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Taurine and Carnitine in Canine Cardiomyopathy

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Dilated cardiomyopathy (DCM) is one of the most common acquired cardiovascular diseases in dogs [1–4]. Although few studies of the prevalence of DCM in the overall population of dogs have been reported, estimates range from 0.5% to 1.1% [5,6]. Only degenerative valvular disease and, in some regions of the world, heartworm infection are more common causes of cardiac morbidity and mortality in dogs. DCM is seen most commonly in large and giant breeds of dogs, although its frequency seems to be increasing in medium-sized breeds, such as the English and American cocker spaniels [4–8]. It has been reported rarely in small and miniature breeds of dogs [9].

DCM is particularly challenging to veterinarians because the cause is often unknown and can vary among dog breeds [10]. Because most cases of DCM in dogs are classified as idiopathic, most therapies can be classified as "Band-Aid therapies" that palliate the effects of this disease for a short duration but do little to address the primary disease process. Therefore, DCM is almost always a progressive disease, and most dogs will eventually succumb to their disease. Survival times in dogs with DCM are variable and can be influenced by several factors, including breed. However, the prognosis for survival of dogs with DCM remains poor, with reported survival rates of 17.5% at 1 year and 7.5% at 2 years [11–13]. Until recently, reported cases of DCM reversal in dogs were very rare.

With advancements in echocardiology, diagnostic capabilities in canine cardiology have improved dramatically over the past 2 decades. Therapeutic advances have made surprisingly little progress. Symptomatic treatment is the standard care and outcome remains poor.

Recently, more promising therapies for dogs with DCM have resulted from a clearer understanding of the importance of biochemistry and nutrition in managing this disease. Nutrition is now widely accepted as an important adjunct to medical therapy in dogs with DCM.

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The importance of nutrition in managing DCM has changed dramatically in the past 10 to 15 years. Historically, dietary sodium restriction was the most common nutritional recommendation for dogs with DCM. The importance of other nutrients in the origin and management of this disease was largely unknown. More recently, widely accepted beliefs about the role nutrient deficiencies could play in DCM have been proven false, further enhancing the ability to direct therapy at an underlying cause rather than just the symptoms.

This article focuses on two nutrients, taurine and carnitine, that play an important role in the cause and treatment of DCM in some dogs. Known risk factors for developing deficiencies of these nutrients are discussed, along with the use of taurine and carnitine for treating DCM in dogs.

TAURINE

What is Taurine?

Taurine is a sulfur-containing amino acid. Unlike most other amino acids, taurine is not incorporated into proteins but rather is one of the most abundant free amino acids in the body. Taurine is found in highest tissue concentrations in cardiac muscle, skeletal muscle, the central nervous system, and platelets [14].

Other than conjugation of bile acids and detoxification of xenobiotics through conjugation and excretion in bile, the function of taurine in mammals is not well understood but is highly diverse [14,15]. Since the mid-1970s, taurine has been known to be essential for normal retinal function in cats [16]. In addition, clinical and experimental evidence collected in the late 1980s documented that taurine is essential for normal myocardial function [17–20].

Taurine is involved with numerous metabolic processes, including antioxidation, retinal photoreceptor activity, development of the nervous systems, stabilization of neural membranes, reduction in platelet aggregation, and reproduction [15,16,21–26]. Although the importance of taurine for normal myocardial function is also well recognized, the mechanisms underlying its effect on the heart remain unknown. Much of the available evidence supports the theory that taurine's major effect on cellular function in the heart is modulating tissue calcium concentrations and availability [14,27,28]. In addition, taurine may inactivate free radicals and protect the heart by changing cellular osmolality [29]. Taurine may also have an effect on osmoregulation in the myocardium. Taurine is a small but highly charged osmotically active molecule, and experts have proposed that alterations in cellular osmolality induced by changes in intracellular taurine concentration are a protective mechanism in nervous tissue and myocardium [29]. Other proposed mechanisms specifically related to myocardial function include *N*-methylation of cell membrane phospholipids [30], direct effects on contractile proteins [31,32], and interactions with the renin–angiotensin–aldosterone system [33]. Taurine is a natural antagonist of angiotension II.

Is Taurine an Essential Amino Acid in Dogs?

Taurine is an essential amino acid in cats, and it is well known that taurine deficiency can cause DCM, retinal degeneration, and reproductive anomalies in this species [18]. However, taurine is not considered an essential amino acid in dogs. One explanation for the differences in taurine requirements between cats and dogs is that the activity of cysteine sulfinic acid decarboxylase (the rate-limiting enzyme in the synthesis of taurine from cysteine and methionine) is higher in dogs than cats [34]. However, the difference in activity of this enzyme between dogs and cats does not fully explain the difference in requirements. The activity of this enzyme in humans is even lower than in cats, and taurine is not considered an essential amino acid in healthy adult humans. Therefore, cats and dogs may have additional differences that may explain why taurine is an essential amino acid in cats and not in dogs.

A study in dogs conducted in the 1980s at the University of California at Davis showed that feeding taurine-free diets or diets found to be taurine-depleting in cats [35] did not result in taurine depletion when fed to a group of eight healthy beagles [36]. In addition, results of an early clinical study in dogs, also conducted at this University soon after the relationship between taurine deficiency and DCM was discovered in cats, were unrewarding. These studies showed that dogs could not become taurine-depleted from diet alone, and that taurine did not play a considerable role in the development of DCM in dogs.

Emergence of Taurine Deficiency in Dogs with Dilated Cardiomyopathy

The belief that taurine deficiency could not cause DCM in dogs was challenged in 1989 when taurine deficiency was linked to DCM in foxes [37]. This study reopened taurine's possible role in DCM in dogs, and a collaborative study between the University of California at Davis and the Animal Medical Center in New York City was initiated [38]. In this study, plasma taurine levels were evaluated in dogs with DCM and in those with chronic degenerative mitral valve disease. Surprisingly, results of this study showed that plasma taurine concentration was low in 17% of 75 dogs with DCM, and this deficiency occurred in breeds not commonly afflicted with DCM, such as American cocker spaniels and golden retrievers. However, because the plasma taurine concentration in breeds more commonly affected with DCM were within the reference range, experts concluded that taurine deficiency was unlikely to play an important role in the etiopathogenesis or therapy of DCM in dogs.

Multicenter Spaniel Trial (MUST) Study

Anecdotal reports emerged regarding supplementing American cocker spaniels diagnosed with DCM with taurine; however, initial reports of taurine supplementation were unrewarding. When Kittelson and colleagues [8] gave taurine and L-carnitine supplements to two American cocker spaniels with DCM, both dogs experienced response. These findings initiated the Multicenter Spaniel Trial (MUST) study. In this study, baseline plasma taurine concentrations and echocardiograms were collected in 11 American cocker spaniels diagnosed

with DCM. All dogs were found to have low plasma taurine concentrations at baseline (<50 nmol/mL). After baseline information was collected, dogs were randomly assigned to receive supplementation with both taurine (500 mg by mouth every 8 hours) and L-carnitine (1000 mg by mouth every 8 hours) or a placebo for 4 months, and echocardiograms were reevaluated after 2 and 4 months of therapy. The group supplemented with both taurine and carnitine showed significant echocardiographic improvement, whereas dogs receiving the placebo did not.

After this initial 4-month period, dogs that had received the placebo initially received supplements of both taurine and carnitine, and subsequently showed echocardiographic improvement after 2 to 4 months of therapy. The magnitude of echocardiographic improvement in the American cocker spaniels was not as dramatic as that seen after taurine supplementation in cats with taurine deficiency DCM. Nonetheless, after 4 months of supplementation, the improvement in myocardial function in each dog was significant enough to allow discontinuation of cardiovascular drug therapy. Improvements were seen in not only cardiovascular function but also survival times. The mean survival time for dogs in this study was 28.3 ± 19.1 months, compared with an average life expectancy for dogs treated with conventional drug therapy of approximately 6 months. Based on results from this study, the current recommendation is to supplement American cocker spaniels diagnosed with DCM with both taurine and carnitine at the doses mentioned earlier.

University of Minnesota Study in Urolith-forming Dogs Diagnosed with Dilated Cardiomyopathy

Around the same time the MUST study was initiated, a separate clinical study was initiated at the University of Minnesota. The population of dogs studied consisted of those with either cystine or urate urolithiasis that developed DCM after long-term consumption of a protein-restricted diet that was being used to manage their stone disease (Sherry L. Sanderson, DVM, PhD, unpublished data, 1998). Dogs in group 1 underwent only conventional drug therapy for their heart disease, whereas those in group 2 underwent and taurine and/or carnitine supplementation in addition to conventional drug therapy as needed. Dogs in group 1 that were in Modified New York Heart Association (MNYHA) functional class I and II heart failure received enalapril (0.25 mg/kg by mouth every 12 hours) and digoxin (0.01–0.02 mg/kg by mouth divided twice a day), and dogs in MNYHA functional class III and IV received furosemide (dose varied depending on severity of heart disease) in addition to enalapril and digoxin. The population of dogs in group 1 (N = 6) consisted of five English bulldogs (four with cystine urolithiasis, one with urate urolithiasis) and one Dalmatian with urate urolithiasis. The population of dogs in Group 2 (N = 8) consisted of five English bulldogs (three with cystine urolithiasis, two with urate urolithiasis), two Dalmatians with urate urolithiasis, and one miniature Dachshund with cystine urolithiasis. Because when this study was initiated experts believed that dogs with DCM did not have low plasma taurine

concentrations, none of the dogs in group 1 had these concentrations evaluated at baseline. Plasma taurine concentrations evaluated before supplementation in seven of eight dogs in group 2 ranged from 2 nmol/mL to 45 nmol/mL (mean, 20.9 nmol/mL). These results were below the reference range of 41 nmol/mL to 97 nmol/mL that the investigators established from healthy adult beagles. Echocardiography was performed at baseline and once every 2 months. Details from this study will be published later, but a few interesting and important results were noted:

1. The average life expectancy for dogs in group 1 was 10.5 months, and all dogs were euthanized because of progressive congestive heart failure that became refractory to therapy. The average life expectancy for dogs in group 2 was 47.1 months, and only three of eight dogs were euthanized because of progressive congestive heart failure. In addition, three of five dogs that did not succumb to their heart disease received only taurine and/or carnitine supplementation and no conventional drug therapy for the management of their heart disease.
2. DCM reversed in three of eight dogs in group 2. DCM returned in one dog after the owner discontinued taurine and carnitine supplementation on their own, and in an additional dog when the dose of carnitine was reduced because of diarrhea associated with carnitine supplementation.
3. Dogs consuming a protein-restricted diet long-term could develop taurine deficiency, in contrast to results from previous studies that concluded that a diet could not induce taurine deficiency in dogs. This finding provided an impetus for further examining the effects on plasma and whole blood taurine levels in healthy adult dogs consuming a protein-restricted diet long-term.

Diet-Induced Taurine Deficiency in Healthy Adult Dogs

Previous reports indicated that dogs could not develop diet-induced taurine deficiency, even when fed a diet devoid of taurine. However, based on the finding of University of Minnesota study that dogs developed low plasma taurine levels after consuming a protein-restricted diet long-term, a more controlled study was undertaken to determine the cause of this problem and evaluate the effects of long-term taurine deficiency on cardiac function in healthy adult dogs [39].

This study involved 17 healthy adult beagles. Baseline plasma and whole blood taurine levels were evaluated, and echocardiography was performed to assess cardiac function. Once baseline data was collected, dogs were fed one of three protein-restricted diets for 48 months. All three diets had similar levels of protein; one diet was also low in fat, a second was high in fat, and a third was high in fat and supplemented with L-carnitine at 200 mg/kg of diet. All diets contained methionine and cystine concentrations at or above recommended minimum requirements established by the Association of American Feed Control Officials (AAFCO) [40]. After diet assignment, plasma taurine and whole blood taurine concentrations and echocardiography were evaluated every 6 months.

All three dietary treatments caused a significant decrease in whole blood taurine concentration compared with baseline concentrations. Dogs in the high-fat

group also experienced a significant decrease in plasma taurine concentration. This study was the first to show that diet could induce taurine deficiency in healthy adult dogs, in contrast to previous studies.

Another important observation was that one dog with taurine deficiency developed DCM, and that taurine supplementation resulted in almost complete reversal of the disease. This study was also the first to clearly document in dogs that taurine deficiency preceded DCM, and that taurine supplementation resulted in substantially improved cardiac function, similar to cats.

Why Did Dogs Develop Taurine Deficiency While Consuming a Protein-Restricted Diet?

The exact mechanism for this problem is unknown. However, this study showed that the AAFCO recommended minimum requirements for amino acids may need to be modified in dogs consuming a protein-restricted diet long-term. Many therapeutic diets for dogs are now supplemented with taurine.

Additional Examples of Diet-Induced Taurine Deficiency in Dogs

Soybean-based diets

Taurine deficiency was identified in two unrelated dogs fed a tofu-based diet [41]. Although the diet was low in protein, it met the National Research Council's published requirements for protein and other nutrients in dogs [42]. The authors attributed taurine deficiency to the fact that the primary protein source was soybean curd, which is low in sulfur-containing amino acids and devoid of taurine compared with meat proteins [43]. In addition, soybean curd has been shown to accelerate the loss of bile acids in cats [44].

Lamb meal and rice diets

Taurine deficiency was also identified in 12 Newfoundlands consuming two different commercially available lamb meal and rice diets [41]. Echocardiography was performed in six of the dogs, and none were diagnosed with DCM. The taurine deficiency was reversed when the diet was either changed or when the lamb meal and rice diets were supplemented with methionine. This study did not identify the exact mechanism for the development of taurine deficiency in the dogs consuming the lamb meal and rice diets.

In a study by Fascetti and colleagues [45], DCM and taurine deficiency were identified in 12 large and giant-breed dogs consuming commercially available diets that contained lamb meal, rice, or both as primary ingredients. All dogs received supplements of with taurine (1000–3000 mg by mouth every 24 hours), and significant echocardiographic improvement occurred in 9 of the 12 dogs that underwent an echocardiogram repeated after taurine supplementation. The authors hypothesized that taurine deficiency caused DCM and was caused by inadequate or unavailable dietary sulfur amino acids, which are essential precursors of taurine synthesis.

In a similar report, five related golden retrievers were diagnosed with taurine deficiency and DCM [46]. Three of five dogs were consuming lamb meal and rice or lamb and rice diets. All showed significant improvement after taurine

supplementation (500 mg by mouth every 12 hours), and all five dogs survived for more than 3 years. The authors attribute the DCM to a suspected autosomal recessive mode of inheritance; however, the potential role diet played in the development of taurine deficiency warrants mentioning.

Potential Causes of Taurine Deficiency in Dogs Consuming Lamb Meal and Rice or Lamb and Rice Diets

Torres and colleagues [47] compared the effects of consuming a lamb meal and rice–based diet with effects of consuming a poultry by-product–based diet in 12 beagles aged 5 to 5.5 months. Although the differences in plasma and whole blood taurine concentrations did not differ among diet groups, dogs consuming the lamb meal and rice–based diet excreted less taurine in their urine than dogs consuming the poultry by-product–based diet. When the lamb meal and rice diet was supplemented with methionine, urinary taurine excretion increased by 54%. Because taurine homeostasis in dogs is achieved primarily through regulating renal taurine excretion, the amount of taurine excreted in urine is a sensitive indicator of the adequacy of either taurine synthesis or absorption of dietary precursor amino acids. The authors concluded that reduced bioavailability of sulfur amino acids in the lamb meal and rice diet is a likely cause of taurine deficiency. This finding is supported by the increase in urine taurine concentrations after supplementation with methionine. Johnson and colleagues [48] showed that ileal digestibility of amino acids in dogs depends on the raw material sources and the temperature used to process feeds and provides a mechanism for these specific dietary effects.

A second potential, although related, cause of taurine deficiency in dogs consuming lamb meal and rice diets was proposed [49,50]. When dietary protein is low in quality, undigested protein reaches the colon, where it serves as a substrate for bacterial growth. Some bacteria produce cholyltaurine hydrolase, an enzyme that causes release of taurine from taurocholic and other bile acids that are normally conserved in the enterohepatic circulation, resulting in increased fecal loss of taurine. Studies in dogs [49] and cats [50] have found that diets containing rice bran and whole rice products provide a source of moderately fermentable fiber and high amounts of fat. These fermentable fibers may increase the number of bacteria in the colon and result in a greater loss of taurine in the feces similar to the mechanism for undigested protein. The fat content of the diet can also affect taurine metabolism through altering intestinal bacteria and subsequent changes in the excretion of bile acids.

How Should Samples be Collected to Evaluate Plasma and Whole Blood Taurine Concentrations?

Fasting versus postprandial blood samples

Although fasting has no effect on plasma taurine concentrations in humans [51], food deprivation causes a small but significant reduction in plasma taurine concentrations in cats [52]. In a study by Torres and colleagues [47], plasma taurine concentrations were significantly reduced in food-restricted dogs compared with ad libitum–fed dogs. Whole blood taurine concentrations were

also reduced, although the whole blood taurine results were not statistically significant between the two groups. Because of the potential for food intake to affect plasma and whole blood taurine concentrations in dogs, withholding food, but not water, is recommended for 8 hours before sampling.

Anticoagulant used for plasma sample collection

Paired analysis of samples comparing taurine concentrations in plasma collected in lithium heparin with those collected in sodium citrate showed that plasma taurine concentrations are higher when lithium heparin is used as the anticoagulant [38]. Because most studies have used heparinized plasma samples to evaluate plasma taurine levels in dogs, these are recommended rather than sodium citrate plasma samples.

Plasma taurine sample collection

Heparinized, nonhemolyzed blood samples should be obtained and stored on ice until they are processed. After centrifuging, the plasma should be separated immediately from the cellular components, and a small amount of plasma should be left above the buffy coat to prevent contamination of the plasma with cells. Hemolysis and platelet or white blood cell contamination falsely elevates plasma taurine concentrations. Samples should be frozen until analyzed for plasma taurine concentrations.

Whole blood taurine sample collection

Heparinized whole blood should be frozen until samples can be analyzed. Because the red blood cells are lysed before analysis, hemolyzed samples do not adversely affect whole blood taurine analysis.

Plasma and whole blood taurine samples can be sent to the Department of Molecular Biosciences at the School of Veterinary Medicine, University of California, Davis, for analysis.

Which is Better: Plasma Taurine Concentrations or Whole Blood Taurine Concentrations

Earlier studies evaluating the relationship between taurine deficiency and DCM in dogs relied primarily on plasma taurine concentrations to predict tissue taurine concentrations. Studies conducted in dogs by this author showed findings similar to those reported in cats [53]. Relying on plasma taurine concentrations alone does not reliably assess tissue taurine concentrations in dogs. Simultaneously evaluating plasma and whole blood taurine concentrations predicts skeletal and cardiac muscle taurine concentrations better than evaluating either test alone. Therefore, when evaluating taurine status in dogs with DCM, plasma and whole blood taurine concentrations should be assessed simultaneously.

Reference Ranges for Plasma and Whole Blood Taurine Concentrations in Dogs

The reference range used in earlier studies evaluating plasma and whole blood taurine concentrations in dogs was extrapolated from the reference range use in

cats. However, reference ranges for plasma and whole blood taurine concentrations in dogs were published recently (Table 1).

Delaney and colleagues [49] have also suggested that plasma taurine concentrations less than 40 nmol/mL are critically low, as are whole blood taurine concentrations less than 150 nmol/mL. In addition, Sanderson and colleagues [53] found that low plasma taurine concentrations can exist without the presence of DCM.

Therefore, results showed that the onset of clinical signs in dogs, just as in cats, was variable when taurine concentrations declined markedly below the normal range [18].

Which Dogs Diagnosed with Dilated Cardiomyopathy Should Receive Taurine Supplementation?

Evaluation of plasma and whole blood taurine concentrations is recommended for all dogs diagnosed with DCM. An association between taurine deficiency and DCM was found in various breeds of dogs, including American cocker spaniels, Newfoundlands, golden retrievers, Labrador retrievers, Dalmatians, English bulldogs, and Portuguese water dogs. Taurine supplementation is highly recommended in any of these breeds that develop DCM.

Not all dogs with DCM will show dramatic improvement with taurine supplementation. However, even if plasma and whole blood taurine concentrations are within the reference range, giving taurine supplements to dogs diagnosed with DCM may still have some benefits. Because taurine is extremely safe and inexpensive, the risks and costs of supplementation are minimal, even if dogs have normal levels of plasma and whole blood. Proposed mechanisms for the beneficial actions of taurine on the myocardium include modulating tissue calcium concentrations and availability in the heart; inactivating free radicals and protecting the heart through altering cellular osmolality; osmoregulating the myocardium; directly affecting contractile proteins; and serving as a natural antagonist of angiotension II. Dogs with DCM that do not have taurine deficiency may still benefit from some of these proposed mechanisms of action for taurine.

Table 1 Normal concentrations of taurine in dogs	
Plasma (nmol/mL)	Whole blood (nmol/mL)
41–97[a]	155–347[a]
72.8–81.2[b]	255.8–276.2[b]

[a]Reference range established from 18 healthy adult beagles consuming a canned commercial maintenance diet. *Data from* Sanderson SL, Gross KL, Ogburn PN, et al. Effects of dietary fat and L-carnitine on plasma and whole blood taurine concentrations and cardiac function in healthy dogs fed protein-restricted diets. Am J Vet Res 2001;62:1616–23.
[b]Reference range established from 131 healthy adult dogs of various breeds consuming a variety of commercial adult maintenance diets. *Data from* Delaney SJ, Kass PH, Rogers QR, et al. Plasma and whole blood taurine in normal dogs of varying size fed commercially prepared food. J Anim Physiol 2003;87:236–44.

Recommended dose for taurine supplementation

This author has successfully used doses of 500 to 1000 mg of taurine administered orally two to three times per day for small dogs (<25 kg), and 1 to 2 g of taurine administered orally two to three times per day for large dogs (25–40 kg). These doses have been shown to normalize plasma and whole blood taurine levels in taurine-deficient dogs. Many other doses for taurine are reported in the literature. Whether a smaller or less frequent dose of taurine than what this author recommends can be used successfully remains to be determined. If doses are used that differ from those this author recommends, plasma and whole blood taurine concentrations must be reevaluated after taurine supplementation is initiated to determine if the dose being given is effective and appropriate. Another important point is that echocardiographic improvement in myocardial function is not usually documented before 2 months of supplementation, and often no improvement is documented before 4 months of supplementation. However, the dogs may feel better clinically and be more active before improvement in cardiac function is documented. Owners must not withdraw taurine supplementation prematurely before deciding if their dogs benefit.

Where Can Taurine be Purchased?

Taurine can be purchased through several retail outlets. If taurine is purchased through a health food store, consumers must look for a product that contains a USP certification symbol on the label. This symbol ensures that what is listed on the label is exactly what is found in the product.

LEVOCARNITINE (*L*-CARNITINE)

What is *L*-Carnitine?

L-carnitine (β-hydroxy-γ-trimethylaminobutyric acid) is a small water-soluble molecule with a molecular weight of 160. In dogs, carnitine is obtained either from dietary protein or endogenous synthesis in the liver using the essential precursor amino acids lysine and methionine. Synthesis also requires iron, vitamin C, and vitamin B_6 as cofactors [54]. Although carnitine is classified as an amino acid derivative, it is not an α-amino acid and the amino group is not free. Therefore carnitine is not used for protein synthesis [55].

Carnitine is found in the body either as free carnitine, short-chain acyl carnitine, or long-chain acylcarnitine. Acylcarnitine is carnitine bound to a fatty acid. Total carnitine is the sum of all the individual carnitine fractions. The free carnitine fraction is normally higher than either the short-chain acylcarnitine fraction or the long-chain acylcarnitine fraction.

Cardiac and skeletal muscles are significant storage sites, containing 95% to 98% of the carnitine in the body [56], and carnitine is concentrated in these tissues through an active membrane transport mechanism. The heart is unable to synthesize carnitine and depends on transport of carnitine from the circulation into cardiac muscle, which results in up to a 100× gradient between extracellular and intracellular concentrations.

Only the *L*-form of carnitine exists naturally in the body. The *D*-form competitively inhibits the actions of the *L*-form, thereby inhibiting carnitine enzyme systems. In addition, mammals are unable to convert *D*-carnitine to *L*-carnitine, and therefore this discussion focuses on *L*-carnitine.

Why is *L*-Carnitine Important for Normal Myocardial Function?

The normal heart obtains approximately 60% of its total energy production from oxidation of long-chain fatty acids [57]. Long-chain fatty acids in the cytosol of myocardial cells combine with coenzyme A (CoA) as the first step toward beta oxidation. However, long-chain fatty acids must be transported across the inner mitochondrial membrane to generate energy, and the inner mitochondrial membrane is normally impermeable to such bulky polar molecules. Therefore, transport is accomplished through a "carnitine shuttle." In the carnitine shuttle, the activated fatty acid in the cytosol reacts with carnitine to form a more permeable molecule. This reaction occurs on the outer surface of the inner mitochondrial membrane and is catalyzed by the enzyme carnitine acyltransferase I. The newly formed long-chain acyl-carnitine ester molecule is permeable to the inner mitochondrial membrane and is transported across this membrane, where the enzyme acyltransferase II converts the long-chain acyl-carnitine back to free carnitine and the long-chain fatty acid. Therefore, carnitine functions as a cofactor of several important enzymes necessary for transport of long-chain fatty acids from the cytosol into the mitochondrial matrix [58,59]. Once inside the mitochondria, fatty acids undergo beta oxidation to generate energy [60].

Another important function of carnitine is its buffering capacity, which modulates the intramitochondrial acyl-CoA:CoA ratio [58]. This process is important because acyl-CoA is the activated form of fatty acids used for beta oxidation and lipid synthesis. However, buildup of acyl-CoA derivatives in the mitochondria results in decreased free CoA, which inhibits oxidative metabolism. Acyl-CoA derivatives also act as detergents at high concentrations. Carnitine also facilitates removal of accumulating short- and medium-chain organic acids from the mitochondria. Therefore carnitine also has a role in detoxification in the mitochondria.

What Causes *L*-Carnitine Deficiency?

Carnitine deficiency can be a primary or secondary disorder. Primary carnitine deficiencies may arise from genetic defects in synthesis, renal transport, intestinal absorption, transmembrane uptake mechanisms, or excessive degradation of carnitine [61]. In humans, primary carnitine deficiencies have been associated with cardiomyopathies that are usually not present at birth but take 3 to 4 years to develop. *L*-carnitine therapy can prevent and reverse cardiac dysfunction in some patients.

Secondary carnitine deficiencies are believed to be much more common in humans and can have many causes [61]. In humans, carnitine deficiency can result from inborn errors of metabolism or develop in patients undergoing long-term total parenteral nutrition, vegetarians, and infants fed formulas not

supplemented with carnitine. Carnitine deficiencies are recognized in dogs, but the incidence is not known.

What are the Consequences of L-Carnitine Deficiency?

Carnitine deficiency has been shown to cause or be associated with DCM in humans [62–64], hamsters [65,66], and dogs [36,67–69]. More widespread studies have not been undertaken in dogs because carnitine status is difficult to thoroughly assess.

What Types of Carnitine Deficiency Exist in Dogs?

Carnitine deficiency in dogs is classified as either (1) plasma carnitine deficiency, characterized by low concentrations of free plasma carnitine; (2) systemic carnitine deficiency, characterized by low concentrations of free plasma and tissue carnitine; or (3) myopathic carnitine deficiency, characterized by low free myocardial carnitine concentrations in the presence of normal and sometimes elevated plasma carnitine concentrations. Plasma carnitine deficiency alone is not a well-documented state and is included to account for the fact that plasma carnitine, but not tissue carnitine sampling, is often pursued in veterinary medicine.

For example, if plasma carnitine concentration is used to assess carnitine status of a dog, it can help diagnose carnitine deficiency when it is low. However, if plasma carnitine concentration is normal, it does not rule out the possibility of the myopathic form of carnitine deficiency, and the myopathic form of carnitine deficiency is estimated to occur in 17% to 60% of dogs with DCM. Evaluating cardiac muscle carnitine concentrations requires a fluoroscopy-guided endomyocardial biopsy, which is not practical to perform in most private practice situations and is not without risk. Therefore, diagnosing and determining the incidence of myopathic carnitine deficiency in dogs with cardiac disease remains elusive, but may be an underdiagnosed cause of DCM in dogs.

L-Carnitine Deficiency and Associated Myocardial Disease States in Dogs

Carnitine deficiency was associated with DCM in dogs in a limited number of clinical reports [8,9,68–70]. The first reported case of carnitine deficiency was in a family of boxers [69]. The sire, dam, and two littermates were diagnosed with DCM. One offspring had a low plasma carnitine concentration and low myocardial carnitine concentration at DCM diagnosis. After undergoing treatment with high-dose L-carnitine (220 mg/kg/d orally), this dog's fractional shortening (FS) increased from 18% to 28%. This dog's littermate had low myocardial and normal plasma carnitine concentrations and responded similarly to high-dose L-carnitine supplementation, with its FS increasing from 2% to 24%. The latter dog experienced a decline in myocardial function after L-carnitine therapy was withdrawn. Both parents of these littermates had normal plasma and low myocardial carnitine concentrations. Unfortunately, both parents died soon after beginning L-carnitine supplementation.

Costa and Labuc [70] presented another case report of two boxers with DCM. One was treated with 250 mg/kg/d of *L*-carnitine orally, and the other was not treated. The myocardial concentration of carnitine was found to be low in the dog that did not receive supplementation and elevated in the dog that did.

Concurrent supplementation with carnitine and taurine has shown benefit in American cocker spaniels with DCM [8]. An unpublished study by this author in 1998 showed beneficial effects from carnitine supplementation in urolith-forming dogs diagnosed with DCM while consuming a protein-restricted diet (Sherry Lynn Sanderson, DVM, PhD, unpublished material). Both studies showed dramatic improvement in myocardial function and survival times in dogs that received supplementation.

Which Came First: Carnitine Deficiency or Dilated Cardiomyopathy?

A common argument made against the role of carnitine deficiency in dogs diagnosed with DCM is that if carnitine deficiency is diagnosed after the onset of DCM, whether carnitine deficiency caused the DCM or DCM caused the carnitine deficiency is unclear. When myocardial cells are damaged, as may occur with DCM, carnitine can leak out of the cells, resulting in low myocardial carnitine levels. In this situation, the DCM caused the carnitine deficiency. Most published studies linking carnitine deficiency to DCM in dogs have shown this scenario when carnitine deficiency was diagnosed after the onset of DCM.

In an unpublished study conducted at the University of Minnesota, this author documented carnitine deficiency before the onset of DCM in three dogs (Sherry Lynn Sanderson, DVM, PhD, unpublished material, 1998). Therefore, the association of carnitine deficiency with DCM at diagnosis may not always imply a cause-and-effect relationship. However, this study indicates that carnitine deficiency can cause DCM in dogs.

Which Dogs with Dilated Cardiomyopathy Should Receive Carnitine Supplementation?

The importance of carnitine supplementation in the treatment and survival times of some dogs with DCM should not be overlooked. In the first reported study linking carnitine deficiency to DCM in boxers, two of four dogs experienced good response to carnitine supplementation [69]. Considering the generally poor prognosis of this disease in boxers, carnitine supplementation provides owners one additional option for treating this disease, and has made a dramatic difference in the survival times and quality of life of some dogs.

The importance of carnitine supplementation in American cocker spaniels with DCM and urolith-forming dogs with DCM should also not be overlooked. Although a few anecdotal reports exist in which American cocker spaniels with DCM experienced good response to taurine supplementation alone, most cases have shown response to combined supplementation with taurine and carnitine. In the above study by this author, a miniature Dachshund diagnosed with carnitine deficiency before the onset of DCM underwent treatment

only with carnitine supplementation, and its heart disease reversed. Although DCM in many dogs is not associated with carnitine deficiency, carnitine and taurine supplementation offer the most promising hope for improved quality of life and survival times in dogs that experience response.

How is Carnitine Deficiency Diagnosed?

Because performing endomyocardial biopsies is impractical for most clinicians in private practice, most screening for carnitine deficiency relies solely on plasma carnitine levels. The method for plasma carnitine sample collection is almost identical to that used for plasma taurine sample collection. Fasting, heparinized, nonhemolyzed blood samples should be obtained and stored on ice until they are processed. The plasma should be immediately separated from the cellular components ideally in a cold-centrifuge, and a small amount of plasma should be left above the buffy coat to prevent contamination of the plasma with cells. Samples should be frozen immediately until analyzed for plasma carnitine concentrations.

What is the Recommended Dose for Carnitine Supplementation in Dogs?

The doses of carnitine being administered may contribute to the lack of favorable results with carnitine supplementation that some investigators observed. The recommended doses for carnitine supplementation in dogs with DCM vary widely in the literature. Although most authors recommend a carnitine dose of 50 to 100 mg/kg orally every 8 hours, the effective dose may depend on the form of carnitine deficiency. In a limited number of cases studied at the University of Minnesota, where pre– and post–carnitine supplemented plasma and cardiac muscle carnitine levels were obtained, this author's clinical impression was that the effective therapeutic dose in dogs with systemic carnitine deficiency was much lower than the effective dose in dogs with myopathic carnitine deficiency.

Some experts speculate that the myopathic form of carnitine deficiency may be caused by a carnitine transport defect in the heart, and much higher plasma levels of carnitine seem to be needed to overcome this defect and achieve normal concentrations of carnitine in the heart than for the systemic form of carnitine deficiency. Based on this work, the dose of carnitine recommended by this author for systemic carnitine deficiency is 100 mg/kg orally every 8 hours. However, if the myopathic form of carnitine deficiency is present or suspected, the author recommends starting carnitine supplementation at 200 mg/kg orally every 8 hours to maximize the chances that carnitine supplementation will improve myocardial function.

Carnitine is a very safe substance. Diarrhea was the only adverse effect of high doses of carnitine, reported in approximately two thirds of dogs. If diarrhea occurs, the highest dose of carnitine that the dog will tolerate without causing diarrhea should be administered. Therefore, like taurine, *L*-carnitine is a safe substance to administer, and, except for the expense, few drawbacks exist to supplementing a dog with DCM with carnitine (carnitine is much more expensive than taurine. Another important point is that the time it takes for

improvement in myocardial function to occur is very similar to that for taurine supplementation. Echocardiographic improvement in myocardial function is not usually documented before 2 months of supplementation with carnitine, and often improvement is not documented for up to 4 months. However, dogs may feel better clinically and be more active before improvement in cardiac function is documented. Owners must not withdraw carnitine supplementation prematurely before determining whether their dogs benefit.

Where Can L-Carnitine Be Purchased?

Although *L*-carnitine can be purchased from health food stores, this source is extremely expensive. Purity of the sample is also of great importance. Therefore, only products that contain the USP certification seal should be purchased from health food stores.

   L-Carnitine can also be purchased less expensively in bulk. Bulk carnitine can be purchased from Ajinamotousa, Inc (500 Frank W Burr Boulevard; Park Central West; Teaneck, New Jersey). At last check, the company required a minimum purchase of 10 kg at one time. However, the individual expense can be reduced if several owners split an order. If carnitine is purchased in bulk, owners must measure out the carnitine they are giving to their dogs. One teaspoon of carnitine is equivalent to 2 g of carnitine. Therefore, fractions of a teaspoon can be administered if necessary. Owners must be sure to purchase *L*-carnitine, not *D*- or the *DL*- isomers, because *D*-carnitine interferes with *L*-carnitine use.

Which Dogs with Dilated Cardiomyopathy Should be Supplemented With Carnitine?

Carnitine supplementation should be recommended for boxers, American cocker spaniels, and dogs with cystine or urate urolithiasis that are diagnosed with DCM. Even if carnitine deficiency did not cause DCM, supplementing dogs with carnitine does not hurt them, and supplementation may be beneficial even if carnitine deficiency is not present. The major drawback to supplementing dogs with carnitine is the expense and occasional gastrointestinal upset.

What are the Reference Ranges for Carnitine Concentrations in Dogs?

The reference ranges for carnitine concentrations in dogs are listed in Table 2 [69].

SUMMARY

Some newer more promising therapies for dogs with DCM do not involve drugs but rather nutritional supplements. Two of the more common nutritional supplements administered to dogs with DCM are taurine and carnitine. Deficiencies of these nutrients have been shown to cause DCM in dogs, and some breeds have been shown to experience dramatic improvement in myocardial function after supplementation with one or both nutrients. Although most dogs diagnosed with DCM do not have a documented taurine or carnitine deficiency, they may still benefit from supplementation. Both nutrients are very

Table 2
Normal concentrations of carnitine in dogs

Carnitine fraction	Plasma carnitine (nmol/mL)	Cardiac muscle carnitine (nmol/mg of NCP)
Free	8–36	4–11
Esterified	0–7	0–4
Total	12–38	5–13

Abbreviation: NCP, noncollagenous protein.

safe to administer to dogs. For some owners, the high cost of carnitine is the only deterrent to giving their dogs supplements of both nutrients.

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