

Carnitine in Neonatal Nutrition

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ABSTRACT

Experimental evidence from several investigators suggests that carnitine is a conditionally essential nutrient for neonates. If carnitine is a conditionally essential nutrient for the neonate, most neonates on total parenteral nutrition in the United States are not receiving adequate nutritional support. The metabolic functions of carnitine are varied and important in several aspects of neonatal physiology. All neonates receiving breast milk receive dietary carnitine and most neonates receiving enteral infant formulas receive dietary carnitine at a level similar to that of the breast-fed neonate. However, most neonates on total parenteral nutrition receive no dietary carnitine. Investigators have been testing the working hypothesis that carnitine is a conditionally essential nutrient for the neonate for many years. This review discusses (1) data supporting the hypothesis, (2) reasons why it has not been either proved or disproved by now, and (3) the author's view of a prudent approach to dietary carnitine supplementation of neonates. (*J Child Neurol* 1995;10(Supp):2S25-2S31).

If carnitine is a conditionally essential nutrient for the neonate, most neonates on total parenteral nutrition in the United States are not receiving adequate nutritional support. Essential nutrients are those nutrients required in the diet of healthy adults because metabolic requirements are greater than the individual's biosynthetic capability. Conditionally essential nutrients are those nutrients that are required in the diet of only certain individuals. A special physiologic condition causes those individuals to have metabolic requirements that are greater than their biosynthetic capability. Immaturity is one of the physiologic conditions frequently associated with conditionally essential nutrients.

For almost 20 years, several investigators have been testing the working hypothesis that dietary carnitine is essential for the neonate.¹ More than 10 years ago, available data supporting the carnitine conditional essentiality hypothesis for neonates resulted in carnitine being added to most enteral infant formulas not containing endogenous carnitine. Today in the United States, all neonates receiving breast milk receive dietary carnitine, and most neonates receiving enteral infant formulas receive dietary carnitine at a level similar to that of the breast-fed neonate. However, most neonates on total parenteral nutrition receive no dietary carnitine. This review addresses the questions: What are the data supporting the

carnitine conditional essentiality hypothesis for neonates? Why has the carnitine conditional essentiality hypothesis for neonates not been either proved or disproved by now? What is the prudent approach to dietary carnitine supplementation of neonates?

METABOLIC FUNCTIONS OF CARNITINE IN THE NEONATE

Carnitine is typical of many metabolites in that the first well-described function of the compound is often assumed to be the only function, and investigators turn their attention to other issues. As a result, additional metabolic roles of the compound may go unrecognized for many years. This scenario describes the last 35 years of research focusing on carnitine.

One extremely important function of carnitine is the transport across membranes of carboxylic acids that have been activated to the coenzyme A (CoA) level (Figure 1). Because all membranes are impermeable to CoA compounds, once a carboxylic acid is activated to CoA, it is trapped in its subcellular location. Conversion of CoA compounds to carnitine compounds makes the carboxylic acid transportable while maintaining the high energy state of the molecule. Thus, the ability of carnitine to confer "transportability" to a high-energy carboxylic acid means that it can facilitate the delivery of a needed substrate, the elimination of a toxin, and the transport of high energy from one subcellular or cellular location to another. The critical role of carnitine in delivering long-chain fatty acid CoA compounds to the mitochondrial matrix and therefore in facilitating β -oxidation of long-chain fatty acids is still often referred to as the function of carnitine. How-

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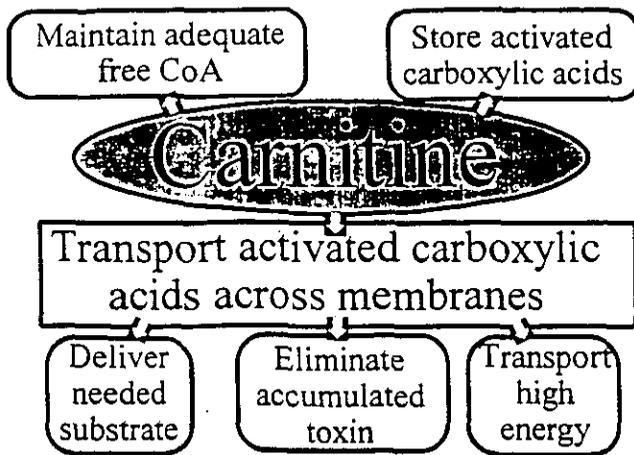


Figure 1. Diagram of five categories of metabolic functions performed by carnitine. Two of the functions (maintaining adequate free CoA and storing activated carboxylic acid) require acylcarnitine transferase activity; transport of the carnitine esters across membranes is not an absolute requirement. The other three categories of metabolic function (delivering needed substrates, eliminating accumulated toxin, and transporting high energy) require transport of the carnitine ester across membranes.

ever, there is a large body of knowledge that identifies additional metabolic functions for carnitine that may have more clinical importance for neonates than the first function described. Because medium-chain fatty acids are activated to the CoA level within the mitochondrial matrix in liver and outside the mitochondrial matrix in other tissues, carnitine is not needed for the oxidation of medium-chain fatty acids in liver but is needed for oxidation of medium-chain fatty acids in skeletal muscle and cardiac muscle. Although it is customary to think of fatty acids as the needed substrates being delivered to the site of further metabolism, several investigators have shown that we are experiencing tunnel vision. The needed substrates may include other energy substrates such as glucose metabolites, acetoacetate, and metabolites of amino acids (especially branched-chain amino acids).²

As diagrammed in Figure 1, the "transportability" of carboxylic acids is also important in the removal of toxins from a particular subcellular or cellular location. The toxins may be either compounds that are not normally found in metabolism or normal metabolites that have accumulated to abnormally high and toxic concentrations. The fact that the carnitine ester maintains the high energy of the CoA compound results in the transport of metabolic energy from one subcellular or cellular location to another.³

CoA compounds are critical metabolites in a wide variety of pathways, but the total CoA concentration in the cell is low. Because the carnitine concentration of a cell is much higher than the CoA concentration, the conversion of a carboxylic acid at the CoA level to the carnitine ester can replenish a dwindling free CoA pool and permit the continuation of metabolism that is dependent on such a pool. This function of carnitine impacts many different metabolic pathways.

Because the carnitine ester is a high-energy compound, the acylcarnitine pool also functions to store activated carboxylic acids that may have many functions that are only now being recognized, such as facilitating the remodeling of membranes.^{4,5} There are many reviews of carnitine metabolism and function,⁶⁻⁹ including those in this supplement.

CARNITINE STATUS OF PRETERM NEONATES VERSUS TERM NEONATES

Assessment of carnitine status is complicated by the fact that blood and urine are not necessarily indicative of the metabolic pools of carnitine in tissues. Plasma, red blood cells, liver, and skeletal muscle appear to be from different metabolic pools of carnitine in adult humans.¹⁰ In addition, the accretion of carnitine in these compartments appears to differ during gestation. Work with experimental animals^{11,12} and autopsy tissues of neonates of varying gestational ages receiving no carnitine and dying within 24 hours of birth¹³ have shown that there is a significant accretion of carnitine by muscle tissue during the last trimester of gestation. Postnatally, the skeletal muscle and liver carnitine concentrations continue to increase.¹⁴

The fetal rat is a major contributor to its own tissue carnitine.¹⁵ In the rat, the rapid accretion of tissue carnitine is so great that at weaning most of the tissue carnitine has been acquired since birth. Approximately 50% of this acquired carnitine comes from milk and approximately 50% from endogenous synthesis in the infant rat.¹⁵ Dietary carnitine also appears to be a major factor in the accretion of carnitine in humans postnatally. Plasma and red blood cell carnitine concentrations of full-term neonates receiving either breast milk or formula containing carnitine increase approximately 1.5- to 2.0-fold during the first 2 weeks of life. They continue to increase until at 3 months of age they are 2.5- to 3.0-fold higher than those in cord blood.¹⁶ In Figure 2, the total plasma carnitine concentration data from cord blood of full-term healthy neonates are set to 1.0 and used to normalize data from all other samples. Preterm neonates have higher plasma and red blood cell carnitine concentrations at birth than do full-term neonates. In contrast to the increase in plasma carnitine seen in full-term neonates postnatally, preterm neonates receiving carnitine-free total parenteral nutrition have plasma and red blood cell carnitine concentrations at 3 weeks of age that are only one third the concentration found in cord blood of full-term neonates. Carnitine supplementation of the total parenteral nutrition at a dose of approximately 50 $\mu\text{mol/kg}$ daily for 1 week and then at 100 $\mu\text{mol/kg}$ daily increased the plasma concentrations at 3 weeks of age to levels approximately 30% higher than the breast-fed full-term neonates.

In Figure 3, the total red blood cell carnitine concentration data from cord blood of full-term healthy neonates are set to 1.0 and used to normalize data from all other samples. The data in Figure 3 show trends similar to those in Figure 2 with one major exception. Whereas carnitine

supplementation of total parenteral nutrition increases the plasma carnitine concentrations of the preterm neonates, but the red blood cell carnitine concentrations remain low.

Oral supplementation of infants requiring long-term total parenteral nutrition who were able to tolerate small enteral feedings increased the plasma carnitine, acetoacetate, and β -hydroxybutyrate concentrations compared to the placebo-treated infants.¹⁷

DIETARY SOURCES OF CARNITINE FOR THE NEONATE

Carnitine biosynthesis requires the essential nutrients lysine, methionine, vitamin B₆, vitamin C, niacin, and iron. A diet deficient in any of these will adversely affect the neonate's ability to make carnitine.

Human milk contains approximately 60 to 70 nmol/mL of carnitine^{18,19} and is a very bioavailable source of carnitine. The dietary carnitine intake for the breast-fed neonate is approximately 2 to 5 mg/kg daily. Milk of all species measured contains carnitine. Cow milk contains approximately twice the concentration of human milk, and when it is used to prepare formula, the carnitine concentration of the formula is approximately the same as the concentration of human milk. Infant formulas based on soy protein have no endogenous carnitine.²⁰ Several investigators have shown that the infants receiving carnitine-free formula have altered carnitine status.^{21,22} Therefore, most commercial infant formulas based on soy protein are now supplemented with carnitine at levels similar to that of human milk.

In contrast to enteral nutrition formulas for neonates that contain carnitine, none of the parenteral nutrition solutions contain carnitine. Thus, the most metabolically stressed neonates are the ones who are routinely receiving no endogenous carnitine.

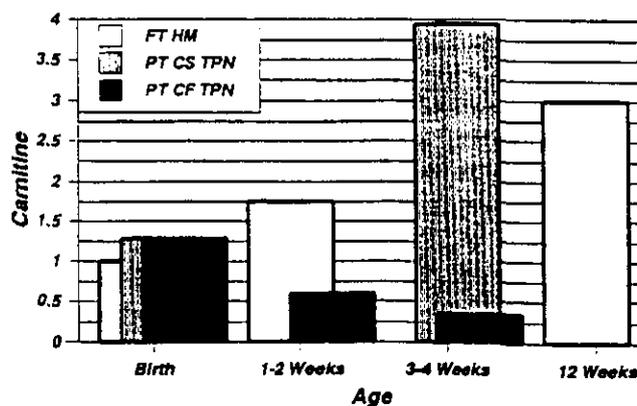


Figure 2. Plasma carnitine concentration data of infants (at different ages and receiving different dietary carnitine intake) normalized to the plasma carnitine data of cord blood from full-term neonates. The units for the original carnitine concentration data are nmol/mL. The full-term neonates received human milk (FT HM), and the preterm neonates received either total parenteral nutrition containing no carnitine (PT CF TPN) or total parenteral nutrition containing carnitine at 50 μ mol/mL and then 100 μ mol/mL (PT CS TPN). Figure is adapted from data reported by Borum et al.¹⁸

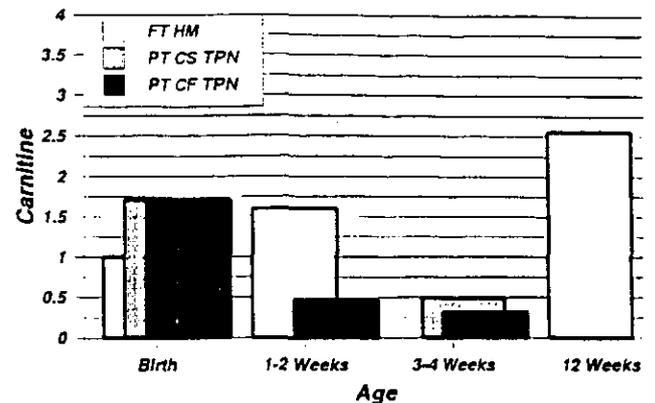


Figure 3. Red blood cell carnitine concentration data of infants (at different ages and receiving different dietary carnitine intake) normalized to the red blood cell carnitine data of cord blood from full-term neonates. The units for the original carnitine concentration data are nmol/mg hemoglobin. The full-term neonates received human milk (FT HM), and the preterm neonates received either total parenteral nutrition containing no carnitine (PT CF TPN) or total parenteral nutrition containing carnitine at 50 μ mol/mL and then 100 μ mol/mL (PT CS TPN). Figure is adapted from data reported by Borum et al.¹⁶

SYMPTOMS OF CARNITINE DEFICIENCY IN THE NEONATE

If delivery of the needed substrates (long-chain fatty acids) to the mitochondrial matrix were the only function of, or even the main function of carnitine, evaluation of the carnitine conditional essentiality hypothesis would be relatively straightforward. Neonates who receive inadequate dietary carnitine would have biochemical and clinical symptoms associated with impaired β -oxidation of long-chain fatty acids. Biochemical symptoms such as an altered intravenous fat tolerance test, decreased oxidation of exogenous fatty acids, and decreased production of ketone bodies would be expected. The expected clinical symptoms would be intolerance of intravenous lipid emulsions, failure to thrive, and impaired function of organs such as cardiac muscle and skeletal muscle that are highly dependent on fatty acid oxidation for fuel. Several studies have shown that preterm neonates maintained on carnitine-free total parenteral nutrition always have decreased plasma carnitine concentrations. Although there is some inconsistency, many of the studies show an impaired ability to use long-chain fatty acids infused intravenously as a commercially available lipid emulsion.²³⁻²⁸

In the past, it has often been assumed that the need for carnitine in the neonatal diet is directly related to the amount of long-chain fatty acids in the diet. Many formulas designed for preterm neonates contain higher concentrations of medium-chain fatty acids than are found in formula designed for full-term neonates. Unfortunately, some of the formulas containing high concentrations of medium-chain fatty acids have been promoted as containing fat that is oxidized independently of carnitine. The medium-chain fatty acids in formulas that contain small percentages of medium-chain triglycerides are probably

oxidized in the liver, where carnitine would not be required. However, when a formula contains 50% or more of the fat as medium-chain triglyceride, tissues such as muscle are expected to use the medium-chain fatty acids as a source of calories, and thus carnitine is required for oxidation.²⁹ When 13 growing preterm infants (mean birth weight, 1.42 kg) received 46% of their dietary triglyceride as medium-chain fatty acids, they had higher concentrations of urinary octanoate, sebacate, suberate, adipate, 7-hydroxyoctanoate, and 5-hydroxyhexanoate than when they received only 4% of their dietary triglyceride as medium-chain fatty acids.³⁰

The interrelationship of carnitine metabolism and medium-chain fatty acid metabolism has also been shown in term infants. Term infants fed formula with predominantly medium-chain fatty acids excreted a higher concentration of acylcarnitine than when they were fed a formula with long-chain fatty acids.³¹ In addition, when infants were fed medium-chain fatty acid formula, they excreted more medium-chain dicarboxylic acids than when they consumed long-chain fatty acids and more than infants fed the same medium-chain fatty acid formula supplemented with carnitine.³¹ In another study, normal male full-term neonates fed soy formula without carnitine from 6 to 9 days to 112 days of life had lower serum carnitine, higher serum free fatty acids, and higher excretion of all their medium-chain fatty dicarboxylic acids than the infants receiving the soy formula supplemented with carnitine.³²

Carnitine also plays an important role in nitrogen metabolism in neonates. Preterm infants were fed human milk or human milk supplemented with carnitine, 300 nmol/mL, for 7 days. At day 7, approximately 50% of the supplement was being excreted in the urine, indicating that some of the supplement was contributing to the tissue accretion of carnitine. The infants receiving the carnitine-supplemented human milk showed increased plasma carnitine, increased β -hydroxybutyrate, lower plasma concentrations of amino acids alanine and glutamine, decreased plasma urea, and decreased nitrogen excretion. The authors reported a trend of decreased excretion of 3-methylhistidine with carnitine supplementation, suggesting a reduced protein catabolism.^{33,34} Consistent with a role of carnitine in nitrogen metabolism, supplementation of total parenteral nutrition with carnitine has been reported to improve nitrogen balance and to improve growth of preterm infants.²⁴ Data from a recent report are consistent with earlier reports that carnitine supplementation of total parenteral nutrition of preterm neonates increases plasma carnitine concentrations and increases tolerance to intravenous fat emulsions, with enhanced ketogenesis.³⁵ Other investigators have found lower plasma free carnitine associated with higher concentrations of blood ammonium in low-birth-weight infants. They suggest that carnitine status may regulate blood ammonium levels.³⁶

In addition to symptoms that are consistent with altered fatty acid metabolism or altered nitrogen metabolism, many case studies have reported carnitine deficiency associated with a wide variety of symptoms in neonates. For example, one group of investigators have suggested that carnitine deficiency is a possible cause of gastrointestinal dysmotility. They studied one infant with a diet containing low concentrations of carnitine until 3 years of age who had gastrointestinal dysmotility manifested by postprandial vomiting, oral drooling, delayed gastric emptying, and infrequent bowel movements. At 3 years of age, the patient had low serum carnitine concentrations, and a muscle biopsy showed deposition of lipid between myofibrils and unusually shaped mitochondria. He was changed to a meat-based diet high in carnitine and showed a dramatic clinical recovery, with disappearance of chronic drooling, improved gastric motility, and improved muscle strength.³⁷

CARNITINE REQUIREMENTS OF NEONATES WITH METABOLIC DISEASE

Children with a variety of metabolic diseases have been shown to have altered plasma carnitine concentrations. Some of the metabolic errors involve the acylcarnitine transferases or the translocase.^{38,39} During the past 20 years, many patients have been described with muscle carnitine deficiency and a lipid storage myopathy.^{40,41} Recently, numerous patients have been identified with medium-chain acyl-CoA dehydrogenase deficiency who have a secondary carnitine deficiency.⁴²⁻⁴⁴ Several types of organic acidemia such as propionic acidemia⁴⁵ are often accompanied by a secondary carnitine deficiency. In addition, some medications such as valproic acid cause a secondary carnitine deficiency in some patients.^{46,47} Many of the secondary carnitine deficiencies appear to be the result of excessive excretion of carnitine as the ester of the accumulating metabolite. Although the detoxification role of carnitine is useful in the effort to maintain normal metabolism, the increased requirement for carnitine exceeds normal biosynthetic capability and typical dietary intake. The role of carnitine in these metabolic diseases are discussed in greater detail in other articles in this supplement.

Children with inborn errors not typically associated with carnitine supplementation may benefit from increased intake. For example, children with cystic fibrosis have abnormally low total, free, short-chain, and long-chain carnitine in plasma.⁴⁸ Dietary carnitine increased the total and free carnitine concentrations to that of the reference population, but short-chain and long-chain carnitine concentrations remained low.⁴⁸

Some neonates being evaluated for incompletely defined syndromes such as sudden infant death syndrome may benefit from carnitine supplementation. It has been recommended that all neonates who are determined to be at risk for sudden infant death syndrome have blood carnitine analysis included in the work-up.⁴⁹

DIETARY SUPPLEMENTATION VERSUS PHARMACOLOGIC TREATMENT

Carnitine is both a nutrient and a drug. The breast-fed neonate appears to benefit greatly from dietary carnitine but receives less than 5 mg/kg daily. In contrast, children with primary and secondary carnitine deficiency are routinely treated with daily doses of 100 mg/kg, and some children receive even higher doses. There is a growing body of evidence that patients such as those with renal disease being treated with hemodialysis benefit from carnitine supplementation at low dosages but may lose that benefit or even experience adverse effects from higher doses. Adverse effects are extremely rare in the many investigations evaluating carnitine supplementation even at oral doses of 100 mg/kg daily.

There is one report of intravenous supplementation at 10 to 30 times the usual oral carnitine intake that resulted in impaired growth. Low-birth-weight infants were given total parenteral nutrition supplemented with 48 mg/kg of carnitine daily for days 4 through 7 of life. Free and total plasma carnitine concentrations increased approximately 10-fold. The supplemented group took 9 days to regain birth weight, whereas the unsupplemented group took 7 days. Fat oxidation was increased in the supplemented group, but protein oxidation as measured by nitrogen excretion in the urine was increased in the supplemented group. The conclusion of this investigation was that the infants should not be supplemented intravenously with such high doses.⁵⁰

PRUDENT APPROACH TO DIETARY INTAKE OF CARNITINE IN NEONATES

A nutrient can be designated essential after it is demonstrated that decreased intake causes decreased body stores accompanied by pathophysiology and that both the decreased stores and the pathophysiology can be reversed or prevented with adequate intake of the nutrient. It is clear that lack of carnitine intake by the neonate alters circulating carnitine and tissue carnitine concentrations. Data concerning pathophysiology accompanying the lack of carnitine intake that can be consistently prevented or reversed with carnitine intake are much more difficult to obtain in a consistent manner. The neonates who are receiving a carnitine-free diet in the United States are usually very immature and very sick, with a broad spectrum of pathophysiologies of multifactorial origin. For both technical and ethical reasons, it has been very difficult to design studies that would tease out the symptoms due to carnitine deficiency. As investigators, we continue to perform studies showing that when compared to preterm neonates receiving exogenous carnitine, preterm neonates not receiving exogenous carnitine (1) have lower blood total and free carnitine; (2) may have reduced tolerance of dietary fat, with reduced blood concentrations of ketone bodies; (3) may have reduced tolerance of dietary protein, with increased blood ammonia concentrations; and (4) may have slightly reduced growth

Table 1. Questions Concerning Carnitine Supplementation of Preterm Neonates That Need to Be Addressed in the Human Neonate or in the Neonatal Animal Model

1.	How does carnitine supplementation affect the profile of individual acylcarnitines (from C2 through C24) in different tissues, in different components of circulating blood, and in excreted carnitine?
2.	What are the pharmacokinetics and tissue metabolic compartmentation of different levels of carnitine supplementation?
3.	Which readily accessible carnitine parameters are the best assessment indicators of carnitine status?
4.	Does carnitine supplementation of preterm neonates alter any or all of the following?
	Oxidation of long-chain and medium-chain fatty acids in specific tissues
	Glucose production and utilization in specific tissues
	Protein synthesis and degradation in specific tissues
	Excretion of exogenous toxic acyl-CoA compounds and endogenous metabolites that accumulate to toxic concentrations
	Brain growth and myelination
	Surfactant synthesis
	Anemia of prematurity
	Antioxidant defenses
	Prostaglandin synthesis and degradation
	Cardiac function
	Skeletal muscle function
	Renal function
	Hepatic function
	Immunologic defenses

rate. Today we have the analytic chemistry techniques and the neonatal animal models that will allow us to address the issues listed in Table 1 and therefore bring us closer to either proving or disproving the essentiality of exogenous carnitine for the neonate.

When caring for neonates, one cannot delay feeding the neonates until the carnitine conditional essentiality hypothesis is either proved or disproved. At this point in the mid 1990s, there are several reports of benefit and no reports of adverse effects when neonates receive carnitine supplementation at approximately 2 to 10 mg/kg daily. The quality of the carnitine being used for supplementation is very important. Many of the non-pharmaceutical-grade products are of very poor quality and should never be administered to neonates.⁵¹

Reports concerning the role of carnitine in metabolism and its usefulness in patient care are appearing in the literature with great rapidity. It is the opinion of this reviewer that in the future, with improved techniques for assessing carnitine status of the individual neonate and with improved techniques for tracking the metabolism of administered carnitine, carnitine supplementation will play an even more important role in care of neonates than it does today.

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