Nutritional Considerations for the Dialytic Patient

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KEYWORDS

• Nutrition • Dialysis • Malnutrition • Protein

There are numerous causes of protein energy malnutrition.[1–10] The simplest and most apparent cause is inadequate dietary intake mainly because of anorexia secondary to uremic toxicity and anorexigenic effects of concurrent disease.[4,11] Dietary intake is also compromised by nausea and vomiting, which can often occur at the onset of the dialytic treatment, especially if the flow rates are rapidly increased. Concurrent diseases and endocrine abnormalities, including insulin resistance, hyperglucagonemia, and hyperparathyroidism, can also contribute to a catabolic state.[12,13] The kidney is also an important metabolic organ that synthesizes some amino acids (cysteine, tyrosine, arginine, serine).[14] It is possible that the loss of these activities in kidney failure can also promote wasting.

In addition to the removal of uremic toxins, the dialytic process is also associated with the removal of free amino acids, peptides or bound amino acids, and water-soluble vitamins, each of which can contribute to wasting.[15–18] Total dialysate amino acid losses of 6 to 13 g per hemodialysis session have been reported in human patients (0.09–0.17 g/kg body weight [BW]).[16,18–20] Dialysate total amino acid loss in healthy dogs has been reported to be 0.12 g/kg BW.[21] This loss can be even higher in peritoneal dialytic patients who develop peritonitis. Losses of glucose can also occur if glucose-free dialysate is used.

Sustained blood loss is an unavoidable consequence of advanced renal disease and hemodialysis. Blood loss is associated with frequent blood drawing for laboratory testing, occult gastrointestinal bleeding secondary to the uremic syndrome, and the sequestration of blood in the hemodialyzer and dialytic tubing. Blood is a rich source of protein; hence, these losses can contribute to protein deficiency and muscle wasting. Furthermore, anemia can contribute to apathy, lethargy, and reduced food intake, further compounding the wasting syndrome. Therefore, the veterinary care team should be conscientious and make every attempt to minimize unnecessary or excessive blood withdrawals.

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Dialytic patients also have increased catabolism from the chronic inflammatory state of uremia, exposure to the extracorporeal circuit (hemodialyzer membranes, tubing, and catheters), or impure dialysate.[22] Hemodialysis activates the complement cascade, triggering the release of catabolic cytokines and acute-phase proteins.[22–28] Activation of these inflammatory mediators as a consequence of the hemodialysis procedure per se has adverse catabolic effects on protein metabolism. An enhanced release of amino acids from skeletal muscle has been reported with sham hemodialysis (ie; in vivo passage of blood through a hemodialyzer but without circulating dialysate) in normal humans.[23,24] In addition, increased plasma concentrations of 3-methylhistidine in sham hemodialytic normal humans demonstrated the importance of increased protein breakdown in the net catabolic process induced by blood-membrane contact.[24] Inflammation may contribute or cause malnutrition because both tumor necrosis factor alpha and interleukin 6 are anorexigens.[29,30] This muscle breakdown can be further aggravated by acidemia.[31,32]

Protein energy malnutrition and chronic inflammation are significant overlapping factors that influence morbidity and mortality.[22,33] Given the significant association of malnutrition with morbidity and mortality, it is clear that every effort must be made to identify those patients at risk and implement proactive nutritional therapies designed to minimize or reverse these complications.

NUTRITIONAL ASSESSMENT

Repeated frequent assessments of the nutritional status of the patient receiving dialytic therapy are extremely important for the timely recognition of nutritional deficiencies. Early proactive nutritional intervention may be able to prevent or improve malnutrition in these patients. In humans, the protein energy nutritional status at the start of chronic dialysis treatment is a good predictor of longevity. Therefore, there is strong impetus to make every effort to maintain or improve nutritional intake during treatment.

Nutritional assessment uses information contained in the history taking, physical examination, and laboratory data to screen for early indicators of malnutrition. All of this information should be clearly documented in the medical record. Indeed, the problem-oriented approach Subjective, Objective, Assessment, Plan (SOAP) should be used for nutritional support to ensure that all metabolic and nutritional problems of patients are assessed and planned for. Accurate documentation facilitates communication between the various members of the veterinary care team and strengthens the importance of nutrition in the overall care of the patient. The importance of clear documentation is exemplified by the study of 276 critically ill dogs in which a negative energy balance occurred in 73% of the hospitalization days.[34] The negative energy balance was attributed to poorly written orders in 22% of cases.

The dietary record should detail the exact amount of food that the patient is consuming, rather than the amount of food that a patient has been offered. If the patient is not consuming food, then the duration of inappetence or anorexia should be recorded. If the patient is consuming food, the name, manufacturer, type (dry, wet, semimoist), amount fed each day (cans or standard 237-mL cups), frequency of food intake, and method of feeding (ad libitum vs meal feeding) should be recorded. The number and type of snacks or human foods that are offered each day and the potential access to other pets' food should be determined. The history should also be explored to fully understand when the current diet was implemented and any changes in the diet or dietary intake, which have recently occurred. The incidence of vomiting and/or diarrhea should be noted, and any additional factors that can affect

the nutritional plan, such as cardiovascular instability; concurrent diseases; fluid, electrolyte, or acid-base imbalance; or metabolic abnormalities, such as hyperglycemia or hypertriglyceridemia, should be recorded.

The BW should be included in the examination of every patient, and for hospitalized patients, it should be recorded daily. BW provides a rough measure of total body energy stores, and changes in BW typically parallel energy and protein balance. In the healthy animal, BW varies little from day to day. However, additional challenges arise in the dialytic patient because BW can be falsely altered by dehydration or fluid accumulation. Therefore, the BW should be interpreted in conjunction with the body condition score (BCS) and muscle cachexia score.

The BCS focuses on the assessment of body fat. The 2 most commonly used scoring systems in small animal practice are a 5-point system in which a BCS of 3 is considered ideal or a 9-point system in which a BCS of 5 is considered ideal. The muscle cachexia score evaluates the loss of metabolically active lean body mass. The initial loss of lean body mass can be subtle and is usually first noted in the epaxial, gluteal, scapular, or temporal muscles. Using a subjective cachexia scoring system facilitates the identification of those patients either with cachexia or at risk of impending cachexia.[35]

Bioelectrical impedance analysis (BIA) is an electrical method of assessing body composition, which has the potential of quantifying total body water, fluid volumes, body cell mass, and fat-free mass. Body cell mass approximates the metabolically active lean body tissue. Hence, BIA may be used to provide instantaneous information of body composition.[36,37]

Biochemical indicators of malnutrition include hypoalbuminemia, decreased blood urea nitrogen, hypocholesterolemia, anemia, and lymphopenia. However, alterations of these common laboratory indicators are not specific for malnutrition and are often indistinguishable from those that can occur with concurrent disease.

The historical data on BW change, dietary intake, gastrointestinal symptoms influencing oral intake/absorption, and physical examination are used collectively to categorize the patient as appropriately nourished, mildly malnourished or suspected of being malnourished, or severely malnourished. Nutritional assessment is not used to determine who should be fed and who should not. Rather it is used to determine how much food and what types of nutrient alterations are required and the most effective way of feeding the patient. If the patient is not voluntarily consuming adequate nutrition, intervention in the form of enteral or parenteral nutrition is required. Regardless of the method of nutritional support selected, it is imperative to reassess the effect of the support, making nutritional assessment a routine and cyclical process.

METHODS OF ADMINISTRATION

The simplest and most obvious way to provide nutrition is to offer food to be consumed orally. However, patients with severe kidney disease often have reduced appetites, have an altered sense of taste or smell, or are anorexic. There are multiple possible causative factors that contribute to anorexia. Dialysis can effectively reduce the blood concentration of some of the uremic toxins that contribute to anorexia, and it is clear that a patient seems to feel better and eats willingly at the cessation of a dialytic session. However, despite effective clearance of many metabolic products of uremia, additional metabolic disorders that can contribute to anorexia (eg, chronic inflammatory conditions, anemia) persist. Furthermore, dialytic patients often require multipharmacologic agents to help manage the consequences of kidney disease. Anorexia is

a potentially significant side effect of some of these drugs. All of these factors in combination contribute to reduced caloric intake and refusal of diet.

Practical measures to improve intake include the use of highly odorous foods, warming the food before feeding, and stimulating eating by positive reinforcement with petting and stroking behavior. The total daily caloric intake can be divided into several smaller meals per day. It is important that fresh food should be offered at each meal, and the amount that the pet does not eat should be removed and discarded. Appetite stimulants can be considered but are typically not an effective solution to continually ensure adequate caloric intake. Enteral tube feeding or parenteral nutritional therapy should be implemented for patients reluctant to eat appropriate amounts of food ad libitum.

Enteral feeding, facilitated by the placement of nasoesophageal, esophagostomy, or gastrostomy tube, is recommended in all patients who can tolerate them because enteral feeding helps to maintain the gastrointestinal barrier and prevent the translocation of bacteria and systemic infections.[38] Enteral feeding of caloric veterinary renal diets blended with water or using specifically formulated liquid diets should be used. The amount of water to liquefy the commercial diet together with the volumes used for flushing the enteral feeding device should be closely monitored. Dialytic patients are often fluid intolerant. In cases with extreme fluid intolerance, the amount of water used to liquefy the diet can be replaced with a commercial liquid preparation. This unique situation requires the assistance of a board-certified veterinary nutritionist to ensure that the nutritional requirements of the pet are met by the combination of 2 commercial formulations.

The feeding solution can be administered intermittently in a meal-type pattern or, for hospitalized patients, by continuously using a syringe pump. Several enteral renal formulations have been specifically developed for human use; however, these formulations should be closely evaluated before administration to dogs or cats to ensure that they contain adequate amounts of protein; amino acids, such as taurine and arginine; and arachidonic acid (cats). Enteral feeding via gastrostomy tube has been shown to be an effective way to manage dogs with kidney disease.[39]

Parenteral nutrition is indicated for patients with severe gastrointestinal or neurologic dysfunction that precludes the use of the enteral route to meet the nutrient requirements. In addition, the patient must be able to tolerate the additional fluid load.[40] Parenteral nutrition is largely divided into partial parenteral nutrition (PPN) or total parenteral nutrition (TPN). TPN refers to the provision of the daily caloric requirement and essential nutrients and is typically formulated using 50% dextrose, 8.5% amino acids with electrolytes, and 20% intralipid. Consequently, the solution is hyperosmolar and requires administration into a central vein, such as the cranial vena cava. Historically, a dedicated central catheter has been recommended for parenteral nutrition. Clearly, this recommendation is not a viable option for patients with an indwelling hemodialysis vascular access catheter. One port of the hemodialysis access catheter can be used to administer the TPN solution; however, this option is far from ideal and increases the likelihood of thrombosis or infection of the vascular access, critical complications that minimize the effectiveness of hemodialysis and are life threatening for the patient.

PPN involves the administration of isotonic nutritional solutions through a peripheral vein, thereby avoiding the requirement of a central vein necessary for TPN. However, PPN cannot provide the complete nutritional requirements for a patient because the solution is required to be isotonic to avoid thrombophlebitis. A PPN solution is typically formulated with a combination of 5% dextrose, 8.5% amino acids (without electrolytes), and 20% intralipid to provide approximately 50% of the resting energy

requirement (RER). The osmolality of the final solution should be in the range of 300 to 600 mOsm/kg to prevent thrombophlebitis. Therefore, PPN should only be used as an adjunct to supplement oral intake or to supply partial temporary nutritional support in animals that are expected to return to normal oral intake in less than 5 days and that can also tolerate the additional fluid burden of the PPN solution.

PPN products are expensive and require strict aseptic formulation, administration, and special monitoring procedures to avoid sepsis and metabolic complications. Modified amino acid formulations for human patients with acute renal failure are available. These preparations have been formulated on the hypothesis that endogenous urea could be use to synthesize nonessential amino acids. However, it is not clear that these specialized formulations are any more effective than traditional amino acid formulations.

There are 2 additional methods that can be considered to provide partial nutritional support and complement enteral feeding. Amino acids and additional glucose can be added to the dialysate fluid, from where they diffuse into the body during the dialytic procedure.[41] Alternatively, supplemental amino acids, glucose, and/or lipids can be infused during the hemodialysis procedure.[42] With this intradialytic form of nutrition, the nutrient solutions are added to the "venous" side of the extracorporeal circuit as the blood leaves the hemodialyzer. This process may also help to minimize the decrease in the circulating amino acid pool as a result of the dialytic process (see the section Protein). The benefits of intradialytic nutrition in human patients are controversial. Intradialytic parenteral nutrition has been shown to improve markers of nutritional status, such as plasma protein concentrations and anthropometric measurements.[43] However, it is not yet clear if intradialytic parenteral nutrition has a significant effect on morbidity or mortality.[42,44,45] Furthermore, intradialytic nutrition has not been reported in canine or feline patients receiving dialysis.

ENERGY

Monitoring caloric intake is vital because consuming too few calories compromises nitrogen balance and causes loss of lean body mass. Studies in human dialytic patients indicate that dietary energy intakes and body fat are low.[46,47] The energy requirements of canine or feline dialytic patients are unknown. The energy expenditure of an individual patient may be assessed by indirect calorimetry; however, this technique is not widely available in veterinary hospitals.[48] For patients with acute kidney injury, provision of the RER ($70 \times [\text{weight in kilogram}]^{0.75}$) is logical. In such critically ill patients, there is little advantage to providing excess calories because energy metabolism can promote hypercapnia, especially if pulmonary function is impaired.

The amount of energy to provide to the patient with CKD who is receiving dialysis should approach the maintenance energy requirements (canine, $132 \times [\text{BW in kilogram}]^{0.67}$; feline, $50 \times$ BW in kilogram). However, energy requirements vary widely, and hence the energy intake needs to be adjusted according to individual patient needs based on serial nutritional assessment. Carbohydrate and fat provide the nonprotein sources of energy in the diet. Diets designed for the management of renal failure are usually formulated with a relatively high fat content because fat provides approximately twice the energy per gram than carbohydrate and increases palatability and energy density of the diet, which allows the patient to obtain nutritional requirements from a relatively smaller volume of food. The reduction in feeding volume with high–energy density diets can help minimize nausea and vomiting secondary to gastric distension.

PROTEIN

Adequate amounts of dietary protein must be provided to the dialytic patient to prevent protein malnutrition, and yet, excessive amounts of dietary protein must be avoided because the accumulation of protein metabolites derived from excessive dietary protein exacerbates uremia. Ideally, protein intake should be matched with catabolism to promote a positive nitrogen balance. However, the measurement of total nitrogen output (TNO) to determine nitrogen balance is not practical for clinical use.

The urea nitrogen appearance rate (UNA) can be used to estimate TNO, and an estimation of nitrogen balance can be determined when the nitrogen intake is known.[49,50] The UNA refers to the amount of urea that appears in body fluids and all body outputs, including urine, dialysate, draining tracts, and diarrhea, and is calculated as follows:

$$\text{UNA (g/d)} = \text{urinary urea nitrogen (g/d)} + \text{change in body urea nitrogen (g/d)} + \text{dialysate urea nitrogen (g/d)}$$

$$\text{Change in body urea nitrogen (g/d)} = (BUN_f - BUN_i\ \text{g/L/d}) \times BW_i\ (\text{kg}) \times 0.6\ \text{L/kg} + (BW_f - BW_i\ \text{kg/d}) \times BUN_f\ (\text{g/L}) \times 1.0\ \text{L/kg}$$

where i and f are the initial and final values for the period of measurement; BUN is the blood urea nitrogen; BW is expressed in kilograms; 0.6 is an estimate of the fraction of body water, which is water; and 1.0 is the fractional distribution of urea in the weight that is gained or lost (ie, 100%).

The UNA is highly correlated with the total urinary nitrogen content in hospitalized, critically ill dogs. The relationship between UNA and TNO is described as TNO = (1.3 × UNA) + 1.3.[50] When both the nitrogen intake and the UNA are known, nitrogen balance can be estimated from the difference between the nitrogen intake and TNO calculated from the UNA.[51] Non–urea nitrogen losses can be estimated as 0.031 g of nitrogen/kg/d. Extensive nitrogen losses that may occur with severe diarrhea, exudative lesions, or peritonitis need to be accounted in the calculation of TNO. The UNA provides a simple and an inexpensive and accurate measurement of net protein breakdown and usually correlates closely with TNO. To calculate the dietary protein intake (g/d), the TNO is multiplied by 6.25.

The UNA can also be calculated in patients receiving hemodialysis by urea kinetic modeling. Central to this has been the concept of Kt/V, which describes the dose of dialysis as the hemodialyzer clearance of urea (K) times the duration of dialysis (t) divided by the urea distribution volume (V). Sargent and colleagues[51] described Kt/V as calculated from predialysis and postdialysis BUN and the next predialysis BUN through urea kinetic modeling, a mathematical description of the generation and removal of urea from patients undergoing hemodialysis. This approach has been modified by Daugirdas[52] to a formula, which uses predialysis and postdialysis BUNs, predialysis and postdialysis BWs, and the duration of dialysis to calculate single- or double-pool Kt/V.

Nitrogen balance studies in humans suggest that the average protein intake necessary to maintain nitrogen balance in hemodialytic patients is 1.0 to 1.1 g protein/kg BW/d and 1.05 to 1.20 g protein/kg BW/d in chronic peritoneal dialytic patients.[53] These protein requirements are approximately 30% higher than the recommended daily allowance for healthy adult humans and are designed to compensate for substrate loss during dialytic therapy.[54] Although the optimal dietary protein requirements for cats and dogs undergoing dialysis therapy are not known, it is clear from human medicine that canine and feline patients need more that the minimal protein requirements for healthy pets (the National Research Council [NRC] canine minimal

requirement, 2.62 g/kg $BW^{0.67}$; the NRC feline adult minimal requirement, 3.97 g/kg $BW^{0.67}$); 25% to 30% seems a reasonable estimate.[55] This level clearly needs to be adjusted based on consecutive nutritional assessment to minimize excesses in azotemia while simultaneously avoiding protein malnutrition.

High-quality protein sources must be used in the formulation of restricted protein diets to minimize the risks of essential amino acid deficiency. Additional supplementation of taurine should be considered for both canine and feline patients. Although not reported in canine or feline patients, serum and tissue levels of taurine are often low in humans receiving dialysis. Furthermore, studies in healthy adult dogs report significant reductions in plasma taurine concentration during the hemodialysis period, and an average of 47 mg of taurine appeared in the dialysate over a 3-hour treatment period.[21] Although these losses may be insignificant to a healthy adult animal, the potential risk of development of dilated cardiomyopathy secondary to taurine deficiency is a complication that the dialytic patient cannot afford.

VITAMINS, MINERALS, ACID-BASE BALANCE

Virtually all dialytic patients may require restriction of sodium, potassium, and phosphorus. Calcium and magnesium intakes need to be adjusted according to the levels in the dialysate and nutritional intake to maintain the concentrations within the reference range. There is minimal information available on the trace element requirements for the dialytic patient. Clearly, iron supplementation is necessary to complement erythropoietin therapy.

Dietary restriction of phosphate is necessary to control blood phosphate concentrations and the subsequent consequences of hyperphosphatemia and secondary hyperparathyroidism. However, dietary restriction alone is unlikely to adequately maintain blood phosphorus concentrations. Most, if not all, dialytic patients require the addition of phosphate binders to the diet.

The requirements for sodium and water must be managed for each patient individually. Those patients with oliguria/anuria require extreme sodium and water restriction to minimize overhydration and its attendant consequences. Patients receiving peritoneal dialysis can typically tolerate more normal sodium and water intakes because salt and water are removed daily by the hypertonic dialysate. Adequate or mildly increased sodium and water intakes in the patients receiving peritoneal dialysis may facilitate the clearance of small molecules into the dialysate.

The kidney is the major route of excretion of potassium. The patient with renal failure who is receiving dialysis is more likely to develop hyperkalemia as a result of a combination of dietary intake, acidosis, oliguria, hyperaldosteronism secondary to decreased renin secretion by the diseased kidney, and concurrent pharmacologic agents, such as angiotensin-converting enzyme inhibitors. Therefore, the dietary potassium intake needs to be modified for each patient to maintain normokalemia.

Deficiencies of water-soluble vitamins are likely because of the combination of poor food intake and the loss of vitamins during the dialysis treatment. B vitamins are critical for many energy-generating reactions in the body, and vitamin B deficiencies may be a contributing cause of anorexia. Therefore, prevention or replacement of the losses may be beneficial in correcting or preventing anorexia. Commercially available renal failure diets contain additional amounts of water-soluble vitamins, and further supplementation may not be required. If, however, a home-prepared diet is formulated, it may be prudent to additionally provide a B-complex vitamin supplement to ensure adequate daily intake. Supplementation with vitamin A is not recommended because serum retinol–binding protein and vitamin A are increased in CKD.[56]

Metabolic acidosis increases net protein degradation and is associated with the symptoms of lethargy and weakness.[32,57] Protein restriction lessens acidosis by decreasing the endogenous generations of acidic products of protein metabolism. The dialysate is also formulated to assist normalization of acid-base balance predominately by the provision of bicarbonate; however, additional alkali therapy may be needed to maintain a bicarbonate concentration higher than 18 mmol/L.

ADDITIONAL NUTRIENTS OF INTEREST

Dialysis is associated with the production of acute-phase proteins, oxidants, reactive carbonyl compounds, and proinflammatory cytokines that are toxic to the endothelium. These factors can be involved in some of the adverse cardiovascular and cerebral events that can occur in humans on dialysis.[22] Oxidative stress is also particularly significant in patients with acute kidney injury. Decreased plasma concentrations of antioxidant vitamins have been reported in dialytic patients compared with healthy humans, with loss of vitamins A, E, and C into the ultrafiltrate. It seems prudent to provide an antioxidant-enriched diet to maintain normal antioxidant status.[58] Although antioxidant stress has not been evaluated in canine and feline patients receiving dialysis, it is clear that antioxidant status is reduced in cats with CKD, antioxidant supplementation reduces markers of DNA damage in cats with stage II/III CKD, and antioxidant status improves glomerular filtration rate in dogs with surgically induced renal mass reduction.[59–61] Therefore, it is logical that dietary antioxidants can be beneficial to dogs and cats receiving dialysis treatments. The most effective levels and synergistic combinations remain to be determined.

L-Carnitine is a quaternary amine that facilitates the transfer of long-chain fatty acids into the mitochondria for energy generation. Serum-free carnitine concentrations and skeletal carnitine concentrations have been reported to be decreased in human dialytic patients and the concentration of serum acylcarnitines is increased.[62] The reduction in carnitine concentrations is most likely the result of losses into the ultrafiltrate, reduced dietary intake, and perhaps reduced synthesis as a consequence of protein malnutrition (L-carnitine is synthesized from the amino acids lysine and methionine).[63,64] Carnitine supplementation is recommended for humans with clinical symptoms or dialysis complications, including intradialytic arrhythmias and hypotension, low cardiac output, interdialytic and postdialytic symptoms of malaise or asthenia, general weakness or fatigue, skeletal muscle cramps, and decreased exercise capacity or low peak oxygen consumption.[53,65,66] Carnitine supplementation has also been recommended for refractory anemia for which no other apparent cause can be determined.

PHARMACOLOGIC STRATEGIES TO PROMOTE ANABOLISM

It is often difficult to overcome the catabolic state of advanced uremia and achieve positive nitrogen balance with nutritional support alone. Therefore, recent interest has focused on evaluating pharmacologic strategies to promote anabolism in human patients receiving dialysis. Metabolic interventions, including the administration of insulin, anabolic steroids, growth hormone, thyroid hormone, antiglucocorticoids, insulin-like growth factor 1, epidermal growth factor, β hepatocyte growth factor, β2 adrenergic agonists, intracellular proteolytic pathway inhibitors, adenine nucleotides, to facilitate the anabolic process and reduce protein degradation are currently being evaluated as nutritional adjunctives in human medicine.[67,68] Although some of these agents seem promising, improvements in morbidity and mortality in humans have

not yet been reported. The efficacy of these interventions in canine and feline patients remains to be seen.

SUMMARY

Although there is a paucity of the literature available on the nutritional requirements of the canine or feline patient receiving dialysis treatments, there is a wealth of information available in human medicine. These studies provide valuable insight, and logical recommendations can be obtained as long as the human data and recommendations are always interpreted in the light of the true, and often unique, nutritional requirements of the dog and cat. It is clear that nutritional intervention must be implemented for patients receiving dialysis. Malnutrition must be prevented. Nutritional therapy must be continually adjusted based on frequent nutritional assessments.

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