-hour urinary urea excretion was significantly lower in the intervention group (0.87±0.27 g/kg/day versus 1.00±0.29 g/kg/day), resulting in lower urinary protein and higher estimated GFR. These results indicate that besides preventing the development of PEW, energy supplementation may also improve adherence to LPD.

Another study that combined epidemiologic and experimental studies revealed that the effect of protein intake on health may vary according to age [42**]. In this analysis of the National Health and Nutrition Examination Survey (NHANES) III, participants aged 50–65 years who had reported high protein intake exhibited a higher risk of all-cause death and cancer death, while high protein intake was associated with lower all-cause and cancer mortality in those aged ≥65 years. Mouse model studies also convincingly supported these results. Given that the elderly comprise a significant proportion of CKD, these findings suggest that nephrologists and dietitians might need to take patients' age into consideration when deciding the extent to which dietary protein should be restricted because the elderly CKD patients are generally frail and at high risk of death rather than reaching ESRD.

Contrary to nondialysis-dependent patients with CKD, much higher protein intake (>1.2 g/kg/day, i.e, 2-times higher than in non-dialysis CKD patients) is recommended for ESRD patients on dialysis for the following reasons: (1) there is no need to protect kidney function after initiation of dialysis, (2) dialysis ameliorates metabolic acidosis caused by protein intake, and (3) the dialysis procedure further stimulates protein catabolism [5*]. Indeed, low

protein intake, expressed as low normalized protein catabolic rate or low protein nitrogen appearance, is associated with high mortality in this population, and protein intake does not reach the recommended level in many patients [43,44]. Oral or parenteral nutritional supplementation should be prescribed when dialysis patients exhibit sign of malnutrition despite standard preventive measures. Several studies have demonstrated that these interventions improve nutritional parameters such as lean body mass or serum albumin concentration [5,45], and recent observational studies suggested that oral nutritional supplement use could decrease hospitalization rates [46] and mortality [47].

Phosphorus management

Phosphorus is considered a uremic toxin. Indeed, hyperphosphatemia is an established risk factor for cardiovascular disease and death in patients with CKD [48], and phosphorus binders, especially those do not contain calcium, mitigate vascular calcification and thus decrease the rate of cardiovascular disease and death [49]. Interestingly, although the amount of dietary protein is generally correlated with dietary phosphorus content and associated with serum phosphorus concentration in ESRD patients [50], high serum phosphorus concentrations are consistently associated with high mortality among hemodialysis patients [51], in contrast to the above-mentioned association of protein intake with death.

This discrepancy could be explained by the link between phosphorus and PEW. Using adenine-induced CKD rats, Yamada et al. showed that dietary phosphorus induces systemic inflammation and oxidative stress dose-dependently without affecting kidney function, resulting in the development of the phenotypes of PEW including weight loss, hypoalbuminemia, and decreased urinary creatinine excretion [52**]. Moreover, high phosphorus diet caused vascular calcification and premature death. Administration of lanthanum carbonate, a non-calcium containing phosphorus binder, ameliorated almost all these pathological changes. Thus, this study reinforced the importance of phosphorus management in CKD highlighting the novel association between hyperphosphatemia and PEW. However, until similar data become available in humans, neither phosphorous binders nor dietary restriction should be advocated as a means to prevent or treat PEW. Indeed, phosphorous restriction is potentially harmful in ESRD patients on dialysis because it often accompanies a reduction in protein intake, resulting in adverse outcomes caused by the development of PEW [5*].

Alkali therapy for metabolic acidosis

Metabolic acidosis is a common complication in advanced CKD, and it induces muscle wasting by stimulating adrenal glucocorticoid secretion [3*]. There is strong evidence that correcting metabolic acidosis has beneficial effects on nutritional parameters in patients with CKD [5*,53], and it also prevents the progression of CKD itself [54,55]. It should be noted that excessive alkalization may also be harmful in nondialysis-dependent patients in terms of the progression of CKD and the risk of death [56,57], and oral bicarbonate supplementation is suggested to maintain serum bicarbonate within the normal range [58]. Meanwhile, low serum bicarbonate concentrations were associated with all-cause mortality in the range of

<22 mEq/L, but not ≥23 mEq/L in ESRD patients requiring dialysis [59]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) also revealed that high dialysate concentration appeared associated with all-cause mortality, especially in patients with low serum bicarbonate concentrations [60*], although these data may reflect confounding by indication as acidemic patients with higher death risk may be prescribed higher dialysate bicarbonate levels [53].

Exercise

Dialysis patients have often extremely low physical activity, and resultant muscle disuse is an underrepresented risk factor for muscle wasting [61,62]. This is important in that exercise interventions could prevent or even reverse muscle wasting. Indeed, a recent systematic review confirmed that progressive resistance training induces skeletal muscle hypertrophy, increases muscular strength, and improves health-related quality of life both in patients with CKD [63]. Another randomized trial found that the anabolic and strength response are similar between healthy participants and hemodialysis patients [64]. Although its long-term effect on clinically relevant outcomes is yet to be determined, resistance exercise training is safe, effective, and costless, and should be encouraged as a potential countermeasure for PEW. In advanced CKD, additional bicarbonate supplementation might contribute to enhance the anabolic effects of progressive resistance training by mitigating exercise-induced lactic acidosis [65].

CONCLUSIONS

There are essential and important differences between the general population and patients with CKD in terms of nutrition and diet. Therefore, prevention and treatment of PEW should involve individualized and integrated approaches specific to this population. Nevertheless, there are only a few treatment options with proven efficacy in terms of quality of life, morbidity, and mortality. Proposed therapeutic interventions need to be evaluated in randomized controlled trials to test whether clinically relevant outcomes could be improved. The results from observational studies should be used when it is unethical to conduct a clinical trial (e.g. standard oral nutritional supplement for patients with established PEW).

Acknowledgments

Financial support and sponsorship

KKZ is supported by the National Institute on Aging of the National Institutes of Health grant R21-AG047036 and the National Institute of Diabetes, Digestive and Kidney Disease grants R01-DK078106, R01-DK096920, U01-DK102163, and K24-DK091419 as well as philanthropist grants from Mr. Harold Simmons and Mr. Louis Chang. CPK is supported by the National Institute of Diabetes, Digestive and Kidney Disease grants R01-DK096920 and U01-DK102163.

References

1. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kaysen G, Lindholm B, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008; 73(4):391–398. [PubMed: 18094682]

2*. Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: Reconciling low protein intake with nutritional therapy. Am J Clin Nutr. 2013; 97(6):1163–1177. Excellent review focusing on PEW in non-dialysis dependent patients with CKD. [PubMed: 23636234]

3*. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, Mitch WE, Price SR, Wanner C, Wang AY, ter Wee P, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: A consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013; 23(2):77–90. A consensus statement for the etiology of PEW in CKD from the ISRNM. [PubMed: 23428357]

4*. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. Nature reviews Nephrology. 2014; 10(9):504–516. Excellent review for the mechanisms of muscle wasting in CKD. [PubMed: 24981816]

5*. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, Kuhlmann MK, Stenvinkel P, TerWee P, Teta D, Wang AY, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: A consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013; 84(6):1096–1107. A consensus statement for the prevention and treatment of PEW in CKD from the ISRNM. [PubMed: 23698226]

6. Su CT, Yabes J, Pike F, Weiner DE, Beddhu S, Burrowes JD, Rocco MV, Unruh ML. Changes in anthropometry and mortality in maintenance hemodialysis patients in the HEMO study. Am J Kidney Dis. 2013; 62(6):1141–1150. [PubMed: 23859719]

7. den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Penne EL, Mazairac AH, Levesque R, Blankestijn PJ, Nube MJ, ter Wee PM, van den Dorpel MA. Clinical predictors of decline in nutritional parameters over time in ESRD. Clin J Am Soc Nephrol. 2014; 9(2):318–325. [PubMed: 24458074]

8. Kim Y, Molnar MZ, Rattanasompattikul M, Hatamizadeh P, Benner D, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis. Int Urol Nephrol. 2013; 45(1):215–227. [PubMed: 22528583]

9. Amparo FC, Cordeiro AC, Carrero JJ, Cuppari L, Lindholm B, Amodeo C, Kamimura MA. Malnutrition-inflammation score is associated with handgrip strength in nondialysis-dependent chronic kidney disease patients. J Ren Nutr. 2013; 23(4):283–287. [PubMed: 23046737]

10. Rattanasompattikul M, Molnar MZ, Zaritsky JJ, Hatamizadeh P, Jing J, Norris KC, Kovesdy CP, Kalantar-Zadeh K. Association of malnutrition-inflammation complex and responsiveness to erythropoiesis-stimulating agents in long-term hemodialysis patients. Nephrol Dial Transplant. 2013; 28(7):1936–1945. [PubMed: 23045431]

11. Riella MC. Nutritional evaluation of patients receiving dialysis for the management of protein-energy wasting: What is old and what is new? J Ren Nutr. 2013; 23(3):195–198. [PubMed: 23611546]

12. Ujszaszi A, Czira ME, Fornadi K, Novak M, Mucsi I, Molnar MZ. Quality of life and protein-energy wasting in kidney transplant recipients. Int Urol Nephrol. 2012; 44(4):1257–1268. [PubMed: 22246594]

13. Czira ME, Lindner AV, Szeifert L, Molnar MZ, Fornadi K, Kelemen A, Laszlo G, Mucsi I, Keszei AP, Kennedy SH, Novak M. Association between the malnutrition-inflammation score and depressive symptoms in kidney transplanted patients. Gen Hosp Psychiatry. 2011; 33(2):157–165. [PubMed: 21596209]

14. Kang SH, Cho KH, Park JW, Yoon KW, Do JY. Geriatric nutritional risk index as a prognostic factor in peritoneal dialysis patients. Perit Dial Int. 2013; 33(4):405–410. [PubMed: 23378470]

15. Jung YS, You G, Shin HS, Rim H. Relationship between geriatric nutritional risk index and total lymphocyte count and mortality of hemodialysis patients. Hemodial Int. 2014; 18(1):104–112. [PubMed: 23941605]

16. Tsai MT, Hu FH, Lien TJ, Chen PJ, Huang TP, Tarng DC. Interaction between geriatric nutritional risk index and decoy receptor 3 predicts mortality in chronic hemodialysis patients. Am J Nephrol. 2014; 40(3):191–199. [PubMed: 25323840]

17*. Beberashvili I, Azar A, Sinuani I, Kadoshi H, Shapiro G, Feldman L, Averbukh Z, Weissgarten J. Comparison analysis of nutritional scores for serial monitoring of nutritional status in

hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8(3):443–451. This is the first study to compare MIS with GNRI by assessing nutritional parameters and clinical outcomes longitudinally. MIS appeared superior to GNRI in this study. [PubMed: 23411424]

18. Cabezas-Rodriguez I, Carrero JJ, Zoccali C, Qureshi AR, Ketteler M, Floege J, London G, Locatelli F, Gorriz JL, Rutkowski B, Memmos D, et al. Influence of body mass index on the association of weight changes with mortality in hemodialysis patients. Clin J Am Soc Nephrol. 2013; 8(10):1725–1733. [PubMed: 24009217]
19. Moradi H, Streja E, Kashyap ML, Vaziri ND, Fonarow GC, Kalantar-Zadeh K. Elevated high-density lipoprotein cholesterol and cardiovascular mortality in maintenance hemodialysis patients. Nephrol Dial Transplant. 2014; 29(8):1554–1562. [PubMed: 24574544]
20. Park J, Ahmadi SF, Streja E, Molnar MZ, Flegal KM, Gillen D, Kovesdy CP, Kalantar-Zadeh K. Obesity paradox in end-stage kidney disease patients. Prog Cardiovasc Dis. 2014; 56(4):415–425. [PubMed: 24438733]
21. Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, Krishnan M, Nissenson AR, Danovitch GM, Kalantar-Zadeh K. Associations of body mass index and weight loss with mortality in transplant-waitlisted maintenance hemodialysis patients. Am J Transplant. 2011; 11(4):725–736. [PubMed: 21446975]
22. Vashistha T, Mehrotra R, Park J, Streja E, Dukkipati R, Nissenson AR, Ma JZ, Kovesdy CP, Kalantar-Zadeh K. Effect of age and dialysis vintage on obesity paradox in long-term hemodialysis patients. Am J Kidney Dis. 2014; 63(4):612–622. [PubMed: 24120224]
23. Hoogeveen EK, Halbesma N, Rothman KJ, Stijnen T, van Dijk S, Dekker FW, Boeschoten EW, de Mutsert R. Obesity and mortality risk among younger dialysis patients. Clin J Am Soc Nephrol. 2012; 7(2):280–288. [PubMed: 22223612]

24*. Lu JL, Kalantar-Zadeh K, Ma JZ, Quarles LD, Kovesdy CP. Association of body mass index with outcomes in patients with CKD. J Am Soc Nephrol. 2014; 25(9):2088–2096. This is a clinically relevant study to demonstrate how the associations between BMI and clinical outcomes change according to kidney function in stage G3–5 CKD. [PubMed: 24652789]

25. Obermayr RP, Temml C, Gutjahr G, Kainz A, Klauser-Braun R, Fugger R, Oberbauer R. Body mass index modifies the risk of cardiovascular death in proteinuric chronic kidney disease. Nephrol Dial Transplant. 2009; 24(8):2421–2428. [PubMed: 19244226]
26. Walker SR, Gill K, Macdonald K, Komenda P, Rigatto C, Sood MM, Bohm CJ, Storsley LJ, Tangri N. Association of frailty and physical function in patients with non-dialysis CKD: A systematic review. BMC Nephrol. 2013; 14(228)
27. Kim JC, Kalantar-Zadeh K, Kopple JD. Frailty and protein-energy wasting in elderly patients with end stage kidney disease. J Am Soc Nephrol. 2013; 24(3):337–351. [PubMed: 23264684]
28. McAdams-DeMarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, Walston JD, Segev DL. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. J Am Geriatr Soc. 2013; 61(6):896–901. [PubMed: 23711111]
29. Bao Y, Dalrymple L, Chertow GM, Kaysen GA, Johansen KL. Frailty, dialysis initiation, and mortality in end-stage renal disease. Arch Intern Med. 2012; 172(14):1071–1077. [PubMed: 22733312]
30. Matsuzawa R, Matsunaga A, Wang G, Yamamoto S, Kutsuna T, Ishii A, Abe Y, Yoneki K, Yoshida A, Takahira N. Relationship between lower extremity muscle strength and all-cause mortality in Japanese patients undergoing dialysis. Phys Ther. 2014; 94(7):947–956. [PubMed: 24578522]

31*. Johansen KL, Dalrymple LS, Delgado C, Kaysen GA, Kornak J, Grimes B, Chertow GM. Association between body composition and frailty among prevalent hemodialysis patients: A US Renal Data System Special Study. J Am Soc Nephrol. 2014; 25(2):381–389. This is the first study to demonstrate body composition evaluated by bioelectrical impedance spectroscopy but not BMI is associated with definite frailty in hemodialysis patients, suggesting the potential utility of this method. [PubMed: 24158987]

32. Reese PP, Cappola AR, Shults J, Townsend RR, Gadegbeku CA, Anderson C, Baker JF, Carlow D, Sulik MJ, Lo JC, Go AS, et al. Physical performance and frailty in chronic kidney disease. Am J Nephrol. 2013; 38(4):307–315. [PubMed: 24107579]

33. John SG, Sigrist MK, Taal MW, McIntyre CW. Natural history of skeletal muscle mass changes in chronic kidney disease stage 4 and 5 patients: An observational study. PLoS ONE. 2013; 8(5):e65372. [PubMed: 23741490]

34*. Di Micco L, Quinn RR, Ronksley PE, Bellizzi V, Lewin AM, Cianciaruso B, Ravani P. Urine creatinine excretion and clinical outcomes in CKD. Clin J Am Soc Nephrol. 2013; 8(11):1877–1883. This study is the first to report long-term data on the rate of decline of urinary creatinine excretion in patients with stage G3–5 CKD and its association with adverse clinical outcomes. [PubMed: 24158796]

35. Patel SS, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D, Heymsfield S, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. Serum creatinine as a marker of muscle mass in chronic kidney disease: Results of a cross-sectional study and review of literature. Journal of Cachexia, Sarcopenia and Muscle. 2013; 4(1):19–29.

36. Canaud B, Granger Vallee A, Molinari N, Chenine L, Leray-Moragues H, Rodriguez A, Chalabi L, Morena M, Cristol JP. Creatinine index as a surrogate of lean body mass derived from urea kt/v, pre-dialysis serum levels and anthropometric characteristics of haemodialysis patients. PLoS ONE. 2014; 9(3):e93286. [PubMed: 24671212]

37*. Park J, Jin DC, Molnar MZ, Dukkipati R, Kim YL, Jing J, Levin NW, Nissenson AR, Lee JS, Kalantar-Zadeh K. Mortality predictability of body size and muscle mass surrogates in Asian vs White and African American hemodialysis patients. Mayo Clin Proc. 2013; 88(5):479–486. This study clearly demonstrated that the associations of high BMI and high creatinine with low mortality appear similar among Caucasian, African American, and Asian. [PubMed: 23562348]

38. Kalantar-Zadeh K, Streja E, Kovesdy CP, Oreopoulos A, Noori N, Jing J, Nissenson AR, Krishnan M, Kopple JD, Mehrotra R, Anker SD. The obesity paradox and mortality associated with surrogates of body size and muscle mass in patients receiving hemodialysis. Mayo Clin Proc. 2010; 85(11):991–1001. [PubMed: 21037042]

39. Kalantar-Zadeh K, Streja E, Molnar MZ, Lukowsky LR, Krishnan M, Kovesdy CP, Greenland S. Mortality prediction by surrogates of body composition: An examination of the obesity paradox in hemodialysis patients using composite ranking score analysis. Am J Epidemiol. 2012; 175(8):793–803. [PubMed: 22427612]

40. Onofriescu M, Hogas S, Voroneanu L, Apetrii M, Nistor I, Kanbay M, Covic AC. Bioimpedance-guided fluid management in maintenance hemodialysis: A pilot randomized controlled trial. Am J Kidney Dis. 2014; 64(1):111–118. [PubMed: 24583055]

41*. Wu HL, Sung JM, Kao MD, Wang MC, Tseng CC, Chen ST. Nonprotein calorie supplement improves adherence to low-protein diet and exerts beneficial responses on renal function in chronic kidney disease. J Ren Nutr. 2013; 23(4):271–276. This is the first clinical trial to demonstrate the efficacy of energy supplement on low protein diet for non-dialysis dependent patients with CKD. [PubMed: 23131574]

42**. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng CW, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J, Passarino G, et al. Low protein intake is associated with a major reduction in IGF-1, cancer, and overall mortality in the 65 and younger but not older population. Cell Metab. 2014; 19(3):407–417. This is an excellent study to demonstrate that the effect of protein intake on health is modified by age. Based on the hypotheses found in the NHANES III cohort, the authors provided the mechanisms by which high protein intake increases cancer mortality in the middle-aged while low protein increases all-cause mortality in the elderly. [PubMed: 24606898]

43. Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K. Nutritional predictors of early mortality in incident hemodialysis patients. Int Urol Nephrol. 2014; 46(1):129–140. [PubMed: 23703546]

44. Ravel VA, Molnar MZ, Streja E, Kim JC, Victoroff A, Jing J, Benner D, Norris KC, Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Low protein nitrogen appearance as a surrogate of low dietary protein intake is associated with higher all-cause mortality in maintenance hemodialysis patients. J Nutr. 2013; 143(7):1084–1092. [PubMed: 23700345]

45. Rattanasompattikul M, Molnar MZ, Lee ML, Dukkipati R, Bross R, Jing J, Kim Y, Voss AC, Benner D, Feroze U, Macdougall IC, et al. Anti-inflammatory and anti-oxidative nutrition in hypoalbuminemic dialysis patients (aionid) study: Results of the pilot-feasibility, double-blind,

randomized, placebo-controlled trial. Journal of Cachexia, Sarcopenia and Muscle. 2013; 4(4): 247–257.

46. Cheu C, Pearson J, Dahlerus C, Lantz B, Chowdhury T, Sauer PF, Farrell RE, Port FK, Ramirez SP. Association between oral nutritional supplementation and clinical outcomes among patients with ESRD. Clin J Am Soc Nephrol. 2013; 8(1):100–107. [PubMed: 23085729]
47. Lacson E Jr, Wang W, Zebrowski B, Wingard R, Hakim RM. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing maintenance hemodialysis: A quality improvement report. Am J Kidney Dis. 2012; 60(4):591–600. [PubMed: 22632807]
48. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, Strippoli GF. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: A systematic review and meta-analysis. JAMA. 2011; 305(11):1119–1127. [PubMed: 21406649]
49. Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, Dorgan M, Lok CE, Fitchett D, Tsuyuki RT. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: An updated systematic review and meta-analysis. Lancet. 2013; 382(9900):1268–1277. [PubMed: 23870817]
50. Streja E, Lau WL, Goldstein L, Sim JJ, Molnar MZ, Nissenson AR, Kovesdy CP, Kalantar-Zadeh K. Hyperphosphatemia is a combined function of high serum PTH and high dietary protein intake in dialysis patients. Kidney international supplements. 2013; 3(5):462–468. [PubMed: 25019031]
51. Lertdumrongluk P, Rhee CM, Park J, Lau WL, Moradi H, Jing J, Molnar MZ, Brunelli SM, Nissenson AR, Kovesdy CP, Kalantar-Zadeh K. Association of serum phosphorus concentration with mortality in elderly and nonelderly hemodialysis patients. J Ren Nutr. 2013; 23(6):411–421. [PubMed: 23631888]
52**. Yamada S, Tokumoto M, Tatsumoto N, Taniguchi M, Noguchi H, Nakano T, Masutani K, Ooboshi H, Tsuruya K, Kitazono T. Phosphate overload directly induces systemic inflammation and malnutrition as well as vascular calcification in uremia. Am J Physiol Renal Physiol. 2014; 306(12):F1418–1428. This is an interesting experimental study to demonstrate that dietary phosphate loading dose-dependently induces systemic inflammation and malnutrition as well as vascular calcification and premature death without affecting kidney function in a rodent CKD model. [PubMed: 24808541]
53. Chen JL, Kalantar-Zadeh K. Is an increased serum bicarbonate concentration during hemodialysis associated with an increased risk of death? Semin Dial. 2014; 27(3):259–262. [PubMed: 24621002]
54. Loniewski I, Wesson DE. Bicarbonate therapy for prevention of chronic kidney disease progression. Kidney Int. 2014; 85(3):529–535. [PubMed: 24107852]
55. Kovesdy CP. Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD? Nephrol Dial Transplant. 2012; 27(8):3056–62. [PubMed: 22851628]
56. Dobre M, Yang W, Chen J, Drawz P, Hamm LL, Horwitz E, Hostetter T, Jaar B, Lora CM, Nessel L, Ojo A, et al. Association of serum bicarbonate with risk of renal and cardiovascular outcomes in CKD: A report from the chronic renal insufficiency cohort (CRIC) study. Am J Kidney Dis. 2013; 62(4):670–678. [PubMed: 23489677]
57. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Association of serum bicarbonate levels with mortality in patients with non-dialysis-dependent CKD. Nephrol Dial Transplant. 2009; 24(4): 1232–7. [PubMed: 19015169]
58. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter Suppl. 2013; 3(1):1–150.
59. Vashistha T, Kalantar-Zadeh K, Molnar MZ, Torlen K, Mehrotra R. Dialysis modality and correction of uremic metabolic acidosis: Relationship with all-cause and cause-specific mortality. Clin J Am Soc Nephrol. 2013; 8(2):254–264. [PubMed: 23184567]
60*. Tentori F, Karaboyas A, Robinson BM, Morgenstern H, Zhang J, Sen A, Ikizler TA, Rayner H, Fissell RB, Vanholder R, Tomo T, et al. Association of dialysate bicarbonate concentration with mortality in the dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis. 2013; 62(4):738–746. This is the first study to demonstrate higher mortality in HD patients treated with higher dialysate bicarbonate concentrations. [PubMed: 23707043]

61. Kim JC, Shapiro BB, Zhang M, Li Y, Porszasz J, Bross R, Feroze U, Upreti R, Kalantar-Zadeh K, Kopple JD. Daily physical activity and physical function in adult maintenance hemodialysis patients. Journal of Cachexia, Sarcopenia and Muscle. 2014; 5(3):209–220.

62. Rhee CM, Kalantar-Zadeh K. Resistance exercise: An effective strategy to reverse muscle wasting in hemodialysis patients? Journal of Cachexia, Sarcopenia and Muscle. 2014; 5(3):177–180.

63. Cheema BS, Chan D, Fahey P, Atlantis E. Effect of progressive resistance training on measures of skeletal muscle hypertrophy, muscular strength and health-related quality of life in patients with chronic kidney disease: A systematic review and meta-analysis. Sports Med. 2014; 44(8):1125–1138. [PubMed: 24696049]

64. Kirkman DL, Mullins P, Junglee NA, Kumwenda M, Jibani MM, Macdonald JH. Anabolic exercise in haemodialysis patients: A randomised controlled pilot study. Journal of Cachexia, Sarcopenia and Muscle. 2014; 5(3):199–207.

65. Watson EL, Kosmadakis GC, Smith AC, Viana JL, Brown JR, Molyneux K, Pawluczyk IZ, Mulheran M, Bishop NC, Shirreffs S, Maughan RJ, et al. Combined walking exercise and alkali therapy in patients with CKD4–5 regulates intramuscular free amino acid pools and ubiquitin e3 ligase expression. Eur J Appl Physiol. 2013; 113(8):2111–2124. [PubMed: 23591985]

KEY POINTS

- PEW is common and closely associated with high mortality and morbidity in patients with CKD.
- PEW is caused by multiple CKD-related factors as well as inadequate nutrient intake.
- There are large differences in epidemiological data between the general population and patients with CKD.
- Therefore, prevention and treatment of PEW should involve individualized and integrated approaches specific to this population against identified risk factors.

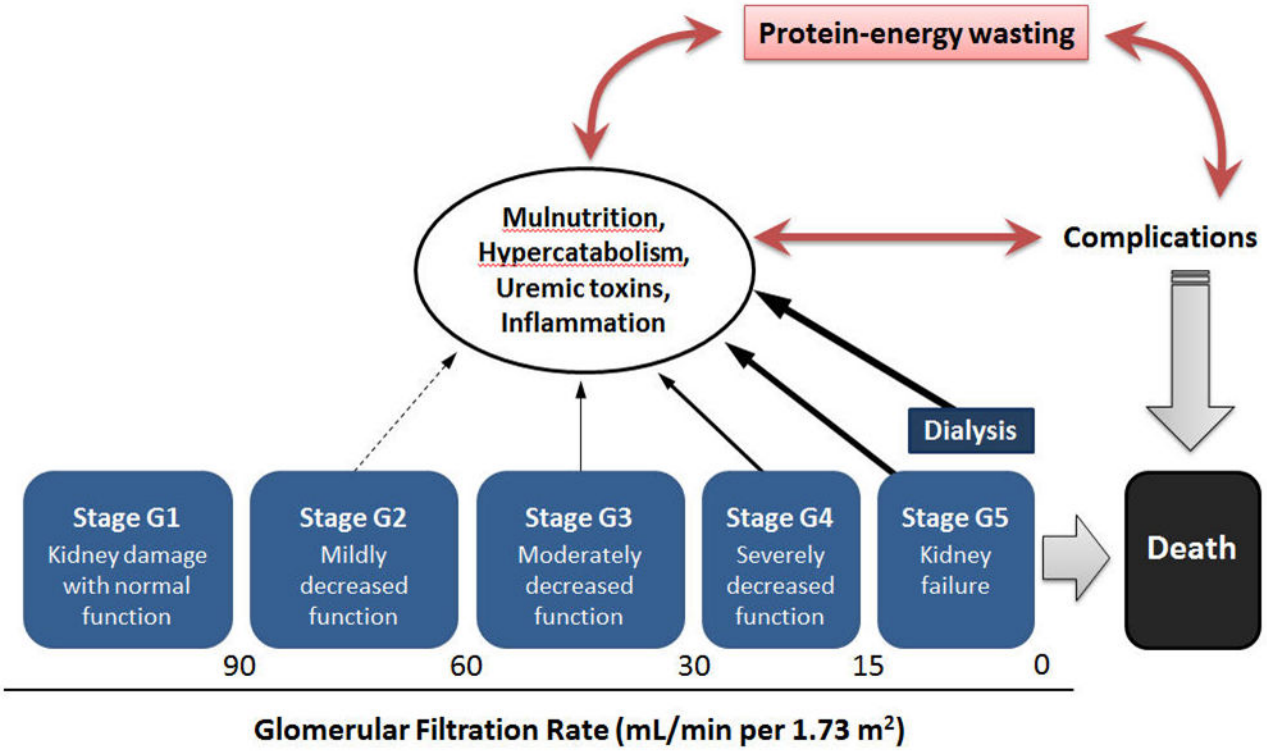

Figure 1. The conceptual model for CKD progression, PEW, and its consequences

Complications include hypertension, anemia, malnutrition, bone and mineral disorder, infection, and decreased quality of life as well as cardiovascular disease.

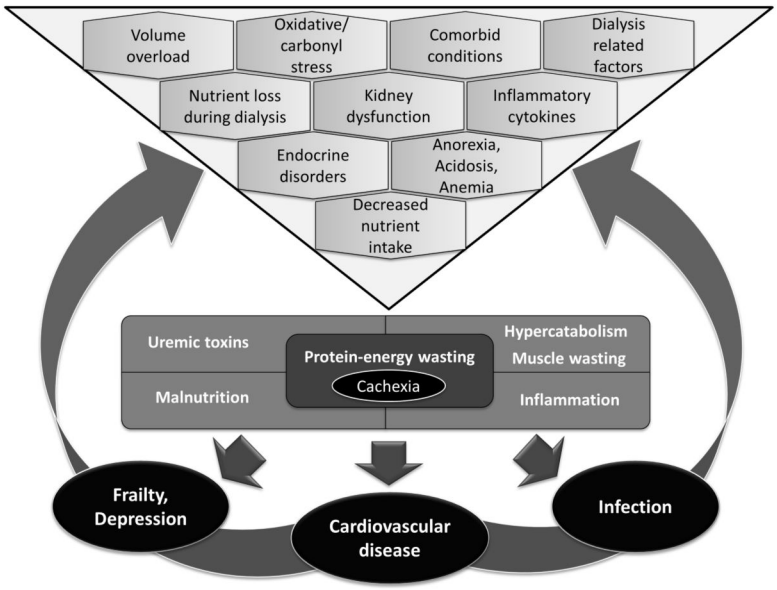

Figure 2. The conceptual model for etiology of PEW in CKD and direct clinical implications

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 induce infection, CVD, frailty, and depression, and these complications may also increase the extent of PEW in CKD.

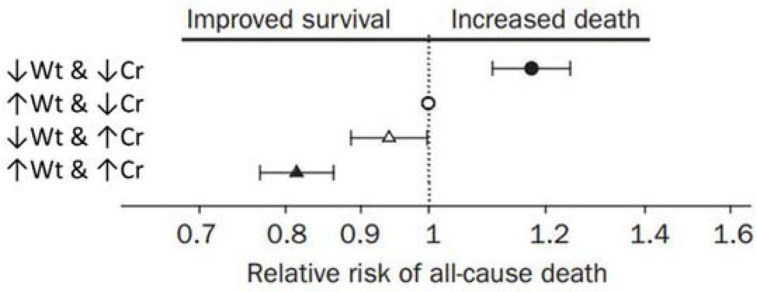

Figure 3. A combination of changes in dry weight and serum creatinine concentrations during the first 6 months of the cohort as a predictor of mortality in 50,831 patients receiving hemodialysis [38]

Cr = serum creatinine; Wt = weight.

Table 1

Readily utilizable criteria for the clinical diagnosis of PEW in CKD (modified from [1])

Serum Chemistry
• Serum albumin <3.8 g/dL[a]
• Serum prealbumin (transthyretin) <30 mg/dL (for maintenance dialysis patients only)[a]
• Serum cholesterol <100 mg/dL[a]
Body mass
• Body mass index (edema free) <23[b]
• Unintentional weight loss over time: 5% over 3 months or 10% over 6 months
• Total body fat percentage <10%
Muscle Mass
• 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/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients with CKD stages 2–5
• Unintentional low DEI <25 kcal/kg/day for at least 2 months

≥3 out of the 4 listed categories along with at least one test in each of the selected category must be satisfied for the diagnosis of kidney disease-related PEW. Each criterion should be documented on at least three occasions, preferably 2–4 weeks apart.

[a] Not valid in abnormally great urinary or gastrointestinal protein losses, liver disease, or cholesterol-lowering medicines;

[b] A lower body mass index might be favorable in certain Asian populations;

[c] Measured by a trained anthropometrist;

[d] Creatinine appearance is influenced by both muscle mass and meat intake.

Abbreviations: CKD, chronic kidney disease, DEI, Diatery energy intake; DPI, dietary protein intake; GFR, glomerular filtration rate; PEW, protein energy wasting.

Table 2

Causes of PEW in CKD Patients (adopted from [3])

1	Decrease 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 resistant secondary to obesity
	iv. Altered adiponectin and resistin metabolism
	b. Hormonal disorders
	i. Insulin resistance
	ii. Increased glucocorticoid activity
3	Metabolic acidosis
4	Decreased physical activity
5	Decreased anabolism
	a. Decreased nutrient intake
	b. Resistant to GH/IGF-1
	c. Testosterone deficiency
	d. Low thyroid hormone levels
6	Comorbidities and lifestyle
	a. Comorbidities(diabetes, 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

Table 3

Traditional criteria for frailty and muscle wasting

1	Weakness
2	Slow gait speed
3	Exhaustion
4	Low physical activity
5	Unintentional weight loss
6	Reduced muscle mass <90th percentile for the age and gender matched population

Patients with 3 or more criteria are considered as frail. It should be noted that assessment using patient self-report overestimates frailty.