

The control of muscle protein turnover in patients on peritoneal dialysis

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Abstract.

Wasting is observed in a large percentage of patients receiving peritoneal dialysis (PD) and it is associated with functional impairment and worse outcome. In this article, we review the current state of our knowledge regarding the effects of PD on protein metabolism and their possible interactions with the uremia-induced and comorbidity-induced alterations in protein metabolism. Available evidence shows that glucose-based PD induces a new state in muscle protein dynamics which is characterized by decreased turnover rates and a reduced efficiency of protein turnover, a condition which may be harmful in stress conditions, when nutrient intake is diminished or during superimposed catabolic illnesses. The effects of PD on protein turnover may overlap with the effects of aging and comorbidities to promote net catabolism. There is a need to develop more effective treatments to enhance the nutritional and functional status of PD patients. New approaches include the use of icodextrin to maintain extracellular volume, amino acids/keto acids-containing supplements combined with physical exercise, vitamin D, myostatin antagonism, and ghrelin agonism for malnourished patients refractory to standard nutritional therapy.

Background

More than 272,000 patients receive peritoneal dialysis worldwide, representing approximately 11% of the global dialysis population (1). Despite advances in treatment technique, mortality is still high in PD patients, as well as in those hemodialysis-treated (2). Besides age, cardiovascular disease, diabetes and residual renal function, markers of nutritional status, including serum albumin and subjective global assessment (SGA) remain powerful predictors of outcome (2-5).

In general population and in patients with chronic diseases loss of muscle mass is associated with adverse outcomes such as functional impairment, lower quality of life and increased mortality (6). In cohort studies, low appendicular muscle mass is associated with mortality in PD patients (7). Factors such as exogenous malnutrition, low vitamin D levels, insulin/IGF1 resistance and inflammation can influence the development of wasting.

PD patients are also exposed to catabolic stressors such as high glucose load, uremia, malnutrition and comorbidities which can accelerate the wasting process.

Assessment of muscle functionality may provide additional diagnostic and prognostic information to muscle-mass evaluation. Both reduced muscle mass and strength are prevalent conditions in dialysis patients and predict a worse outcome. Of note, muscle strength and muscle mass are not necessarily congruent; since muscle strength can diminish even though muscle mass is maintained or increased.

In a prospective study of 330 incident dialysis patients low muscle strength was more strongly associated with aging, protein-energy wasting, physical inactivity, inflammation, and mortality than low muscle mass (8). Muscle atrophy has been showed to be more common in female dialysis patients and it is associated with

inflammation, poor nutritional and anthropometric status (9).

In France, in the French Language Peritoneal Dialysis Registry (RDPLF), 1.7% of transfers to hemodialysis and 3.2% of deaths have been estimated to be due to malnutrition. Although a causal link between malnutrition and patient outcome is difficult to prove because of the presence of confounders (inflammation and comorbidity, for example), identification and management of malnourished PD patients should be a central target. Traditionally, different terms have been used to identify an altered state on nutrition in patients on PD: “malnutrition”, “wasting”, “muscle atrophy” and “cachexia”. Recently, the diagnostic criteria for the wasting syndrome in patients with chronic kidney disease (CKD) have been revised (10). Notably the occurrence of protein-energy wasting (PEW) syndrome (as defined by multiple markers of nutritional status) has been reported in a percentage of 18% to 56% of this population depending on the assessment method used (5).

Superimposed on factors due to uremia, nutritional problems caused by PD can play “per se” a role in the pathogenesis of wasting. Peritoneal dialysis is most commonly based on the exchanges between blood and a glucose-containing peritoneal solution, thus exploiting the fluid and solute transport characteristics of the peritoneum. One of the untoward effects of PD is the loss of proteins and amino acids into the dialysate effluent. Patients undergoing PD lose amino acids (1–3.5 g a day) and a substantial amount of proteins (5–10 g per day), mainly albumin (6-8 g), but also immunoglobulins, complement, transferrin, β_2 -microglobulin, and α_2 -macroglobulin (11-12-13). In particular, the type of peritoneal membrane transport might influence the amount of protein loss; in high transporters protein losses are considerably greater than in patients with a low solute transport rate (14). Whether rapid transport status or protein loss affects nutrition is debatable (15).

Furthermore “inherent” fast transport (that is, the fast solute transport rate is from the start of peritoneal dialysis) and “acquired” fast transport (that is, when the transport rate increases with time on peritoneal dialysis) have different clinical implications; inherent fast transport is associated with worse outcomes and increased mortality because it is linked with greater levels of comorbidity and inflammation than acquired fast transport (15). Protein losses markedly increase during peritonitis. The continuous loss of proteins and amino acids through peritoneal clearance accounts for almost a third of the reported increase in dietary protein requirements (13) and can be compensated by adequate dietary intake, but a poor appetite or anorexia limit intake in many patients. Balafa et al. demonstrated that baseline peritoneal albumin clearances and dialysate losses were associated with some signs of comorbidity, like the presence of a fast peritoneal transport status, but this did not have a measurable effect on patient survival (16).

Some major metabolic effects of PD can be due to the absorption of glucose. On one hand the peritoneal glucose uptake (as much as 400-800 KCal are provided daily by different PD regimens) allows for most PD patients to meet the energy intake requirements, in fact the caloric load from a single glucose-based exchange can contribute to >30% of the total daily energy intake of a patient on PD (17). Even though it is plausible to think that caloric absorption could reduce appetite, the glucose absorption from PD fluid did not suppress calories or protein intake in a large cohort study (18).

On the other hand, ongoing glucose uptake is responsible for the development of truncal adiposity, sustained hyperinsulinemia and increase in triglycerides, as well as for the occurrence or aggravation of atherosclerosis which are observed after the initiation of

treatment (19). Of note, the survival advantage associated with obesity observed in hemodialysis (HD) patients appears to be less likely in PD patients (20).

The PD procedure may impair appetite by causing abdominal discomfort and also through the absorption of the osmotic agent and other factors. Furthermore, a delayed gastric emptying is often seen in patients on PD (21). The mechanism of delayed gastric emptying is not clear. It has been proposed that the cause might be the elevated indwelling PD fluid (22). Other factors may contribute to delayed gastric emptying time, as diabetes, dialysate glucose reabsorption (23) and abnormal gastric myoelectric activity (24). Actual protein and energy intakes < 1.0 g/kg/day and 26 kcal/kg are often reported. An increased peritoneal solute transport rate has been linked to PEW and also to the malnutrition, inflammation, and atherosclerosis syndrome, which has been associated to poor appetite. The use of new PD solutions free of glucose degradation products and at neutral-pH has been reported to be associated with higher plasma levels of acylated ghrelin and adiponectin than classic solutions. These findings may contribute to explain improved appetite scores rates reported with the use of so-called biocompatible PD solutions (25).

Alterations in muscle biology induced by uremia

Decrease in nutrient intake, metabolic acidosis, physical inactivity and co-morbid conditions such as diabetes and sepsis can promote muscle wasting through an increase in protein degradation and/or a decrease in protein synthesis (26). However, uremia per se promotes net protein catabolism, as suggested by studies in animal models. Bailey et al. recently identified a series of abnormal post-receptor signaling changes in the insulin/IGF-1

pathway in muscle of rats with CKD (27). These included the occurrence of functional abnormalities in the IRS/PI3-K cascade that decrease the phosphorylation of Akt. The low phosphorylated Akt activity can stimulate the expression of specific E3 ubiquitin conjugating enzymes, atrogin-1/MAFbx and MuRF1. Furthermore, a decrease in muscle PI3K activity could activate Bax, leading to stimulation of caspase-3 activity and could increase apoptosis and protein degradation. These defects which are specific to uremia can overlap with those due to aging, acidosis, diabetes and sepsis.

Recently, Zhang et al (28) in a rodent model of CKD demonstrated that myostatin is upregulated in skeletal muscle and that myostatin suppression decreases the levels of circulating inflammatory cytokines, including TNF- α and IL-6. In exploring the influence of myostatin on these cytokines, they observed that TNF- α stimulates myostatin expression, whereas myostatin stimulates IL-6 production. Recently, we (29) observed an upregulation of myostatin gene expression in skeletal muscle of pre-dialysis CKD patients. Myostatin was associated with upregulated IL-6 expression, suggesting that microinflammatory changes taking place in muscle cells and myostatin are metabolically linked in CKD patients before the start of PD. Recently it has been demonstrated that the upregulation of myostatin in skeletal muscle in CKD follows an IL-6 dependent stimulation of Stat3 to increase the expression of CCAAT/enhancer-binding protein δ (C/EBP δ). The signalling pathway following binding of myostatin to its receptor involves activation of Smad2/Smad3 and phosphorylation of Akt in muscle (30).

Effects of peritoneal dialysis on albumin metabolism

Hypoalbuminemia and hyperfibrinogenemia are frequently observed in PD-treated patients. Serum albumin is a powerful predictor of outcomes in both HD and PD patients (31-34). In a study of 130,052 PD patients, those with baseline serum albumin level <3.0 g/dL had a more than 3-fold higher adjusted risk of all-cause and cardiovascular mortality and 3.4-fold higher risk of infection-related mortality. A significant increase in death risk was evident for PD patients with serum albumin <3.8 g/dL. Of note, hypoalbuminemia predicts an increased risk of both cardiovascular and infection-related mortality in PD patients (34).

Serum albumin levels are the resultant of several processes. These include rate of hepatic synthesis of albumin and other proteins, dietary protein intake, distribution in the intra/extravascular compartments, hydration state, protein losses in the peritoneal effluent and urinary protein losses in patients with residual renal function and degradation of albumin. Both albumin and fibrinogen are lost in PD fluid.

In stable PD patients recommendations for dietary protein intake are 1.1-1.3 g/kg/daily (35). Protein losses into peritoneal effluent are typically 5–10 g per day, mainly albumin (6-8 g) (11-13) and urinary losses are possible in patients with residual kidney function. To counterbalance these losses hepatic albumin synthesis in the liver is about 12-15 g daily. This compensatory increase in albumin synthesis typically maintains normal plasma albumin concentrations during PD and explains why peritoneal albumin losses into dialysate are not predictive of worse outcome (16); this suggests that other factors which can control serum albumin levels are responsible of the association between serum albumin and mortality in PD patients.

Similar findings are observed in the nephrotic syndrome, where urinary loss of

proteins is associated with increased synthesis of albumin and fibrinogen (36). Of note the calculated oncotic pressure has been shown to be related to the increase in fractional albumin synthesis, suggesting that a change in oncotic pressure is the drive for the upregulated liver protein production and release (36,37).

Even if several studies suggest that caloric and protein intake and the route of administration of the nutrients are major nutritional factors regulating albumin synthesis (38), wasting due to semistarvation (39) or to anorexia nervosa (16) does not lead to hypoalbuminemia, indicating an extraordinary ability of liver to maintain albumin synthesis during nutrient deprivation in absence of disease. In keeping with these findings, a weak correlation has been observed between protein intake and albumin levels in PD patients. Kaysen (40) observed that although both transperitoneal albumin loss and inflammation are strongly associated with serum albumin, the two variables are statistically independent. Furthermore, he observed no relationship between serum levels of C-Reactive Protein and transperitoneal albumin losses to account for the lower serum albumin levels in patients with high loss rates. These findings suggest that the increase in albumin synthesis in response to transperitoneal albumin loss is blunted by inflammation.

Low oncotic pressure may adversely affect water shift between the intravascular and interstitial space. Hypoalbuminemia may per se be an important determinant of tissue overhydration in PD patients because of the reduced plasma filling as a result of reduced oncotic pressure. Recently John et al. (41), in a cross-sectional study, observed that overhydration was not associated with an increased plasma volume and that the only independent predictor of whole body overhydration was reduced plasma albumin,

which potentially favours extra-vascular, extra-cellular water accumulation.

Albumin also has important roles as a scavenger of free radicals, it is a binding agent for toxic compounds and a carrier for a wide variety of drugs and hormones (42). Reduced albumin binding of drugs and endogenous ligands is a feature of uremia (43). In PD patients a state of inflammation directly suppresses hepatic albumin synthesis preventing compensatory increases in albumin production (44).

Taken together, available data indicate that the development of hypoalbuminemia in most PD patients appears to be a marker of comorbidity and illness rather than a marker of malnutrition and is characterized by a combination of the acute-phase response, with a reduction in serum albumin, combined with a true increase in albumin synthesis to compensate for protein losses into the peritoneal effluent.

Effects of residual renal function on nutrition

The preservation of residual kidney function is likely to play an important role in the prevention of wasting in PD patients. Higher subjective global assessment (SGA) scores, dietary protein intake, and dietary caloric intake have been observed in patients with preserved residual renal function as compared to anuric patients undergoing PD (45).

Although underlying mechanisms are not known, it is worth to consider that the human kidney has a major role on extracellular fluid volume overload (which may be associated with PEW) (46). In addition the human kidney plays a major role on the removal of middle molecules and potentially toxic low molecular weight proteins (47-49).

Finally, recent studies show that the human kidney plays an important role in the

transamination of leucine and essential amino acids (50), giving support to the hypothesis that defective kidney metabolic activity blunts amino acids metabolism.

Effects of peritoneal dialysis “per se” on protein metabolism

Peritoneal dialysis can provide a further catabolic stimulus in uremic patients. Despite substantial glucose absorption, loss of lean body mass, with increase or no change in fat stores have been reported in longitudinal studies in PD patients (4, 51,52). PD patients present circulating and intracellular levels of essential amino acids (mainly leucine and valine) which are even lower than those observed in HD patients, which suggests a response of protein turnover to depletion or reduced release from tissue because of hyperinsulinemia (53).

Effects of peritoneal dialysis on whole body and muscle protein turnover

Early studies have shown that whole body protein degradation declines in response to glucose administration (54). Castellino et al. (55) observed that basal rates of protein degradation, leucine oxidation and whole body protein synthesis were reduced in PD patients as compared to controls. In addition, during euglycemic hyperinsulinemic clamp leucine flux declined by about 30% and leucine net balance became less negative. When insulin was infused together with amino acids, protein synthesis rose and leucine balance became similarly positive in patients and controls. Taken together, data from these studies suggest that the response of protein turnover to PD is to activate mechanisms to minimize protein loss from the body.

The anticatabolic drive of persisting hyperinsulinemia could contribute to the

preservation of muscle mass. However, this assumption is in contrast with the clinical finding of muscle wasting observed in many PD patients. In a series of cross-over studies in stable, non-malnourished PD patients, we evaluated muscle and whole body protein dynamics: a) during the systemic, moderate hyperinsulinemia associated with the substrate removal induced by peritoneal dialysis; b) during locally-induced moderate hyperinsulinemia, without systemic effects on amino acid availability and hormones (56,57). During locally-induced moderate hyperinsulinemia the overall response, which was observed both in healthy controls and in CKD patients, was a switch from a negative protein balance observed in the basal state to a neutral one, which was due to an insulin-related decrease in protein degradation. These data are in accordance with the exquisite sensitivity of muscle protein metabolism to insulin. PD with dextrose induced a similar increase (by ~2-3 fold) in insulin levels, and a similar acute decrease in muscle protein degradation (56). In skeletal muscle, despite the decrease in protein degradation, there was not a net anticatabolic effect since a concurrent decrease in muscle protein synthesis was observed. This decrease in muscle protein synthesis correlated with the decline in blood of several essential amino acids, suggesting that the removal of substrates for protein synthesis via peritoneal drainage blunts muscle protein turnover. In addition, in PD patients, most of the anticatabolic effect of insulin was obtained in extra-muscle tissues (56,57). Data from these studies indicate that PD acutely induces a new state in muscle protein dynamics which is characterized by decreased turnover rates and a reduced efficiency of protein turnover. Accordingly, the major effect of PD is to restrain muscle protein turnover. On one hand, a reduced rate of overall body protein synthesis and breakdown might be considered unfavourable, since they

would decrease the individual ability to withstand successfully a major stressful stimulus. On the other hand, the benefits of a high rate of endogenous protein turnover can be inferred if one considers that the stimulation of growth is accompanied by a high protein turnover (58). Because low rates of protein turnover may result in a limited potential for protein accretion, one could speculate that suppression of protein turnover may result in a limited potential for net skeletal muscle protein anabolism. Taken together, these data suggest that glucose-based PD predisposes the body to reduced anabolism, a condition which may be harmful when nutrient intake is diminished or during superimposed catabolic illnesses.

Effects of icodextrin on muscle protein metabolism

Icodextrin is a glucose polymer which acts as an alternative osmotic agent with an osmolarity almost similar to that of plasma. Since the absorption of icodextrin by the peritoneum is very restricted, icodextrin-based solutions cause ultrafiltration (UF) in PD patients using colloid osmosis. On nutritional ground, the insulin response to icodextrin is minimal or absent, but there is a significant increase in essential amino acids (EAA) and non essential amino acids (NEAA) loss without change in plasma levels (59) which suggests that icodextrin-based PD favours net protein degradation.

In a pilot study, we evaluated acute effects of icodextrin dwell on muscle protein turnover in 5 non diabetic PD patients.

Every patient was evaluated twice: at basal state and during a 10-12 hours dwell with icodextrin. After the icodextrin dwell no change in muscle protein degradation and in protein synthesis were observed. Net protein balance was negative both in basal conditions and in response to icodextrin dwell.

Protein turnover efficiency was unchanged. Consistent with these findings, skeletal muscle protein metabolism is not affected by icodextrin, suggesting that icodextrin has neutral metabolic effects on protein turnover.

Effects of intraperitoneal amino acid administration

Changes in muscle metabolism of specific amino acids induced by uremia could impair both muscle regeneration and protein turnover. In patients with CKD a reduced release of valine and leucine from muscle is likely responsible for their reduced levels in blood (60,61). It is of note that leucine cooperates with IGF-1 in stimulating the activation of satellite cells which are responsible for muscle regeneration in different situations, such as damage-induced muscle loss, aging and progressive neuromuscular diseases. The leucine-induced activation of satellite cells is obtained through the mammalian target of rapamycin (mTOR) signaling, one of the main pathways responsible for protein synthesis and cell proliferation. Of note this signaling pathway is partly attenuated in skeletal muscle of chronically uremic rats (62).

With this regard, PD acutely decreases leucine levels and further worsens the already unbalanced plasma amino acids pattern. Amino acids, leucine in particular, can act as strong insulin secretagogues when administered in combination with carbohydrate. Furthermore, amino acids, mainly leucine, have been shown to stimulate mRNA translation, thereby increasing muscle protein synthesis.

Different studies have shown that in PD patients the use of a 1.1% dialysis solution containing all nine essential amino acids, six nonessential amino acids and 40 mmol/L lactate increases protein synthesis, nitrogen balance and weight gain (63-65).

However these effects are reported to be mixed because of the accompanying metabolic acidosis. Asola and coworkers (66) found that the use of amino acids solutions increased skeletal muscle amino acids uptake as compared to the use of glucose-based solutions only, both in the fasting state and during insulin stimulation. PD solutions containing a mixture of amino acids and glucose can serve as a source of both proteins and calories but are not commercially available. However they can be used in patients on automated PD (67). Supplying amino acids together with calories could bring about utilization of amino acids for the synthesis of proteins rather than the oxidation of amino acids, thereby limiting production of acid and urea. Using dialysis solutions with a high buffer concentration (40 mmol/L) can contribute to maintaining acid-base homeostasis.

When we evaluated muscle protein turnover during PD with dialysates containing dextrose plus amino acids, the decline in blood amino acids and in muscle protein synthesis was prevented and net protein balance across muscle was less negative, indicating that increased amino acids availability is a crucial determinant of muscle protein turnover in PD patients (56). Taken together these data support the hypothesis that in patients who are treated with PD, when fasting or when nutrient intake is reduced, muscle mass could be maintained better by the combined use of dextrose and amino acids. However, clinical trials are still required to evaluate the long-term effects of this strategy on morbidity and mortality of PD patients.

Amino acids solutions may induce anorexia, metabolic acidosis and increased serum urea levels. In addition, the optimal formula and amount of amino acids supplementation need to be explored further.

It is unknown if the provision of larger quantities of amino acids via PD is safe or

efficacious. McCormick et al. (65) demonstrated that higher than conventional doses of amino acids mixed with glucose can be tolerated with relatively minor changes in acid-base status provided that a bicarbonate/lactate-buffered solution is used.

PEW in uremia: interactions with the effects of aging and comorbidities

Sarcopenia is often observed in the aged population, and it may express in PD patients the combined events occurring in aging and renal disease. It is interesting that both apoptosis and myostatin are upregulated in sarcopenia of aging, suggesting that the findings observed in CKD patients may represent an acceleration of processes 'naturally' leading to sarcopenia in elderly subjects. Elderly patients are expected in Western countries to soon become the majority of those who will need renal replacement therapy. In elderly subjects a decreased sensitivity of insulin action regarding protein metabolism and selected deficits of myosin heavy chain and mitochondrial protein have been described (68). These aging-related alterations in protein metabolism likely potentiate those caused by uremia. PEW is also often observed in patients with co-morbid conditions, such as sepsis or heart failure. PD patients with previous circulatory congestion have significantly more inflammation, more muscle wasting, and higher energy expenditure but lower food intakes in keeping with an anorexia-cachexia syndrome (69). It is of note that some of the alterations observed in uremia overlap with those present in cardiac cachexia. Endocrine alterations, such as resistance to GH/IGF-1, excess glucocorticoid and angiotensin II cause net protein degradation and are common to uremic and cardiac cachexia (70). In addition, the serum concentrations of pro-inflammatory cytokines

(mainly TNF- α , IL-6, and IL-1) are known to be high in patients with cachexia due to chronic heart failure (CHF) and CKD and in both conditions they are associated with a poor prognosis (71). Studies in animals indicate the involvement of multiple catabolic signal transduction pathways which may promote wasting and impair muscle regeneration in uremia and CHF. Emerging data have uncovered the role of new mediators such as myostatin and activin (72). Myostatin binds to the type II receptor ActRIIB, leading to phosphorylation of SMAD2 and SMAD3, which translocate to the nucleus to regulate gene expression. Myostatin stimulation also leads to inhibition of the protein kinase B/Akt and the mammalian target of rapamycin (mTOR) (73). In addition Akt inhibition by myostatin increases expression of atrogin-1 which causes proteosomal degradation (73).

Treatment of wasting in PD patients, new approaches

During the last years much progress has been made in the understanding of mechanisms leading to PEW in CKD and dialysis-treated patients. However, the results of intervention studies are unsatisfactory (4). There are several new issues to be addressed on therapy of PEW in PD patients, such as the effects of physical exercise combined with amino acids/keto acids supplementation, vitamin D, myostatin antagonism and ghrelin agonism. Amino acids either given via intraperitoneal route or orally may have different effects on protein metabolism. Substituting a single exchange with intraperitoneal amino acids in a patient undergoing PD is a potential therapeutic option for PEW. This approach may be more appropriate for patients with malnutrition secondary to reduced protein intake, rather than as a result of inflammation in which the extra amino acids may not undergo metabolism.

Vitamin D is involved in energy metabolism and adipocyte biology in vivo in part through regulation of β -oxidation and uncoupling protein (UCP) expression (74). Vitamin D deficiency is highly prevalent in patients with CKD and is associated with various adverse health outcomes (75). In cross-sectional studies higher 25(OH) vitamin D levels are associated with significantly improved survival. Of note, in cohort studies vitamin D supplementation improves muscle strength, functional ability and balance in both CKD and dialysis patients (76). Inadequate levels of vitamin D are associated with inflammatory factors such as high-sensitivity C-reactive protein and neutrophil-lymphocyte ratio in a study of a total of 176 hemodialysis patients and 32 peritoneal dialysis patients (77). However, a metanalysis of interventional studies of vitamin D supplementation in CKD patients (78) failed to show a clinically evident benefit of vitamin D supplementation, besides the improvement of biochemical endpoints. Specifically, there were insufficient data as for cardiovascular and skeletal effects. In addition, six months of therapy with calcitriol or cholecalciferol did not improve vascular endothelial function and did not improve inflammation in patients with CKD, in a recent study (79). Therefore, whether vitamin D supplementation translates into clinically significant outcomes is yet to be determined.

Another potential initiator of muscle wasting is myostatin which is upregulated in muscle of animal models of uremia, in patients with CKD and cardiac cachexia. Recently, pharmacologic suppression of myostatin was found to counteract inflammation and impaired insulin/IGF-1 signaling and most importantly, it prevented muscle wasting in rodent models of cancer and kidney failure (80). These lines of evidence highlight the therapeutic potential of myostatin antagonism for treating sarcopenia

by inhibiting protein degradation and/or apoptosis. In fact a recent experimental study demonstrated that vitamin D receptor agonists (VDRAs) stimulates myogenic differentiation by inhibiting cell proliferation, by increasing the expression of pro-myogenic factors and by depressing the expression of myostatin mRNA (81).

A clinical study showed that vitamin D supplementation increases skeletal muscle mass in CKD patients (82).

A more recent experimental study showed that ablation of vitamin D receptor or vitamin D deficiency increased myostatin expression and decreased skeletal muscle mass in mice (83).

Recently, a small randomized trial demonstrated that oral supplement with ONCE (Otsuka Nutrition Pharmaceutical) dialyze formula (ODF) ameliorates low dietary energy and nutrient intake as well as improves serum prealbumin and body weight in patients with long-term CAPD (84).

Furthermore, improving fluid status is associated with better nutritional status and worse fluid status results in malnutrition. In peritoneal dialysis patients, volume overload causes low intake of calories and of dietary proteins (85). Fluid overload may be associated with higher serum endotoxin and inflammatory cytokines levels in PD patients (86). Elevated levels of proinflammatory cytokines suppress appetite and induce anorexia by inhibiting the adaptive feeding response to energy deficits (86-88). Inflammation results in loss of muscle mass by activating the ubiquitin-proteasome proteolytic pathway (89,90). Controlling fluid overload can improve systemic endotoxin level, inflammation and then malnutrition (85, 91).

Taken together, these evidences suggest that substituting one glucose peritoneal dialysis exchange with icodextrin improves

malnutrition and reduces systemic inflammation. Icodextrin dialysis remarkably reduces high sensitive C reactive protein (hsCRP) levels and other inflammatory markers, likely because of a better fluid balance (92). Other mechanisms, other than fluid balance, are implicated with beneficial effects with icodextrin use. Dialysis using icodextrin exchange decreases leptinoemia (93), a hormone that suppresses appetite. Furthermore substitution of glucose for icodextrin, decreasing glucose exposition, reduces insulin resistance, both in diabetic and in non-diabetic patients (94). Insulin is an anabolic that exerts anticatabolic effects on skeletal muscle. Insulin resistance might dampen the anabolic effect of insulin on skeletal muscle and might cause loss of muscle mass. Indeed, insulin resistance correlated with muscle wasting in 21 patients on peritoneal dialysis, which suggests that insulin resistance is closely linked to PEW (95).

A high prevalence of low-performance capacity and sedentarism has been found among elderly patients on PD or with CKD stage 3-4. Apart from age, a condition of malnutrition-inflammation was the major determinant of poor physical activity and capacity in PD patients. Better body composition seems to be positively associated with physical activity in PD. Routine clinical management should include a close evaluation of nutritional status and of physical activity and capacity (96). Cobo et al. reported a high prevalence of sedentarism (63%) in a cohort of 64 PD patients as assessed by pedometers. They detected that better physical activity was associated with lower comorbidity and better nutritional status (depicted by albumin and subjective global assessment), higher lean body mass and lower fat body mass. Higher levels of physical activity were accompanied by lower levels of C-reactive protein in PD (97). The

relationship between nutritional status and physical activity is of special value in PD patients, who are both at high risk of protein depletion and at risk of obesity (98). Recently, a 6-month multicenter, randomized clinical trial demonstrated the utility of a simple, personalized walking exercise program at home, managed by dialysis staff, in improving functional status in adult patients on dialysis. The main study outcomes included change in physical performance at 6 months assessed by the 6-minute walking test and the five times-sit-to-stand test and in quality of life (99).

In this setting, implementation of a regular physical activity could contribute to maintain muscle mass/strength/functionality and to increase energy expenditure. Achieving better

muscle functionality may in fact be a step toward improved physical functioning and reduction of frailty (100).

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Conflict of interest

There is no information to disclose

References

1. Philip Kam-Tao Li et al, Changes in the worldwide epidemiology of peritoneal dialysis, *Nature Reviews Nephrology*, Vol. 13, February 2017
2. Young GA, Kopple JD, Lindholm B, Vonesh EF, De Vecchi A, Scalamogna A, et al. Nutritional assessment of continuous ambulatory peritoneal dialysis patients: an international study. *Am J Kidney Dis*. 1991; 17:462-71.
3. Mehrotra R, Chiu YW, Kalantar-Zadeh K, Bargman J, Vonesh E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* 2011; 171:110-8.
4. Han SH, Han DS. Nutrition in patients on peritoneal dialysis. *Nat Rev Nephrol* 2012; 8:163-75.
5. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int*. 2008; 73:391-8.
6. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bemabei R et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013; 14: 392–397).
7. Kang SH, Cho KH, Park JW, Do JY. Low appendicular muscle mass is associated with mortality in peritoneal dialysis patients: a single-center cohort study. *Eur J Clin Nutr*. 2017 Jun 28.
8. Isoyama N, Qureshi AR, Avesani CM, Lindholm B, Bàràny P, Heimbürger O, Cederholm T, Stenvinkel P, Carrero JJ. Comparative associations of muscle mass and muscle strength with mortality in dialysis patients, *Clin J Am Soc Nephrol*, 2014 Oct 7;9(10):1720-8
9. Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimbürger O, Barany P, Suliman ME, Lindholm B, Stenvinkel P, Qureshi AR: Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin Nutr* 27: 557-564, 2008
10. Stenvinkel et al, Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol, Dial Transplant* 2000; 15(7): 953-960
11. Krediet RT, Zuyderhoudt FM, Boeschoten EW, Arisz L. Peritoneal permeability to proteins in diabetic and non-diabetic continuous ambulatory peritoneal dialysis patients. *Nephron* 1986; 42:133-40.
12. Westra WM, Kopple JD, Krediet RT, Appell M, Mehrotra R. Dietary protein requirements and dialysate protein losses in

- chronic peritoneal dialysis patients. *Perit Dial Int.* 2007; 27:192-5.
13. Morrison G. Metabolic effects of continuous ambulatory peritoneal dialysis. *Annu Rev Med* 1989; 40:163-72
 14. Kathuria, P. et al Effect of dialysis modality and membrane transport characteristics on dialysate protein losses of patients on peritoneal dialysis. *Perit. Dial. Int.* 17, 449-454 (1997).
 15. Chung, S. H., Heimbürger, O. & Lindholm, B. Poor outcomes for fast transporters on PD: the rise and fall of a clinical concern. *Semin. Dial.* 21. 7-10 (2008)
 16. Balafa O, Halbesma N, Struijk DG, Dekker FW, Krediet RT. Peritoneal albumin and protein losses do not predict outcome in peritoneal dialysis patients. *Clin J Am Soc Nephrol* 2011; 6:561–6.
 17. Grodstein GP, Blumenkrantz MJ, Kopple JD, Moran JK, Coburn JW. Glucose absorption during continuous ambulatory peritoneal dialysis. *Kidney Int.* 1981;19(4):564-567
 18. Davies SJ, Russell L, Bryan J, Phillips L, Russell GI. Impact of peritoneal absorption of glucose on appetite, protein catabolism and survival in CAPD patients. *Clin. Nephrol.* 1996;45(3): 194-198
 19. Abbott KC, Oliver DK, Hurst FP, Das NP, Gao SW, Perkins RM. Body mass index and peritoneal dialysis: "exceptions to the exception" in reverse epidemiology? *Semin Dial.* 2007; 20:561-5.
 20. Chung SH, Carrero JJ, Lindholm B. Causes of poor appetite in patients on peritoneal dialysis. *J Ren Nutr* 2011; 21:12-5.
 21. Ross EA, Koo LC. Improved nutrition after the detection and treatment of occult gastroparesis in nondiabetic dialysis patients. *Am J Kidney Dis.* 1998 ; 31 (1): 62-66
 22. Schoonjans R, Van Vlem B, Vandamme W, et al. Gastric emptying of solids in cirrhotic and peritoneal dialysis patients: influence of peritoneal volume load. *Eur J Gastroenterol Hepatol.* 2002; 14(4): 395-398
 23. Van V, Schoonjans RS, Struijk DG, et al. Influence of dialysate on gastric emptying time in peritoneal dialysis patients. *Perit. Dial. Int.* 2002; 22(1): 32-38
 24. Lee SW, Song JH, Kim GA, Yang HJ, Lee KJ, Kim MJ. Effect of dialysis modalities on gastric myoelectrical activity in end-stage renal disease patients. *Am J Kidney Dis.* 2000; 36(3): 566-573
 25. Rodríguez-Carmona A, Pérez-Fontán M, Guitián A, Peteiro J, García-Falcón T, López-Muñiz A, et al. Effect of low-GDP bicarbonate-lactate-buffered peritoneal dialysis solutions on plasma levels of adipokines and gut appetite-regulatory peptides. A randomized crossover study. *Nephrol Dial Transpl.* 2012; 27:369-74.
 26. Wang XH, Mitch WE, Mechanisms of muscle wasting in chronic kidney disease. *Nat Rev Nephrol.* 2014 Sep;10(9):504-16.
 27. Bailey JL, Zheng B, Hu Z, Price SR, Mitch WE. Chronic kidney disease causes defects in signalling through the insulin receptor substrate/phosphatidylinositol 3-kinase/Akt pathway: implications for muscle atrophy. *J Am Soc Nephrol.* 2006; 17:1388-94
 28. Zhang L, Rajan V, Lin E, Hu Z, Han HQ, Zhou X et al. Pharmacological inhibition of myostatin suppresses systemic inflammation and muscle atrophy in mice with chronic kidney disease. *FASEB J* 2011; 25:1653-63.
 29. Verzola D, Procopio V, Sofia A, Villaggio B, Tarroni A, Bonanni A et al. Apoptosis and myostatin mRNA are upregulated in the skeletal muscle of patients with chronic kidney disease. *Kidney Int* 2011; 79:773-82.
 30. Zhang L, Pan J, Dong Y, Tweardy DJ, Dong Y, Garibotto G, Mitch WE; Stat3

- activation links a C/EBP δ to myostatin pathway to stimulate loss of muscle mass. *Cell Metab.* 2013 Sep 3;18(3):368-79.
31. Ikizler TA, Wingard RL, Harvell J, Shyr Y, Hakim R. Association of morbidity with markers of nutrition and inflammation in chronic hemodialysis patients: A prospective study. *Kidney Int* 1999; 55:1945–51.
 32. Foley RN, Pafrey PS, Harnett JD, Kent GM, Murray DC. Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 1996; 7:728–36.
 33. Mehrotra R, Duong U, Jiwakanon S, Kovesdy CP, Moran J, Kopple JD, et al. Serum albumin as a predictor of mortality in peritoneal dialysis: comparisons with hemodialysis. *Am J Kidney Dis* 2011; 58:418-28.
 34. Prinsen BH, Rabelink TJ, Beutler JJ, Kaysen GA, De Boer J, Boer WH, et al. Increased albumin and fibrinogen synthesis rate in patients with chronic renal failure. *Kidney Int.* 2003; 64:1495-504.
 35. Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *AM J Kid Disease* 2000;35 (suppl 2): S1-140
 36. Kang J, Holland M, Jones H, Kaysen GA. Coordinate augmentation in expression of genes encoding transcription and liver secretory proteins in hypo-oncotic states. *Kidney Int* 1999; 56:454–60
 37. Tessari P. Protein metabolism in liver cirrhosis: from albumin to muscle myofibrils. *Curr Opin Clin Nutr Metab Care.* 2003 ;6:79-85.
 38. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor H. *The Biology of Human Starvation*, Minneapolis. University of Minnesota Press; Minneapolis, MN, USA: 1950.
 39. Rigaud D, Hassid J, Meulemans A, Poupard AT, Boulrier A. A paradoxical increase in resting energy expenditure in malnourished patients near death: the king penguin syndrome. *Am J Clin Nutr.* 2000;72:355-60.
 40. Kaysen GA. Biological basis of hypoalbuminemia in ESRD. *J Am Soc Nephrol* 1998; 9:2368-76.
 41. John B, Tan BK, Dainty S, Spanel P, Smith D, Davies SJ. Plasma volume, albumin, and fluid status in peritoneal dialysis patients. *Clin J Am Soc Nephrol.* 2010; 5:1463-70.
 42. Emerson TE. Unique features of albumin: A brief review. *Crit Care Med.* 1989;17:690–4.
 43. Bergstrom J. Nutrition and mortality in hemodialysis. *J Am Soc Nephrol* 1995; 6:1329–41.
 44. Yeun JY, Kaysen GA. Factors influencing serum albumin in dialysis patients. *Am J Kid Dis* 1998;32 Suppl 4:S 118-25
 45. A.Y. Wang, M.M. Sea, R. Ip, et al. Independent effects of residual renal function and dialysis adequacy on actual dietary protein, calorie, and other nutrient intake in patients on continuous ambulatory peritoneal dialysis, *J Am Soc Nephrol*, 12 (11) (2001), pp. 2450-2457
 46. Cheng, W. Tang, T. Wang; Strong association between volume status and nutritional status in peritoneal dialysis patients; *Am J Kidney Dis*, 45 (5) (2005)
 47. G. Garibotto, A. Sofia, S. Saffioti, A. Bonanni, I. Mannucci, D. Verzola Amino acid and protein metabolism in the human kidney and in patients with chronic kidney disease; *Clinical Nutrition* 2010 Aug;29(4): 424-433)
 48. P. Tessari, G. Deferrari, C. Robaudo, M. Vettore, N. Pastorino, L. De Biasi, G. Garibotto: Phenylalanine hydroxylation across the kidney in humans rapid

- communication, *Kidney Int.* 1999 Dec;56(6):2168-72
49. G. Garibotto, A. Sofia, M. Balbi, V. Procopio, B. Villaggio, A. Tarroni, M. Di Martino, V. Cappelli, M.T. Gandolfo, A. Valli, D. Verzola D; *Kidney and splanchnic handling of interleukin-6 in humans. Cytokine.* 2007 Jan;37(1):51-4.
50. G. Garibotto, D. Verzola, M. Vettore, Tessari P. The contribution of muscle, kidney and splanchnic tissues to leucine transamination in humans, *Can J Physiol Pharmacol*, 2017 Sep 11.
51. Jager KJ, Merkus MP, Huisman RM, Boeschoten EW, Dekker FW, Korevaar JC, et al. NECOSAD Study Group. Nutritional status over time in hemodialysis and peritoneal dialysis. *J Am Soc Nephrol.* 2001; 12:1272-9.
52. Lievens H, Kalantar-Zadeh K, Lukowsky LR, Molnar MZ, Duong U, Nissenson A, et al. Relationship of body size and initial dialysis modality on subsequent transplantation, mortality and weight gain of ESRD patients. *Nephrol Dial Transplant* 2012; May 2.
53. Garibotto G, Pastorino N, Dertenois L. Protein and amino acid metabolism in renal disease and in renal failure: in Kopple JD, Massry S (eds): *Nutritional management of renal diseases.* Baltimore, William & Wilkins, 2003.
54. Roberts JJ, Bier D, Schoeller D, Wolfe R, Matthews D, Munro HN, et al. Effects of intravenous glucose in whole body leucine dynamics, studied with 1-¹³-Leucine, in healthy young and elderly adults. *J Gerontol* 1984; 39:673 -81.
55. Castellino P, Luzi L, Giordano M, Defronzo RA. Effects of insulin and amino acids on glucose and leucine metabolism in CAPD patients. *J Am Soc Nephrol* 1999; 10:1050-8.
56. Garibotto G, Sofia A, Canepa A, Saffioti S, Sacco P, Sala M et al. Acute effects of peritoneal dialysis with dialysates containing dextrose or dextrose and amino acids on muscle protein turnover in patients with chronic renal failure. *J Am Soc Nephrol* 2001; 12:557-67.
57. Sofia A, Russo R, Saffioti S, Sacco P, Dertenois L, Pastorino N et al. Acute effects of peritoneal dialysis on muscle protein turnover. *G Ital Nefrol* 2002; 19: 37-43.
58. Lindeman RD. Overview: Renal physiology and pathophysiology of aging. *Am J Kidney Dis* 1990; 16:275-82.
59. Van Hoeck KJ, Rusthoven E, Vermeylen L, Vandesompel A, Marescau B, Lilien M, Schroder CH; Nutritional effects of increasing dialysis dose by adding an icodextrin daytime dwell to Nocturnal Intermittent Peritoneal Dialysis (NIPD) in children. *Nephrol Dial Transplant.* 2003 Jul;18(7):1383-7.
60. Garibotto G, Paoletti E, Fiorini F, Russo R, Robaudo C, Deferrari G, et al. Peripheral metabolism of branched-chain keto acids in patients with chronic renal failure. *Miner Electrolyte Metab* 1993; 19:25-31
61. Price SR, Reaich D, Marinovic AC, England BK, Bailey JL, Caban R et al. Mechanisms contributing to muscle-wasting in acute uremia: activation of amino acid catabolism. *J Am Soc Nephrol* 1998; 9:439-43
62. Chen Y, Sood S, McIntire K, Roth R, Rabkin R. Leucine-stimulated mTOR signaling is partly attenuated in skeletal muscle of chronically uremic rats. *Am J Physiol Endocrinol Metab.* 2011;301:E873-81
63. Oren A, Wu G, Anderson GH, Marliss E, Khanna R, Pettitt J, et al. Effective use of amino acid dialysate over four weeks in

- CAPD patients. *Perit Dial Bull* 1983; 3: 66-73.
64. Jones M, Hagen T, Boyle CA, Vonesh E, Hamburger R, Charytan C, et al. Treatment of malnutrition with 1.1% amino acid peritoneal dialysis solution: results of a multicenter outpatient study. *Am J Kidney Dis* 1998; 32:781-9.
65. McCormick BB, Mujais S, Poirer F, Page N, Lavoie S, et al. Metabolic effects of incremental doses of intraperitoneal amino acids on automated peritoneal dialysis. *Perit Dial Int* 2010; 30: 201-7.
66. Asola M, Virtanen K, Nagren K, Helin S, Taittonen M, Kastarinen H, et al. Amino-acid based peritoneal dialysis solution improves amino acid transport into skeletal muscle. *Kidney Int Suppl* 2008; 108:S131-36.
67. Tjiong HL, van den Berg JW, Wattimena JL, Rietveld T, van Dijk LJ, van der Wiel AM et al. Dialysate as food: combined amino acid and glucose dialysate improves preprotein anabolism in renal failure patients on automated peritoneal dialysis. *J Am Soc Nephrol* 2005; 16:1486-93.
68. Boirie Y, Gachon P, Cordat N, Ritz P, Beaufrère B. Differential insulin sensitivities of glucose, amino acid, and albumin metabolism in elderly men and women. *J Clin Endocrinol Metab* 2001; 86:638-44.
69. Wang AY, Sea MM, Tang N, Lam CW, Chan IH, Lui SF et al. Energy intake and expenditure profile in chronic peritoneal dialysis patients complicated with circulatory congestion. *Am J Clin Nutr* 2009; 90:1179-84.
70. Dei Cas A, Muoio A, Zavaroni I. Chronic heart failure and cachexia: role of endocrine system. *Minerva Cardioangiol* 2011; 59:601-12.
71. Sharma R, Anker SD. Cytokines, apoptosis and cachexia: the potential for TNF antagonism. *Int J Cardiol* 2002; 85:161-71.
72. Elkina Y, von Haehling S, Anker SD, Springer J. The role of myostatin in muscle wasting: an overview. *J Cachexia Sarcopenia Muscle*. 2011; 2:143-51.
73. Sartori R, Milan G, Patron M, Mammucari C, Blaauw B, Abraham R et al. Smad2 and 3 transcription factors control muscle mass in adulthood. *Am J Physiol Cell Physiol* 2009; 296:C1248-57.
74. Wong KE, Szeto FL, Zhang W, Ye H, Kong J, Zhang Z, et al. Involvement of the vitamin D receptor in energy metabolism: regulation of uncoupling proteins. *Am J Physiol Endocrinol Metab* 2009; 296:E820-8.
75. Pilz S, Iodice S, Zittermann A, Grant WB, Gandini S. Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. *Am J Kidney Dis* 2011;58:374-82.
76. Taskapan H, Baysal O, Karahan D, Durmus B, Altay Z, Ulutas O. Vitamin D and muscle strength, functional ability and balance in peritoneal dialysis patients with vitamin D deficiency. *Clin Nephrol* 2011; 76:110-6.
77. Mirchi, E. et Al. Association between 25-Hydroxyvitamin D level and inflammatory and nutritional factors in hemodialysis and peritoneal dialysis patients in Qom, Iran, *Int Jour of Kidney Diseases*, 2016; 10:205-12
78. Kandula P, Dobre M, Schold JD, Schreiber MJ, Mehrotra JR, Navaneethan SD. Vitamin D Supplementation in Chronic Kidney Disease: A Systematic Review and Meta-Analysis of Observational Studies and Randomized Controlled Trials. *Clin J Am Soc Nephrol*. 2011; 6:50-62.
79. Kendrick J, Andrews E, You , Moreau K, Nowak KL, Farmer-Bailey H, Seals DR, Chonchol M; Cholecalciferol, Calcitriol, and Vascular Function in CKD: A

- Randomized, Double-Blind Trial, *Clin J Am Soc Nephrol*. 2017 Sep 7;12(9):1438-1446.
80. Zhang L, Rajan V, Lin E, Hu Z, Han HQ, Zhou X et al. Pharmacological inhibition of myostatin suppresses systemic inflammation and muscle atrophy in mice with chronic kidney disease. *FASEB J* 2011; 25:1653-63.
81. Garcia LA, King KK; Ferrini MG, Norris KC, Artaza JN (2011) 1,25 (OH)₂ vitamin D₃ stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells. *Endocrinology* 152: 2976-2986
82. Taskapan H, Baysal O, Karahan D, Durmus B, Altay Z, Ulutas O. Vitamin D and muscle strength, functional ability and balance in peritoneal dialysis patients with vitamin D deficiency; *Clin Nephrol*. 2011 Aug;76(2):110-6
83. Girgis CM, Cha KM, Houweling PJ, Rao R, Mokbel N, Lin M, Clifton-Bligh RJ, Gunton JE (2015) Vitamin D receptor ablation and vitamin D deficiency result in reduced grip strength, altered muscle fibers, and increased myostatin in mice. *Calcif Tissue Int* 97:602-610
84. Satirapoj B, et al. Nutritional status among peritoneal dialysis patients after oral supplement with ONCE dialyze formula. *International Journal of Nephrology and Renovascular disease*. 2017;10 145-151
85. Cheng LT, Tang W, Wang T, Strong association between volume status in peritoneal dialysis patients. *Am J Kidney Dis*. 2005;45(5):891-902
86. Aguilera A, Codoceo R, Selgas RR, Selgas R et al. Anorexigenic (TNF- α , cholecystokinin) and orexigen (neuropeptide Y) plasma levels in peritoneal dialysis (PD) patients: Their relationship with nutritional parameters. *Nephrol Dial Transplant*. Jun 1998; 13(6):1476-1483.
87. Fantino M, Wieteska L. Evidence for a direct central anorectic effect of tumor-necrosis-factor- α in the rat. *Physiology and Behavior*, 1993 Mar; 53(3): 477-483
88. Kirchgessner TG, Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Tumor necrosis factor α contributes to obesity-related hyperleptinemia by regulating leptin release from adipocytes. *The Journal of Clinical Investigation*, 1997 Dec 1;100 (11); 2777-2782
89. Mitch WE Malnutrition: A frequent misdiagnosis for hemodialysis patients. *J Clin Invest*. 2002; 110(4):437-439
90. Mitch WE, Goldberg AI, Mechanism of muscle wasting. The role of ubiquitin-proteasome pathway. *N Engl J Med* 1996; 335(25): 1897-1905.
91. Chung SH, Heimbürger O, Stenvinkel P, Wang T, Lindholm B. Influence of peritoneal transport rate, inflammation and fluid removal on nutritional status and clinical outcome in prevalent peritoneal dialysis patients. *Perit. Dial. Int.* 2003;23(2): 174-183
92. Wei Lin, Yung-Chih Chen, Mai-Szu Wu, Heng-Jung Hsu, Chiao-Yin Sun, Ying-Kuang Lin & I-Wen Wu, Icodextrin dialysate improves nutritional and inflammatory profiles in peritoneal dialysis patients, *Renal Failure*, 2009, 31:2, 98-105
93. Opatrna S, Racek J, Stehlik P et al. Effect of a dialysis solution with icodextrin on ultrafiltration and selected metabolic parameters in patients treated with peritoneal dialysis. *Cas. Lek. Cesk.* 200;141(9) 281-285
94. De Moraes TP, Andreoli MC, Canziani ME, da Silva DR, Caramori JC, Ponce D, Cassi HV, de Andrade Bastos K, Rio DR, Pinto SW, Filho SR, de Campos LG,

- Olandoski M, Divino-Filho JC, Pecoits-Filho R, Icodextrin reduces insulin resistance in non-diabetic patients undergoing automated peritoneal dialysis: results of a randomized controlled trial (STARCH), *Nephrol Dial Transplant* 2015, 30: 1905-1911
95. Lee SW, Park GH, Song JH, Hong KC, Kim MJ Insulin resistance and muscle wasting in non diabetic end-stage renal disease patients. *Nephrol Dial Transplant*. 2007, 22, 2554-2562
96. Cupisti A, D'Alessandro C, Finato V, Del Corso C, Catania B, Caselli GM, Egidi MF, Assessment of physical activity, capacity and nutritional status in elderly peritoneal dialysis patients, *BMC Nephrology* 18:180, 2017, May 30.
97. Cobo G, Gallar P, Gama Axelsson T, Di Gioia C, Qureshi AR, Camacho R et al, Clinical determinants of reduced physical activity in hemodialysis and peritoneal dialysis patients. *J Nephrol*. 2015; 28-503-510
98. Tennankore KK, Bergman JM. Nutrition and the kidney: recommendations for peritoneal dialysis *Adv Chronic Kidney Dis*. 2013;20:190-201
99. Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R et al, Exercise in patients on dialysis: A Multicenter, Randomized Clinical Trial, *J Am Soc Nephrol* 28 1259-1268, 2017
100. Johansen KL, Chertow GM, Jin C, Kutner NG: Significance of frailty among dialysis patients. *J Am Soc Nephrol* 18:2960-2967,2007