Causes and Prevention of Protein-Energy Wasting in Chronic Kidney Failure

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Summary: Protein-energy wasting (PEW), defined as reduced somatic and/or circulating body protein mass, decreased fat mass, and usually reduced protein and energy intake, has a prevalence that is variously estimated to be 18% to 75% in maintenance hemodialysis and chronic peritoneal dialysis patients. PEW is associated with increased morbidity and mortality and often is preventable or treatable. Thus, it has been argued that maintenance hemodialysis and chronic peritoneal dialysis patients should be monitored routinely for PEW and treated for this condition, when it occurs. A trend toward PEW can emerge in early stage 3 chronic kidney disease with an increasing risk toward the development and worsening of PEW as chronic kidney disease progresses. A main cause of PEW is inflammation, which may occur with or without clinically evident illness and can be associated with the most severe forms of PEW. Another major cause of PEW is decreased nutrient intake relative to the patient's nutritional needs, and may be caused by anorexia, which may be engendered by uremic toxicity, emotional depression, medications, or inflammatory disorders. Nonanorexic causes of reduced nutrient intake include inadequate finances to purchase or prepare foods; medical or surgical illnesses that impair the person's ability to ingest, digest, assimilate, or process the nutrients; impaired cognitive function; other mental or physical disabilities; and loss of dentures. Losses of nutrients during dialysis treatments or in urine (eg, the nephrotic syndrome), acidemia, and hormonal disorders can contribute to the development of PEW. Early initiation and adequate doses of renal replacement therapy, rapid treatment of reversible inflammatory processes, ensuring an adequate nutrient intake, and prevention of acidemia may be used to prevent and treat PEW.

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An array of terms has been used to describe conditions associated with loss of adequate nutrient intake, decreased body protein (often assessed by the individual's muscle mass), and/or reduced body energy reserves (often assessed by the patient's fat mass). Arguably the 2 major causes of these conditions are malnutrition and inflammation. The terms for these conditions include *protein-energy malnutrition*, *malnutrition–inflammation complex syndrome*, *malnutrition–inflammation atherosclerosis syndrome*, *kidney disease wasting*, and *uremic cachexia*. To arrive at a consensus in applying a uniform terminology for the diagnosis of this syndrome and to avoid the use of misleading terms, the International Society of Renal Nutrition and Metabolism convened an expert panel[1] that proposed the following term for these conditions: *protein-energy wasting* (PEW).

The International Society of Renal Nutrition and Metabolism expert panel recommended the term *protein-energy wasting* (PEW), to define the loss of somatic and circulating body

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protein mass and energy reserves.[1] Cachexia, a PEW syndrome that occurs in many cancers, is a term that is used when there is severe PEW and generally is associated with severe debility and a poor prognosis. It is characterized by anorexia and severe weight loss, muscle wasting, and generalized debility. This degree of PEW is not seen commonly in kidney disease. Protein-wasting and energy-wasting also can each occur in isolation. The term *protein-energy malnutrition* is a form of PEW that is caused by inadequate nutrient intake relative to a given individual's nutritional needs. On the other hand, although PEM generally can be corrected by increasing nutrient intake, when PEM is at least partly caused by other nonnutritional causes, it cannot be corrected solely by increasing nutrient intake. The terms, *malnutrition–inflammation complex syndrome* and *malnutrition–inflammation atherosclerosis syndrome*, are limited in that they do no reflect all of the various causes of PEW (Table 1). Moreover, there are syndromes of malnutrition and inflammation that are not associated with atherosclerosis.

Table 1. Causes of PEW

Inflammation
Associated with clinically apparent diseases (eg, infected vascular access sites, systemic infectious illnesses including tuberculosis, diabetes mellitus, myocardial infarction, stroke, peripheral vascular ischemia, vasculitis)
Unassociated with clinically apparent diseases (eg, inflammatory reaction to vascular access catheters or grafts, peritoneal dialysis catheters, dialysis tubing, impure dialysate, old nonfunctioning transplant kidneys, kidney failure per se)
Decreased food intake
Anorexia (eg, caused by uremic toxicity, emotional depression, medications, inflammatory disorders [see earlier])
Nonanorexic causes (financial constraints, medical or surgical illnesses—particularly but not exclusively of the gastrointestinal tract, impaired cognitive function, other mental disability, physical disability, loss of dentures)
Dialysate nutrient losses
Losses of amino acids, peptides, and proteins into dialysate
Losses of water-soluble vitamins and minerals during dialysis
Metabolic acidemia
Hormonal disorders
Resistance to anabolic hormones such as insulin, growth hormone, insulin-like growth factor-I
Increased levels of counterregulatory hormones, such as glucagon and parathyroid hormone
Increased fecal excretion of nitrogen*
Decreased levels of anti-oxidants such as vitamin E, C, selenium, reduced glutathione (GSH)†
Physical deconditioning†
Carbonyl stress†

*A possible minor cause of PEW.
†A theoretically possible cause of PEW.

EPIDEMIOLOGY OF PEW

PEW, as measured by classic criteria, has been estimated to have a prevalence of 18% to 75% in maintenance hemodialysis (MHD) and chronic peritoneal dialysis patients.[2-4] The prevalence of severe PEW has been estimated to be 6% to 8%. In these individuals, there have not been any rigorously conducted epidemiologic studies that have examined the comparative incidence of PEW over the past few decades. Therefore, it is unclear whether the prevalence of PEW is increasing or decreasing or has remained the same in maintenance dialysis patients. There are less studies of PEW in nondialyzed stage 3, 4, or 5 chronic kidney disease (CKD) patients, although the prevalence of PEW in these individuals also seems to be greater than in the general population.[5] Inflammation, as defined by increased serum C-reactive protein levels, is observed in about 30% to 60% of North American and European MHD patients.[6,7] Why is diagnosing PEW important to the nephrology community? PEW has been associated with increased morbidity and mortality in patients with CKD; this increase in mortality has been shown to be almost entirely the result of cardiovascular causes.[8-11] A declining GFR in patients with stage 3, 4, or 5 CKD leads to increasing risk of developing PEW.[5]