What Are the Causes of Protein-Energy Malnutrition in Chronic Renal Insufficiency?

Protein-energy malnutrition (PEM) is a common occurrence in end-stage renal disease (ESRD) patients before the start of dialysis, and it becomes even more common after patients start on peritoneal dialysis (PD) or hemodialysis (HD). It is now well established that PEM is one of the most important predictors of survival in ESRD patients, whereas less is known about PEM and its impact on clinical outcome in patients with only a modest degree of chronic renal insufficiency (CRI).

Some recent studies, however, show that signs of PEM and low protein and energy intake are present even in patients with moderate CRI. One of these studies is by O’Sullivan et al in this issue of the Journal. These investigators found reduced lean body mass (despite a rather high dietary protein intake of 1.0 ± 0.1 g/kg/d) but well-maintained fat body mass (despite a rather low energy intake, 23.8 ± 1.6 kcal/kg/d). This raises questions about the determinants of body composition in CRI patients. The large Modification of Diet in Renal Disease Study in 1,785 clinically stable CRI patients with a glomerular filtration rate (GFR) of 39.8 ± 21.1 mL/min/1.73 m² (mean ± SD) showed that a low GFR was associated with impaired nutritional parameters as well as with decreased protein and energy intake; however, an overt PEM was rare. In the NHANES III study, 2.3% of 5,248 adult “non-renal” participants 60 years of age and older had a GFR < 30 mL/min/1.73 m², and the participants with this degree of CRI demonstrated signs of PEM and low energy and protein intake (as well as higher serum markers of inflammation, see below).

In general, parameters of PEM correlate directly with the GFR and this relationship is observed over a wide GFR range (10th to 90th GFR percentiles, 15.5 and 67.3 mL/min/1.73 m² in the MDRD study) in all subgroups of patients, not only in CRI patients but also in predialysis ESRD patients as well as PD and HD patients. Why then does declining GFR result in progressive impairment in nutritional parameters? Is it because loss of renal function is associated with reduced nutritional intakes (caused by anorexia) or because alterations in protein and energy metabolism in ESRD patients, induced by uremia as such or by comorbidity, result in increased net catabolism? And, why do some but not other patients develop PEM? Unfortunately, there is no simple answer as the pathophysiology of PEM in renal patients is complex and involves a whole range of factors contributing to anorexia and catabolism.

It is evident that nutrients must be ingested and utilized in sufficient amounts to serve as metabolic fuel and as a substrate for tissue growth; if a macronutrient (protein, energy) or an essential nutrient (amino acids, fatty acids, vitamins and trace minerals) is provided in insufficient amounts, this will sooner or later result in malnutrition. Many studies show that anorexia caused by retention of uremic toxins and anorexins is a major cause of PEM in renal patients. It is well established that the gradual decrease of nutritional intake of protein and energy, occurring simultaneously with the fall of GFR in CRI patients, is associated with impaired nutritional status. However, there are large interpatient variations in the requirements of protein and energy; some ESRD patients with low protein and energy intake may exhibit neutral or positive nitrogen balance, whereas others may benefit from very high intake.

The low daily caloric intake reported by O’Sullivan et al is similar to caloric intakes reported in other studies on CRI patients who had signs of PEM; however, note that caloric intake was not different from that of the normal subjects in the study by O’Sullivan et al. Two important questions are whether increased nutritional intake may preserve overall body stores of protein and energy and how various factors determining energy and protein metabolism may influence nutritional requirements in CRI and ESRD patients.

Energy deficiency due to a low energy intake
or increased energy expenditure (REE) is probably an important but often neglected cause of wasting in ESRD patients. A low energy intake reduces the utilization of protein, and energy intake therefore has a direct effect on nitrogen balance in ESRD patients; this effect may be even stronger than the effect of protein intake on nitrogen balance. However, energy requirements are to a large extent dependent on REE. In general, failure to downregulate REE as an adaptation to low energy intake may be a major cause of weight loss and wasting, whereas a small reduction in energy expenditure may increase the risk for developing obesity. Such an ability to conserve energy may constitute a survival advantage in ESRD patients in whom obesity appears to be a favorable prognostic factor.

Although REE may be increased in other patient groups with wasting disorders such as chronic heart failure, cancer, rheumatoid arthritis, and AIDS, normal or increased REE has been observed previously in ESRD patients. In contrast, the study by O’Sullivan et al shows that REE may in fact be suppressed in CRI patients. The reason for these discrepant findings is not known but may be caused by factors such as inflammation and genetic variations. Thus, inflammation repeatedly has been shown to be associated with increased REE in other patient groups with wasting disorders. It might therefore be speculated that ESRD patients with signs of chronic inflammation have elevated REE compared to a matched group of patients with no signs of inflammation. To the best of our knowledge, no information is available on the inflammatory status in the ESRD patients in the previous studies on REE. The CRI patients in the study by O’Sullivan et al had normal serum albumin, indicating that they were not inflamed; this may be one factor allowing adaptation to the low energy intake by suppression of REE.

Uncoupling proteins (UCP) are a group of mitochondrial transport proteins that transport free fatty acid anions, thus allowing free fatty acids to function as proton carriers. Consequently, activation of UCP causes uncoupling of respiration from oxidative phosphorylation, which results in generating heat without driving ATP synthesis. It has been calculated that the overall contribution of this proton leak to REE is about 20%. In general, genetic factors may contribute to about 70% of the variations in body mass index in nonrenal patient groups. Moreover, del/del UCP2 polymorphism has been shown to be associated with lower 24-hour energy expenditure in Pima Indians. UCP2 polymorphism also may be of importance as a cause of interpatient variation in body composition in ESRD patients. Thus, UCP activity seems to be of importance for body fat stores and REE, and it could be speculated that increased REE is linked to increased UCP-activity in humans. As a recent study demonstrated that administration of tumor necrosis factor-α (TNF-α) upregulates UCP2 and UCP3 gene expression 1.7- to 1.8-fold in rat muscle, it could be speculated that one mechanism by which inflammation causes increased REE is via a cytokine-induced stimulation of UCPs.

Low-grade chronic inflammation (the microinflammatory state of uremia) with increased circulating levels of C-reactive protein (CRP) and proinflammatory cytokines such as TNF-α and interleukin-6 (IL-6) has been recognized increasingly as one of the most important contributors to PEM in ESRD patients. Proinflammatory cytokines may cause PEM by increasing REE and protein catabolism, and they may also affect appetite and eating behavior. Assessment of inflammatory markers is of value to distinguish two types of PEM in ESRD patients, pure PEM (type 1) or “inflammatory” PEM (type 2). The latter form of PEM is associated with inflammation usually reflected by low serum albumin, comorbidity, elevated REE, increased oxidative stress, increased protein catabolism, and inability to reverse PEM by nutritional support. The prognosis of patients with only type 1 PEM and no inflammation, comorbidity, and other complicating factors is usually more favorable.

There are many causes of elevated proinflammatory cytokines in ESRD patients. First of all, deteriorating renal function is associated with an increase in serum cytokines and their soluble receptors. Secondly, a number of conditions and comorbidities prevalent in ESRD patients are associated with inflammation (and therefore with PEM), such as cardiovascular disease combined with fluid overload, congestive heart failure, and, in some cases, cardiac cachexia, hypertension, and chronic infections. Analyses of causes of PEM in ESRD patients should therefore in-
clude an assessment of comorbidities present in the investigated population.

Another important determinant of body composition and PEM in renal patients is acidosis. The CRI patients in the study by O’Sullivan et al\(^5\) were more acidotic than the control group, and this may have contributed to protein catabolism and the reduction in lean body mass observed in this study. Recent evidence suggests that increased catabolism in rats with chronic renal failure is largely, if not entirely, due to acidemia, particularly if these rats are compared to pair-fed control rats.\(^8\) The type of acidosis seen in CRI patients changes with decreasing GFR. Initially, a non–anion gap acidosis is observed secondary to the loss of bicarbonate, but with increasing loss of GFR, failure to excrete organic and inorganic acids results in an increased anion gap.\(^24\) However, the relationship between acidosis and nutritional status is confounded by the fact that increased protein intake, which could contribute to improved nutritional status, also results in increased acidosis. Therefore, well-nourished ESRD patients with high protein intake often exhibit a mild to moderate degree of metabolic acidosis.\(^25\) Correction of acidosis in CRI and ESRD patients may prevent acidosis-related protein wasting.\(^8\) It is therefore strongly recommended that oral sodium bicarbonate be provided to all CRI and ESRD patients to correct any tendency towards acidosis.

The results of the study by O’Sullivan et al\(^5\) and other recent studies\(^6,7\) show that signs of PEM, in particular reduction of lean body mass, may occur in renal patients with only a modest degree of CRI. The causes and consequences of PEM in CRI patients are not well understood, but contributing factors such as acidosis and inadequate nutritional intake should be considered to deal with in clinical practice. Specific treatment and prevention of other factors such as the micro-inflammatory state of uremia require further investigation.

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