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AMINO ACID DEFICITS IN FELINE CHRONIC KIDNEY DISEASE: CAUSES AND SOLUTIONS

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INTRODUCTION

Chronic kidney disease (CKD) poses a significant challenge in the realm of veterinary medicine, particularly in cats given its commonality in this species. Among the various metabolic disturbances associated with CKD, deficits in amino acids and dysmetabolism play a crucial role in the progression and management of the disease in people. Emerging evidence in veterinary medicine shows that cats with CKD have altered amino acid profiles with significant deficits in essential amino acids. Understanding the intricate interplay between amino acid metabolism and renal function is paramount for developing effective therapeutic strategies to mitigate the clinical manifestations of CKD in companion animals. The aim of this session is to elucidate the current state of knowledge regarding amino acid deficits and dysmetabolism in cats afflicted with CKD, drawing upon recent literature to shed light on pathophysiological mechanisms and potential therapeutic interventions in the management of this complex condition.

ESSENTIAL AND NONESSENTIAL AMINO ACIDS

Amino acids are fundamental molecules with diverse functions crucial to overall health and wellbeing. The primary functions of amino acids are protein synthesis. They are also an energy source through oxidative pathways and are important for the synthesis of non-protein molecules (such as neurotransmitters and nucleotides), maintenance of acid-base balance, immune function, transport and storage of nutrients, and regulation of gene expression. Amino acids are broadly categorized as essential or nonessential. Essential amino acids cannot be synthesized by the body and must be obtained through diet. Cats have 11 essential amino acids: arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, taurine, threonine, tryptophan, valine. Isoleucine, leucine, and valine are also categorized as branched-chain amino acids (BCAA). Nonessential amino acids (alanine, asparagine, aspartate, citrulline, cysteine, glutamate, glutamine, glycine, proline, serine) can be synthesized by the body and obtained from dietary intake.

AMINO ACID METABOLISM DYSREGULATION IN CKD

The kidney plays a multifaceted role in amino acid metabolism, encompassing synthesis, degradation, filtration, reabsorption, and urinary excretion processes. The kidney's pivotal function lies in the filtration of amino acids from the blood through the glomerular filtration barrier. Subsequently, the proximal tubules, comprising the bulk of renal tubular reabsorption, actively reabsorb most filtered amino acids, ensuring their conservation, and preventing their loss in the urine. In CKD patients with tubular disease, total urinary amino acid excretion increases with proteinuria and contributes to amino acid loss. Additionally, the kidney is partially responsible for the disposal of the nonessential amino acids citrulline, glutamine and proline, and for the generation and release of the nonessential amino acids serine, tyrosine, and arginine. As such, renal dysfunction can lead to either an accumulation (citrulline, glutamine, proline) or deficiency (serine, tyrosine, arginine) in these nonessential amino acids.

Several other factors beyond urine amino acid loss and kidney dysfunction promote net protein catabolism and protein dysmetabolism in patients with CKD, including metabolic acidosis, systemic inflammation, and low protein diet. Protein malassimilation in the intestines can also contribute to net loss of amino acids.

Metabolic Acidosis
Metabolic acidosis is a well-documented cause of increased protein degradation, muscle weakness, and lean body mass wasting in people with CKD. Correction of metabolic acidosis is shown to decrease protein degradation, improve survival, and rate of progression of CKD highlighting the importance of treatment.[3] Although metabolic acidosis is common in cats with CKD, little is known about clinical consequences and long-term effect of treatment.

Systemic Inflammation
Inflammation in CKD is the consequence of concurrent infections, uremic immune dysfunction, and inadequate renal removal of cytokines. Inflammation contributes to malnutrition by promoting muscle proteolysis, increasing resting energy expenditure, worsening appetite, and causing resistance to insulin and growth hormone.

Low Dietary Protein Intake
Therapeutic renal diets that are restricted in protein and phosphorus have been shown to mitigate signs of uremia and improve survival in cats with CKD. Thus, a reduction in protein intake and feeding a therapeutic renal diet is recommended in cats with International Renal Interest Society (IRIS) Stage 3 and 4 CKD and considered in IRIS Stage 1 and 2 CKD for those with evidence of phosphorus overload or proteinuria. However, low protein intake in conjunction with poor caloric intake has been linked to loss of lean body mass and amino acid deficits, particularly essential amino acids and BCAAs, in people with CKD.

Protein Malassimilation
CKD is associated with dysbiosis that affects microbial community diversity and the intestinal wall. Impaired epithelial barrier structure and function leads to increased absorption of gut-derived uremic toxins and malassimilation of nutrients. People with CKD are less able to absorb amino acids from diet as compared to healthy controls, and the same is thought to be true in cats.

AMINO ACID DEFICITS IN CKD
Protein-energy wasting (PEW) refers to a state of malnutrition characterized by the depletion of protein and energy reserves in the body and is common in patients with CKD. PEW is caused by increased protein catabolism, malnutrition, uremic toxins, and inflammation and is associated with significant muscle wasting, weight loss, weakness, fatigue, poor wound healing, and impaired immune function. Amino acid profiles can serve as markers of PEW in patients with chronic illness.

Human
In people with CKD not receiving hemodialysis, derangements in amino acid profiles have been documented with overall trend being a reduction in essential amino acids, and an increase in nonessential amino acid concentrations. These changes occur in the early stages of disease, worsen with declining renal function, and in some cases, particularly the BCAA leucine, are linked to malnutrition. Leucine is of particular importance in regards to CKD and PEW because leucine is vital for muscle protein synthesis. Low leucine concentrations signals muscle wasting and malnutrition in CKD patients with inadequate caloric intake.

Veterinary
Two studies have measured blood amino acid concentrations in cats with CKD.[1,2] Both studies showed that cats with CKD had lower tryptophan and tyrosine concentrations. Other deficiencies reported included the essential amino acids leucine, phenylalanine, threonine, valine and the nonessential amino acid serine. Both studies showed elevated concentrations of the nonessential amino acid citrulline. Other nonessential amino acids reported to be increased in CKD cats include aspartate, asparagine, alanine, and ornithine. In a untargeted serum metabolomics study, amino acids were the second largest chemical class contributing to differences between healthy and IRIS Stage 1-4 CKD cats and between cats with early- versus late-stage CKD.[3] This study also showed deficiencies in 5 of 11 essential amino acids (arginine, histidine,

phenylalanine, threonine, tryptophan) in cats with CKD, with lower concentrations of all essential amino acids except taurine in cats with late-stage CKD compared to those with early-stage CKD. These studies support that alteration in amino acid profiles occur in cats with early-stage CKD (IRIS Stage 1 and 2) and magnitude of the derangement is often greater in cats with IRIS Stage 3 and 4 CKD.

TREATMENT

To combat PEW in cats with CKD, cats should have daily physical activity and veterinarians should recommended treatment of metabolic acidosis and eliminate correctible inflammatory factors (e.g., intestinal disease, UTI). In addition, optimizing nutritional therapy is important. Several studies have demonstrated that cats with CKD fed a renal therapeutic diet with restricted protein is effective and should not cause PEW if the protein source is complete and highly digestible, and the pet is eating enough to meet their energy requirement. However, loss of body weight and muscle mass has been documented in cats with CKD when fed a renal therapeutic diet with inadequate caloric intake, highlighting the importance of dietary counseling and monitoring after transitioning to a renal therapeutic diet.[4,5] The degree of dietary protein restriction in cats with CKD should be individualized, taking into account the pet's current protein intake, the severity of azotemia and/or proteinuria, the presence of uremic clinical signs, and appetite. For reference, a low-protein diet for cats contains < 70 g protein/1000 kcal, a moderate-protein diet contains 70–100 g/1000 kcal, and a high-protein diet contains > 100 g/1000 kcal. High-protein diets should be avoided in all stages of CKD. Cats with severe azotemia and clinical signs of uremia (e.g., Stage 3–4 CKD) may benefit from a low-protein diet, but maintaining adequate caloric intake is critical to prevent protein–energy wasting (PEW). In earlier stages of CKD (Stage 1–2), some cats—particularly those accustomed to high-protein diets—may be managed with a moderate-protein diet. Assessing a cat's current dietary protein intake is a valuable step in guiding the degree of restriction and tailoring diet recommendations to minimize the risk of PEW while managing CKD.

Recent studies have focused on the importance of the quality and diversity of proteins rather than on quantity for management of CKD. A previous study in cats with IRIS Stage 1 and 2 CKD showed that enhanced intake of the essential amino acid threonine using a low-protein renal therapeutic diet (67 g/1000 kcal) for 6 months maintained lean body mass.[4] Threonine is an amino acid that is depleted in cats with CKD, which further supports the potential benefit of supplementation of this amino acid. Based on this study, renal therapeutic diets fortified with essential amino acids might be beneficial in cats with CKD in the hope of maintaining lean body mass and potentially improving blood amino acid concentrations; however, the latter remains to be elucidated.

A potential concern of amino acid supplementation is increasing the production of uremic toxin precursors by gut microbiota and subsequently worsening uremic toxin accumulation in systemic circulation. Several deleterious uremic toxins, including indoxyl sulfate and p-cresol sulfate, are formed because of fermentation of aromatic amino acids (specifically, tryptophan, phenylalanine, tyrosine) by microbiota in the distal intestine. Similar to people, cats with CKD have elevated serum concentrations of these gut-derived uremic toxins and reducing protein intake has been shown to decrease concentrations.[6,7] These aromatic amino acids are commonly depleted in patients with CKD, thereby supporting a need for enhanced supplementation. There is some concern that supplementing aromatic amino acids in the diet will increase uremic toxin concentrations, however an association has not been documented in cats or people with CKD.

CONCLUSION

Through the examination of amino acid profiles and metabolic dysregulation in CKD patients, both in humans and cats, this session has shed light on the multifactorial nature of PEW and its impact on clinical outcomes. Furthermore, the discussion surrounding nutritional therapy highlights the importance of dietary management, including the individualized selection of the degree of protein restriction, in combating PEW and optimizing the overall health and wellbeing of cats with CKD. Moving forward, continued research in this field is essential to further elucidate the underlying mechanisms and to develop targeted therapeutic interventions aimed at improving the quality of life for cats afflicted with CKD.

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