Nutritional Care in PD Patients

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복막투석 환자에서의 영양관리

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〈요 약〉

Protein-energy malnutrition and wasting (PEM/wasting) is common in peritoneal dialysis (PD) patients and is a strong predictor of morbidity and mortality. Among various catabolic factors contributing to PEM/wasting in PD patients, inflammation, which is highly prevalent in chronic renal failure patients, is the most important. Mechanisms by which inflammation may cause PEM/wasting are ATP-ubiquitin-proteasome pathway, insulin resistance, increased resting energy expenditure, and anorexia. As PEM/wasting in PD patients is multifactorial, single therapeutic strategies are not likely to be successful. Non-traditional management, such as appetite stimulants, anti-inflammatory diets, and anti-inflammatory pharmacological agents, in combination with traditional forms of nutritional support, might improve the nutritional status of PD patients.

Introduction

Protein-energy malnutrition and wasting (PEM/wasting) is common in peritoneal dialysis (PD) patients and is a strong predictor of morbidity and mortality. Although various catabolic factors contribute to PEM/wasting in PD patients (Table 1), inflammation, which is highly prevalent in PD patients, may be one of the most important[1]. Thus, in this review, we will briefly discuss the role of inflammation in PEM/wasting and also propose management of malnutrition in PD patients.

Role of inflammation in PEM/Wasting

Persistent inflammation with elevated levels of pro-inflammatory cytokines is a common feature in PD that may contribute to PEM/wasting by several mechanisms (Fig. 1). One important mechanism by which pro-inflammatory cytokines may cause PEM/wasting is by increasing protein hydrolysis and muscle protein breakdown via the *ATP-ubiquitin-proteasome proteolytic pathway*[2]. Another important mechanism by which pro-inflammatory cytokines may cause PEM/wasting is insulin resistance. Although the mechanisms by which pro-inflammatory cytokines mediate insulin

Table 1. Factors Contributing to PEM/wasting in PD Patients

Factors due to uremia *per se*
Poor food intake caused by uremic toxicity (underdialysis)
Increased circulating levels of anorexigenic agents
Abnormal protein and amino acid metabolism
Acidosis
Decreased biologic activity of anabolic hormones
Abnormal cell energy metabolism, carbohydrate intolerance, and impaired lipid metabolism
Inflammation
Factors related to PD procedure *per se*
Dialytic losses of nutrients
Protein losses in dialysate
Bioimcompatable PD solutions
Suppression of appetite by glucose absorption from dialysate
Abdominal discomfort induced by the dialysate
Infectious complications such as peritonitis and exit site infection
Other factors
Comorbidity such as cardiovascular disease and diabetes mellitus
Gastrointestinal problems
Low physical activity
Aging
Frequent blood sampling

resistance are not fully understood, it has been proposed that several mechanisms, such as a defect in insulin intracellular signalling pathways during inflammation, induction of lipolysis by tumor necrosis factor (TNF)-α and reduced production of adiponectin may contribute to inflammation-induced insulin resistance[3]. Thus, decreased insulin sensitivity sinduced by chronic inflammation may cause loss of muscle mass by decreasing the anabolic action of insulin on the skeletal muscle. In fact, Pupim et al[4] observed increased muscle protein breakdown in hemodialysis (HD) patients with type-2 DM. Another important mechanism by which pro-inflammatory cytokines may cause PEM/wasting is *increased resting energy expenditure* (REE). The significant correlation between inflammation and increased REE has been demonstrated in both dialysis[5] and chronic kidney disease (CKD) patients[6, 7]. Finally, pro-inflammatory cytokines may also cause PEM/wasting by *suppression of appetite and eating behavior*. The mechanism(s) by which elevated serum levels of pro-inflammatory cytokines may cause anorexia are not clear.

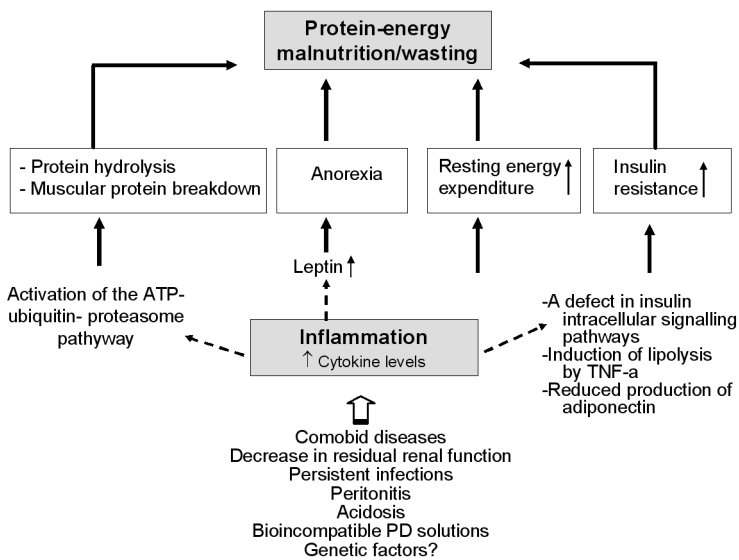

Fig. 1. *Mechanisms by which pro-inflammatory cytokines may cause PEM/wasting.*

However, inflammation may mediate anorexia through the anorexic hormone leptin, which has been demonstrated to be upregulated by pro-inflammatory cytokines in animal studies[8]. In a study of PD patients, Aguilera et al[9] reported that plasma levels of TNF-α were significantly higher in PD patients with anorexia (or anorexia with nausea and vomiting) than in PD patients without these symptoms.

Nutritional Care in PD Patients

As PEM/wasting in PD patients is multifactorial, single therapeutic strategies are not likely to be successful. New strategies for malnourished PD patients may include non-traditional management, such as appetite stimulants, anti-inflammatory diets, and anti-inflammatory pharmacological agents, in combination with more traditional forms of nutritional support (Table 2).

1. Appetite stimulants

In order to prevent and treat PEM/wasting in PD patients, maintenance of sufficient intake of energy and protein is essential (Table 3)[10]. However, anorexia is a common phenomenon in PD patients. There are several factors contributing to anorexia in PD patients, including inadequate dialysis, delayed gastric emptying, elevated levels of anorectic substances, and intraperitoneal infusion of PD solution. Although part of anorexia can be treated by an increased dialysis dose and decreased intraperitoneal volume, it is evident that these treatments are not always effective.

The use of appetite stimulants (such as megesterol acetate, cannabinoids, and cyproheptadine) may increase intake of energy and protein for malnourished PD patients. Megesterol acetate has been suggested to stimulate appetite in HD and PD patients[11, 12]; however, megesterol acetate is

Table 2. Management of Malnutrition in PD Patients

Traditional management	PD-related management	Non-traditional management
Optimize dialysis dose	Avoid potential source of inflammation during PD procedure	Appetite stimulants
Preserve residual renal function	- Peritonitis	Anti-inflammatory diets
Prevent catabolic factors	- Bioincompatible PD solutions	- Dietary phytoestrogens
- Correct acidosis	Maintain optimal fluid balance	- Dietary fibers
- Treat comorbidity and inflammation	Use of PD solution containing amino acids	- Omega-3 fatty acids
Maintain optimal nutrition		- Inhibitors of glycation end-products
- Nutritional counseling		Anti-inflammatory treatment
- Nutritional supplementation (oral, enteral, or parenteral)		- Statins
Correct anemia		- Glycation end-products inhibitors
Encourage physical activity		- Peroxisome proliferator-activated receptor (PPAR) agonists
Emotional support		- Anti-oxidants
		Anti-cytokine treatment

Table 3. Recommended Nutritional Intakes per Day for PD Patients

Protein	≥1.2 g / kg body weight (≥ 50 % with high biological value)
Energy	≥35 kcal/kg body weight (including glucose absorption from the dialysate)
Fat	30% of total energy supply (high content of unsaturated lipids)
Water and sodium	As tolerated by fluid balance

associated with several side effects including hypogonadism, impotence, and increased risk of thromboembolism. Thus, the treatment must be monitored closely and controlled, prospective, and randomized trials are required.

2. Anti-inflammatory diets

As the phytoestrogen genistein is effective in blocking inflammatory gene expression[13] and *dietary phytoestrogens* contained in soybeans could provide significant anti-inflammatory properies, the use of phytoestrogens might be of value for PD patients. In fact, a recent study with HD patients suggested a trend towards a reduction in the CRP concentration after 8-week ingestion of an isoflavone soy based supplement [14]. However, other studies confirming this finding in PD patients are still necessary. The importance of *dietary fibers* is underscored by a recent study demonstrating that non-renal subjects with high fiber consumption had a lower risk of elevated CRP[15]. The anti-inflammatory effect of *the omega-3 fatty acids* of fish oil, mainly eicosapentaenoic acid, is well recognized. Indeed, dietary fish oil decreases CRP and IL-6 levels in non-renal subjects[16].

Although reduced renal clearance and increased oxidative stress may be the most important causes of elevated glycation end-products (AGEs) in CKD patients, diet may be a significant source of highly reactive AGEs. Indeed, Uribarri et al[17] have shown that dietary glycotoxins contribute to significantly elevated AGE levels in CKD patients. Importantly, a reduction in dietary AGE content can be obtained safely without compromising the content of vital nutrients, such as dietary protein, fat, and carbohydrates[18].

3. Anti-inflammatory pharmacological treatment

As there are strong associations between pro-inflammatory cytokines and PEM/wasting in CKD patients, various pharmacological treatment strategies with anti-inflammatory effects, including HMG-CoA reductase inhibitors (statins), angiotensin converting enzyme inhibitors (ACEI), peroxisome proliferator-activated receptor (PPAR) agonists and anti-oxidative agents, such as α- and β-tocopherol have been proposed for these patients[19].

4. Anti-cytokine treatment

Targeted anti-cytokine treatment strategies may also be of interest in CKD patients. Indeed, central administration of specific IL-1Ra attenuates some, but not all, of the metabolic responses secondary to systemic infection and endotoxins and prevents sepsis-induced inhibition of protein synthesis in rats[20]. However, available toxicity data should caution clinicians against use of these agents until large randomized trials have been conducted to prove their efficacy and safety in this patient group.

Conclusions

Inflammation is associated with PEM/wasting by several mechanisms, such as ATP-ubiquitin-proteasome pathway, insulin resistance, increased REE, and anorexia. Prospective and randomized trials are needed to evaluate whether non-traditional management of malnutrition, including the use of appetite stimulants, anti-inflammatory diets, and anti-inflammatory pharmacological agents, in combination with more traditional forms of nutritional support, might improve the nutritional status of PD patients.

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