Review

Secondary Hyperparathyroidism and Protein-Energy Wasting in End-Stage Renal Disease

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Abstract: Protein-energy wasting (PEW), a syndrome involving adverse changes in nutrition and body composition, is a serious problem associated with morbidity and mortality in patients with end-stage renal disease (ESRD). The pathogenesis of PEW is multifactorial, and the underlying mechanisms are not fully understood. However, recent translational work has provided compelling evidence for a causal role of parathyroid hormone (PTH) in the pathogenesis of adipose tissue browning and increased energy expenditure, a critical component of PEW in ESRD. These results provide a biological explanation for the clinical association between secondary hyperparathyroidism (SHPT) and PEW in hemodialysis patients and may serve as an additional rationale for treating SHPT. Large-scale clinical and epidemiological studies should determine the clinical significance of SHPT as a contributor to PEW and establish the optimal management of SHPT to ameliorate PEW.

Keywords: Cachexia, End-stage renal disease, Parathyroid hormone, Protein-energy wasting, Secondary hyperparathyroidism.

Individuals with chronic kidney disease (CKD), especially those with end-stage renal disease (ESRD) on maintenance dialysis, have an unacceptably high risk of mortality (1). This high risk of mortality in patients with ESRD cannot be explained solely by traditional risk factors, and several ESRD-specific risk factors have been postulated. Among these factors, protein-energy wasting (PEW), a syndrome involving adverse changes in nutrition and body composition, plays a major role (2–4).

Protein-energy wasting is common in patients with ESRD, and many studies have shown that indicators of PEW are closely associated with increased risk of hospitalization and death in this population (5–7). Importantly, PEW is different from malnutrition because it cannot be overcome by nutritional supplementation and appetite stimulants. Therefore, an urgent need exists for new therapeutic targets for preventing and treating PEW. The pathogenesis of PEW is multifactorial, and the underlying mechanisms are not fully understood. However, recent clinical and experimental studies have demonstrated that secondary hyperparathyroidism (SHPT), characterized by elevated levels of parathyroid hormone (PTH), plays a key role in increased energy expenditure, a critical component of PEW in ESRD (8–10).

This review outlines the pathophysiology of PEW, summarizes clinical data on the associations between SHPT and PEW, presents recent insights into the role of PTH in energy metabolism, and discusses the importance of treating SHPT in the context of preventing PEW and improving the outcomes of hemodialysis patients.

Poor nutritional intake and increased energy expenditure in ESRD

Insufficient food intake due to poor appetite and dietary restrictions is likely the major cause of malnutrition in ESRD patients. However, the extent to
which poor nutritional intake contributes to PEW is unknown. To examine the contribution of low protein intake to PEW, we analyzed baseline cross-sectional data from our historical cohort study of 2292 maintenance hemodialysis patients in Japan. The design of the historical cohort study was described previously (11). The International Society of Renal Nutrition and Metabolism proposed four levels of diagnostic criteria for PEW: biochemical criteria; low body weight, reduced total body fat, or weight loss; a decrease in muscle mass; and low protein or energy intakes (2). For the present analysis, we used body mass index (BMI) as a representative measure of PEW and the normalized protein catabolic rate (nPCR) as a surrogate for protein intake. We excluded 71 patients with missing BMI or nPCR data. A total of 2221 patients were available for analysis.

Figure 1 illustrates the BMI distribution in the whole cohort and according to quartiles of nPCR. In the whole cohort, 37% of the patients had a BMI less than 20 kg/m², and 61% of the patients had a BMI less than 22 kg/m², highlighting the high prevalence of PEW in the hemodialysis population. As expected, a close association was observed between the nPCR and BMI. The BMI distribution shifted to the right with increasing nPCR, suggesting that poor nutritional intake contributes substantially to PEW. Nonetheless, a subset of the patients had a low BMI despite a high nPCR. Even among the patients with an nPCR in the highest quartile (>0.97), 13% had a BMI less than 20 kg/m², and 31% had a BMI less than 22 kg/m², suggesting that undernutrition was not the sole cause of this syndrome.

One of the major factors that contributes to PEW, independent of or in addition to poor protein intake, is increased energy expenditure. Elevated resting energy expenditure (REE) leads to the wasting of adipose tissue and skeletal muscle through enhanced fat and protein catabolism. In a study of
stable maintenance hemodialysis patients, Ikizler et al. (12) measured the REE using a whole-room indirect calorimeter and showed that hemodialysis patients had a significantly higher REE on nondialysis days than healthy controls and that the REE further increased during the hemodialysis procedure.

A key characteristic of increased REE is a phenotypic switch from white adipose tissue to brown fat, a phenomenon termed adipose tissue browning (13). This phenomenon is associated with increased activity of mitochondrial uncoupling protein 1 (UCP1), which uncouples mitochondrial respiration and favors thermogenesis instead of ATP synthesis, leading to increased lipid mobilization and energy expenditure (14). The browning of adipose tissue has been identified and characterized in cancer cachexia, but this phenomenon also accompanies many other chronic diseases, including renal failure. Cheung et al. (15) demonstrated that 5/6 nephrectomized mice developed cachexia characterized by decreased food intake, increased metabolic rate, and loss of lean body mass, along with increased expression of UCP1 mRNA and protein in brown adipose tissue. Importantly, even when nephrectomized mice were force fed to restore their energy intake to the level of control mice fed ad libitum, the nephrectomized mice still gained less weight and continued to lose lean body mass and fat mass.

The underlying mechanism of adipose tissue browning is likely to be multifactorial, and the pathophysiology of renal failure has been poorly understood until recently. However, accumulating experimental and clinical data indicate a key role of PTH in adipose tissue browning and in the increased REE in ESRD patients.

**Clinical associations of SHPT with increased REE and muscle wasting**

The potential contribution of PTH to increased REE in ESRD has been suggested by clinical observations of hemodialysis patients with SHPT. Cuppuri et al. (8) measured the REE of hemodialysis patients with SHPT by indirect calorimetry and demonstrated that PTH was an independent determinant of the REE. After adjustment for lean body mass, the patients with severe SHPT had a significantly higher REE than those with the mild to moderate SHPT or control subjects. Furthermore, the researchers measured the REE in six patients with severe SHPT preoperatively and at 6 months after parathyroidectomy (PTx) and showed that the REE had decreased significantly in all of the patients with a mean reduction of 23%, accompanied by a marked reduction in PTH levels. Thus, these data suggested that severe SHPT contributes to PEW by increasing the REE of ESRD patients and that PTx could reverse that condition.

In another study of hemodialysis patients undergoing PTx for severe SHPT, Chou et al. (9) evaluated the degree of general weakness and extension force of the quadriceps femoris muscle preoperatively and at 3 months after surgery. The investigators found significant improvement in the subjective scores of general weakness and both average and peak extension force of the right knee after PTx. Because loss of muscle or muscle wasting is a valid criterion for the presence of PEW (2), these results provide a second line of evidence suggesting the pathogenic role of PTH in PEW.

**PTH triggers adipose tissue browning and wasting during renal failure**

As outlined above, several clinical studies suggest a role for PTH in PEW in ESRD patients. In this respect, a notable breakthrough was made recently by Kir et al., who revealed that PTH and PTH-related protein (PTHrP), which share the same receptor, serve as mediators of the loss of adipose tissue and muscle mass in rodent models of renal failure and cancer (10).

In their previous work on cancer cachexia, Kir et al. (16) used mouse models of Lewis lung carcinoma and found that tumor-derived PTHrP plays an important role in the browning of adipose tissues and wasting by driving the expression of UCP1 and other genes involved in energy expenditure and thermogenesis. The investigators next injected a neutralizing antibody specific for PTHrP into tumor-bearing mice and found that neutralization of PTHrP blocked adipose tissue browning and the loss of muscle mass and strength. These findings indicate that PTHrP mediates energy wasting in fat tissues and contributes to the broader aspects of cancer cachexia.

Because PTHrP and PTH share the same receptor and because SHPT has been associated with increased energy expenditure in ESRD patients, the same investigators suspected that PTH might share some of the cachectic effects of PTHrP. To test this hypothesis, they studied the role of PTH in mice with cachexia induced by 5/6 nephrectomy (10). They found that the nephrectomized mice developed SHPT and cachexia, which was associated with adipose browning and wasting. They further generated mice with fat cell-specific deletion of the
PTH/PTHrP receptor (PTHR) and demonstrated that these mice were resistant to adipose browning and skeletal muscle atrophy after nephrectomy. These data indicated that PTHrP and PTH mediate wasting through a common mechanism involving PTHR, providing an explanation as to why PEW is common in hemodialysis patients with SHPT and why treatment of SHPT is associated with improvement of this condition.

FGF23, another potential mediator of PEW?

Parathyroid hormone plays a crucial role in PEW associated with ESRD, but this paradigm does not exclude the involvement of other factors in the pathogenesis of PEW. One such candidate may be fibroblast growth factor 23 (FGF23). FGF23 is a bone-derived hormone that has endocrine effects on the regulation of phosphate and vitamin D metabolism (17). These effects are dependent on the presence of FGF receptors and the transmembrane protein Klotho (18). In CKD patients, circulating FGF23 levels increase progressively (19). While increased FGF23 enhances phosphate excretion as a compensatory response to maintain a normal phosphate balance, recent investigations have shown that FGF23 induces pathological left ventricular hypertrophy via FGFR4 in a Klotho-independent manner (20,21). Furthermore, emerging experimental evidence suggests that FGF23 directly contributes to immune dysfunction (22) and hepatic production of inflammatory cytokines (23), indicating a causative role of FGF23 in chronic inflammation. Because systemic inflammation and pro-inflammatory cytokines such as interleukin-6 have been shown to increase UCP1 expression in adipose tissue and thereby induce cancer cachexia (24), it is intriguing to speculate that FGF23-mediated systemic inflammation contributes to PEW in ESRD patients. Notably, PTH is one of the major drivers of FGF23 secretion (25). Treatment for SHPT, including cinacalcet (26), etelcalcetide (27), and PTx (28), decreases both PTH and FGF23 levels. Thus, it is possible that the observed improvement in increased REE and muscle weakness after PTx may in part be explained by a reduction in FGF23. Future research should study the role of FGF23 in the complex pathogenesis of PEW associated with ESRD.

CONCLUSIONS

Protein-energy wasting is a serious problem associated with morbidity and mortality in ESRD patients. Recent translational work has provided compelling evidence for a causal role for PTH in the pathogenesis of PEW. These results provide a biological explanation for the clinical association between SHPT and PEW in hemodialysis patients and may serve as an additional rationale for treating SHPT. Large-scale clinical and epidemiological studies will be required to determine the clinical significance of SHPT as a contributor to PEW and to establish the optimal management of SHPT to ameliorate PEW.

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