Invited Review

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The Use of Carnitine in Pediatric Nutrition

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ABSTRACT: Carnitine is synthesized endogenously from methionine and lysine in the liver and kidney and is available exogenously from a meat and dairy diet and from human milk and most enteral formulas. Parenteral nutrition (PN) does not contain carnitine unless it is extemporaneously added. The primary role of carnitine is to transport long-chain fatty acids across the mitochondrial membrane, where they undergo β-oxidation to produce energy. Although the majority of patients are capable of endogenous synthesis of carnitine, certain pediatric populations, specifically neonates and infants, have decreased biosynthetic capacity and are at risk of developing carnitine deficiency, particularly when receiving PN. Studies have evaluated for several decades the effects of carnitine supplementation in pediatric patients receiving nutrition support. Early studies focused primarily on the effects of supplementation on markers of fatty acid metabolism and nutrition markers, including weight gain and nitrogen balance, whereas more recent studies have evaluated neonatal morbidity. This review describes the role of carnitine in metabolic processes, its biosynthesis, and carnitine deficiency syndromes, as well as reviews the literature on carnitine supplementation in pediatric nutrition.

Carnitine, a nutrient that is synthesized from methionine and lysine in the liver and kidney, has gained increasing attention as a therapeutic agent over the last 4 decades. The use of carnitine supplementation in pediatric parenteral nutrition (PN) and enteral nutrition (EN) has been studied in neonates and infants, both premature and term, as well as in children.[1–24] Early studies focused on the potential benefits of carnitine supplementation on markers of fatty acid metabolism, including improved IV fat emulsion (IVFE) tolerance, whereas the most recent data have evaluated its effects on neonatal morbidity. This review will thoroughly discuss the role of carnitine in metabolic processes, its biosynthesis, carnitine deficiency syndromes, as well as give an overview of the literature studying the effects of carnitine supplementation in pediatric nutrition.

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Role of Carnitine in Metabolism

Carnitine plays an important role in fatty acid oxidation. Without the facilitation of carnitine, long-chain fatty acids (LCFAs) are unable to pass through the mitochondrial membrane to the site of β-oxidation and energy production. Therefore, one of the most critical functions of carnitine is the transport of LCFAs into the mitochondria, which is delineated in Figure 1. Although medium-chain fatty acids do not require carnitine transport into the mitochondria, carnitine is also involved in the oxidation of mediumchain fatty acids in the cytosol.[25–31] These functions occur under the control of the carnitine acyltransferases, specifically, carnitine acetyltransferase for short-chain acyl groups, carnitine octanoyltransferase for medium-chain acyl groups, and carnitine palmitoyltransferase for long-chain acyl groups.[32] For the purposes of this review, however, the enzymes will be referred to simply as acyltransferases. Under the influence of acyltransferase I, carnitine initially binds to long-chain acyl CoA on the cytosolic side of the mitochondrial membrane, thereby freeing CoA. The newly formed acylcarnitine esters are then ready for transport across the mitochondrial membrane *via* the enzyme carnitine translocase. Once the acylcarnitine esters are inside the mitochondria, carnitine is removed from the acyl group *via* acyltransferase II, thereby yielding CoA available for β-oxidation.

Through carnitine's mediated transport of LCFAs, it also has 3 other distinct functions (Figure 2).[25–31] A free CoA pool, both in the cytosol and within the mitochondrial membrane, is necessary for many metabolic processes and pathways, including the citric acid cycle, ketogenesis, and gluconeogenesis.[27,28] When the acyl group of acyl CoA combines with carnitine, acylcarnitine esters are formed which can then be removed from the mitochondrial membrane and cell and thereby eliminated by the

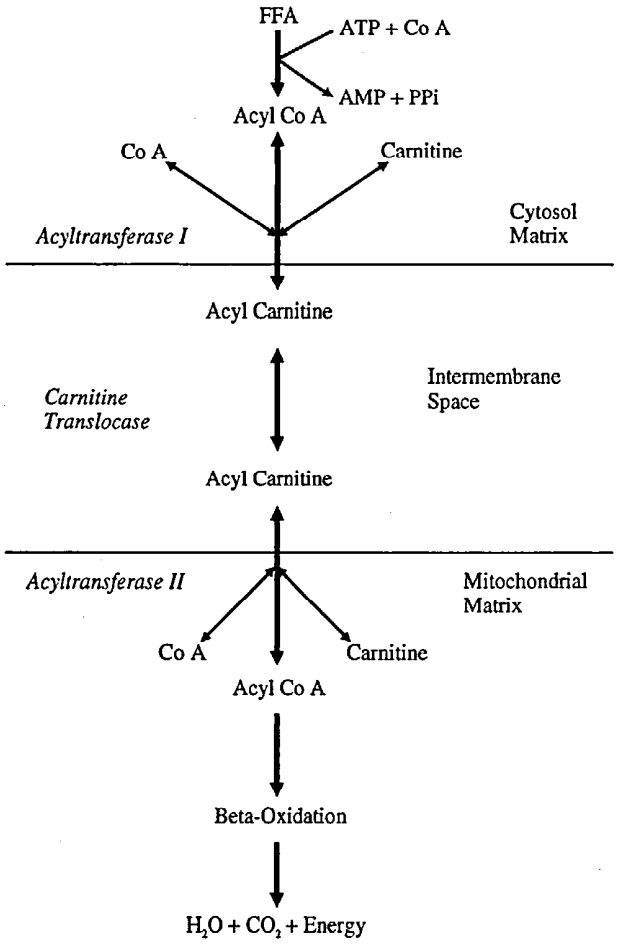

Figure 1. Carnitine-mediated transport of long-chain fatty acids into mitochondria. Reprinted with permission from *Hosp Pharm.* 1993;28:843, 847–850.
FFA, fatty free acids.

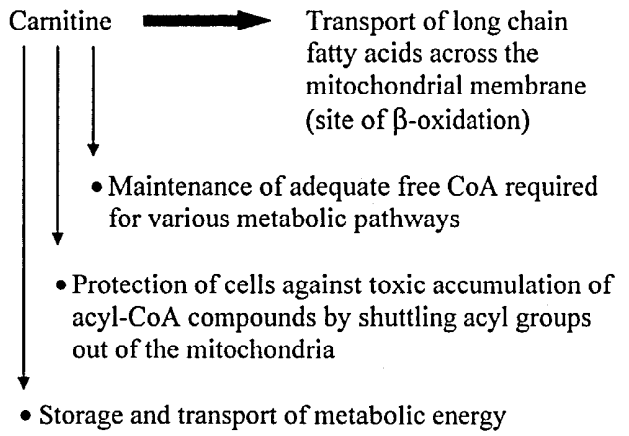

Figure 2. Functions of carnitine. Reprinted with permission from Crill CM, Wang B, Storm MC, Helms RA. Carnitine: a conditionally essential nutrient in the neonatal population? *J Pediatr Pharmacol Ther.* 2001;6:225–236.

liver or kidney.[26] This transport of acylcarnitine esters out of the mitochondria serves 2 purposes. First, it maintains a pool of free CoA at the mitochondrial membrane, and second, it protects cells against high, and potentially toxic, concentrations of acyl CoA compounds that could inhibit enzyme activity in metabolic processes, thereby ultimately altering cellular ATP production.[26,33] It is through this mechanism that carnitine is essential in certain disorders of fatty acid metabolism and organic acidurias.[26,31,34] Finally, through its transport of acyl CoA compounds in and out of the mitochondria, carnitine stores and transports metabolic energy within and between cellular compartments.[25,26]

Carnitine Biosynthesis

Carnitine is derived from meat and dairy products in the diet. Even with a strictly vegetarian diet, sufficient carnitine concentrations are maintained through endogenous synthesis from its amino acid precursors, lysine and methionine, derived from nonmeat protein in the diet. The carnitine biosynthetic pathway, shown in Figure 3, is important in that most individuals are capable of endogenous carnitine synthesis. This pathway is a series of biochemical reactions that rely on the availability of several cofactors, namely, ascorbic acid, iron, and B vitamins (niacin and pyridoxine). The initial step in the pathway is synthesis of peptide-linked trimethyllysine, whereas the final step in the pathway requires the hydroxylation of γ-butyrobetaine into L-carnitine under the enzymatic control of γ-butyrobetaine hydroxylase.

Neonates and infants may be at risk for developing carnitine deficiency because they lack sufficient activity of γ-butyrobetaine hydroxylase; activity of this enzyme is approximately 12% of that seen in adults.[35] For this reason, it is thought that decreased activity of this enzyme is the rate-limiting step for carnitine biosynthesis in infants, and the reason why they are at risk of carnitine deficiency. Individuals with renal or hepatic insufficiency, as well as those with deficiency in any or all of the cofactors necessary for the various metabolic reactions in the pathway, may not be able to synthesize carnitine sufficiently.[36] Studies have suggested that trimethyllysine production, which requires protein synthesis from lysine and methionine, also limits carnitine biosynthesis.[37,38] For this reason, other individuals may be at risk for developing carnitine deficiency, specifically, those with decreased methionine or lysine stores, decreased total protein stores and protein synthesis, or those undergoing protein catabolism.[31] In premature infants, the decreased ability to synthesize carnitine is further exacerbated by decreased carnitine tissue stores and a lack of placental carnitine transfer from mother to infant during the third trimester.

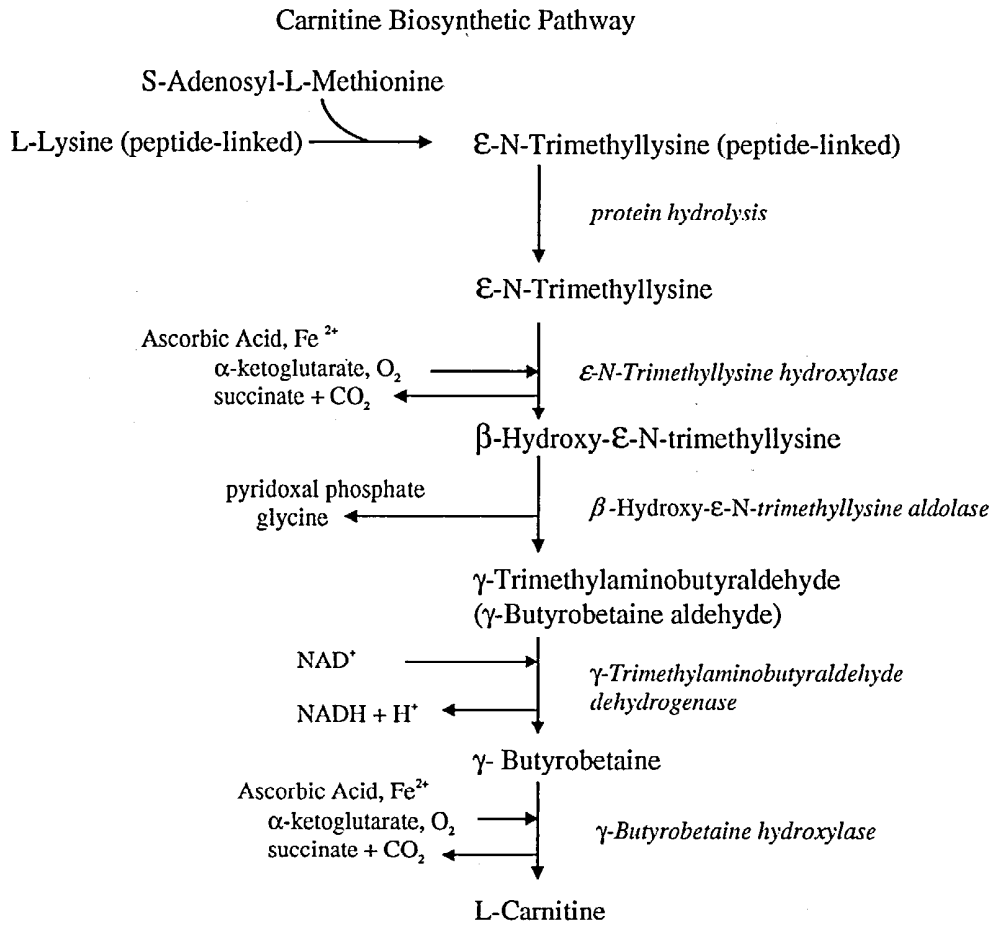

Figure 3. Carnitine biosynthetic pathway. Reprinted with permission from Crill CM, Wang B, Storm MC, Helms RA. Carnitine: a conditionally essential nutrient in the neonatal population? *J Pediatr Pharmacol Ther.* 2001;6:225–236.

Carnitine Assessment

A preferred marker for evaluating body carnitine status has yet to be defined. Carnitine is present in plasma, erythrocytes, and in tissue compartments (heart, kidney, liver, brain, and muscle). Most research studies have assessed carnitine status with plasma total or free carnitine concentrations, acylcarnitine or esterified fractions, and tissue or erythrocyte concentrations. The most common measurements used in the clinical setting are plasma total and free carnitine and acylcarnitine concentrations; free concentrations should be greater than acylcarnitine concentrations. In general, muscle carnitine concentrations are higher than plasma concentrations or any other tissue compartment. Carnitine insufficiency has previously been defined as a plasma free carnitine concentration <20 nmol/mL or an acylcarnitine:free carnitine ratio >0.4.[31,33,39]

Plasma total carnitine concentrations have been reported in children >1 year and adolescents maintained on a typical meat and dairy diet. Concentrations ranged from 28 to 84 nmol/mL, which is similar to normal adult carnitine concentrations.[31,40,41] A reference range for carnitine concentrations in the neonatal and infant population is reported to be between 31 and 61 nmol/mL for plasma total carnitine and >0.2 nmol/mg hemoglobin for red blood cell (RBC) total concentration.[25,42,43] Although RBC total carnitine concentrations have been suggested as a marker for tissue carnitine stores,[44] recent data in a group of premature infants suggest that RBC total carnitine is not influenced by circulating plasma total carnitine concentrations.[24]

Carnitine Deficiency Syndromes

The diagnosis of carnitine deficiency is based on clinical symptomatology and laboratory analysis. Because the primary function of carnitine is the transport of LCFAs to the site of β-oxidation, deficiency will result in LCFA accumulation in the cytosol, and decreased ketone and energy (ie, ATP) production *via* β-oxidation. During neonatal development, decreased ketone production can be detrimental, given that ketones provide a critical energy source for the developing brain and nervous system.[36] Furthermore, since the immediate postnatal

period is characterized by an increased reliance on endogenous and exogenous fat to meet energy needs; the availability of carnitine is critical for optimal fatty acid metabolism and ketogenesis. Decreased energy production has the potential to affect all metabolic processes and functions in the body. In particular, skeletal and cardiac muscles primarily rely on the breakdown of fatty acids for energy needs.[36,45]

Primary carnitine deficiency responds well to exogenous carnitine supplementation. Carnitine deficiency can present as myopathy or limb weakness, or as a systemic syndrome, and is characterized in both clinical presentations by depleted tissue stores and impaired fatty acid oxidation.[33,36] When all tissue carnitine concentrations are depleted, the systemic syndrome may occur, with symptoms that include myopathy, failure to thrive, hypotonia, hypoglycemia, hypoketonemia, encephalopathy, coma, and possible death.[31,33,36,46,47]

The most common causes of secondary carnitine deficiency are inborn errors of metabolism, organic acidurias, and acquired deficiency. With secondary deficiency, plasma total and free carnitine concentrations will be higher than that seen with primary deficiency; however, the acylcarnitine:free carnitine ratio will be >0.4. Acquired deficiency occurs with decreased synthesis (eg, renal or hepatic dysfunction, prematurity), increased urinary losses, and hemodialysis therapy, as well as with decreased absorption (eg, patients with short bowel syndrome), decreased dietary intake, decreased carnitine stores (eg, prematurity), low endogenous production (eg, decreased carnitine biosynthetic capacity), drug therapy (eg, zidovudine or valproic acid), and low exogenous intake (eg, infants receiving human milk or formula low in carnitine content or those receiving long-term carnitine-free PN).[31,33,36,46,47] In human milk-fed infants, decreased maternal carnitine status may promote acquired secondary carnitine deficiency in neonates/infants *via* a combination of decreased carnitine stores, low endogenous production, and low exogenous intake.[48]

Other clinical symptoms of carnitine deficiency include hypotonia, muscle weakness, hyperbilirubinemia, hepatic insufficiency, hyperammonemia, failure to thrive, recurrent infections, encephalopathy, nonketotic hypoglycemia, metabolic acidosis, and cardiac anomalies including cardiomyopathy, cardiomegaly, and cardiac failure.[29,30,36,49,50] Individuals with impaired fatty acid oxidation may present with increased triglyceride concentrations, decreased tolerance of IVFE, and decreased weight gain.[25,50,51] Clinical nutrition practitioners should be aware of the potential presentations and clinical symptoms of carnitine deficiency syndromes. Periodic assessment of carnitine status in patients at risk for deficiency or in those presenting with symptoms should be considered.

Carnitine Supplementation in Nutrition

As previously discussed, carnitine is present in a meat and dairy diet. Although human milk—assuming the mother has normal carnitine concentrations—is a good source of carnitine in the infant diet, providing approximately 60–70 nmol/mL carnitine,[25,52,53] premature human milk and some enteral formulas, such as modified protein formulas, may not contain adequate carnitine concentrations. For example, soy-based formulas are now supplemented with carnitine as a result of documented carnitine deficiencies in infants receiving all-soy diets.[3] The concentration of various cow's-milk infant formulas has been found to be comparable to or higher than that in human milk.[52] Although most infant formulas provide or are supplemented to provide a carnitine content similar to human milk, little is known regarding the bioavailability of carnitine in formulas. PN does not contain carnitine unless it is extemporaneously added.

The benefit of carnitine supplementation in pediatric nutrition is poorly understood. It has been documented that PN without carnitine supplementation in term and premature infants and children results in decreased plasma carnitine concentrations.[1,9,17,18,20–22,24,54–60] In addition, neonates and infants are incapable of sufficient endogenous production of carnitine and therefore must rely on exogenous supply. Premature neonates also have limited tissue stores. Although carnitine is considered a nonessential nutrient in adults, it may be considered a conditionally essential nutrient in pediatric populations, particularly neonates receiving PN.

A search of the literature identified 24 papers (Table 1) evaluating the effects of carnitine supplementation in PN and EN on carnitine status (total, free, RBC, and acylcarnitine concentrations), markers of β-oxidation and ketogenesis (plasma β-(OH)-butyrate, acetoacetate, free fatty acids, triglycerides, ketone production), nutrition markers (IVFE tolerance, weight gain, and nitrogen balance), and neonatal morbidity (apnea, time on mechanical ventilation, hospital stay, growth).[1–24] In studies assessing carnitine status, supplementation resulted in increased carnitine concentrations.[1–3,7–13,15–18,20–22,24] Only 1 report documented consistently low carnitine concentrations despite supplementation, and this occurred in a patient with short bowel syndrome receiving oral supplementation in 3 divided doses daily.[19]

Fatty Acid Oxidation and Nutrition Markers

In neonates, both premature and term, and infants, carnitine supplementation *via* PN has resulted in improved fatty acid metabolism.[1,4,9,16–18,31]; similar effects have been seen with carnitine supplementation in EN.[3,8,11–14] A few studies evaluating supplementation *via* PN have documented only a slight effect or no effect.[2,5,7] Term infants fed a soy-based formula with-

Table 1
Studies of L-carnitine supplementation in parenteral and enteral nutrition

Study	Design	Patient characteristics	Intervention	Results
Schmidt-Sommerfeld, 1983[1]	RCT	29 preterm neonates receiving PN Enrolled ≤DOL 2	10 mg/kg/d C IV over 5 h *via* PN for ~7 d IVFE infusion post supplementation	Increased plasma total C. Lower FFA:BOB ratio and greater increase in acyl-C in neonates 29–33 wk GA.
Curran, 1983[2]	RCT	24 preterm neonates receiving PN Enrolled ≤DOL 7	PN (no IVFE/no C) PN (no IVFE/oral C) PN (IVFE/no C) PN (IVFE/oral C) C supplement = 13 μmol/kg/d in 4 divided doses for 12 d	Increased serum total C. No difference in TG, FFA, BOB or N retention.
Novak, 1983[3]	RCT	12 term infants receiving EN Enrolled ≤DOL 2	Soy formula + 50 nmol/mL C Supplemented for up to 5 mo	Increased plasma total C and acyl-C. Decreased FFA, TG, and VLDL at 2–3 mo. No difference in BOB.
Orzali, 1983[4]	CT	21 term/preterm neonates receiving PN Enrolled ≤DOL 2	4-h IVFE infusion, followed by 100 mg/kg C bolus + 100 mg/kg C over 6 h 4-h IVFE infusion after bolus; single-dose supplementation	Greater plasma BOB, ACA, and FFA. No difference in TG.
Orzali, 1984[5]	LS	11 surgical term/preterm neonates after 7 d of C-free PN	4-h IVFE infusion, followed by 100 mg/kg C bolus + 100 mg/kg C over 6 h 4-h IVFE infusion after bolus; single-dose supplementation	No change in plasma FFA, TG, or BOB.
Rubecz, 1984[6]	LS	5 infants	C supplementation for 3 d IVFE infusion pre/post supplementation	Increased disappearance rate of TG.
Coran, 1985[7]	RCT	12 surgical term/preterm neonates after 7 d of C-free PN	70 μmol/L of C/kg/d given orally every 3 h for 7 d IVFE challenge pre/post supplementation	Increased plasma total C and RBC-C. No difference in FFA, TG, or ketone production.
Melegh, 1986[8]	CT	10 preterm neonates receiving combined PN/EN Enrolled by 1–2 wk of age	9.6 mg/kg/d C to pooled HM divided equally among feedings for 7 d IVFE infusion post supplementation	Increased plasma total C, BOB, and ketone production.
Helms, 1986[9]	RCT	14 infants receiving long-term C-free PN Enrolled ~ 3 mo of age	10 mg/kg/d C *via* continuous NG or GT for 7 d IVFE infusion pre/post supplementation	Increased plasma total C, BOB, and ACA. Greater urinary C excretion. No difference in FFA or TG.
Novak, 1987[10]	RCT	32 term infants receiving EN (SCMF) Enrolled by DOL 3–7	Soy formula Soy formula + 50 nmol/mL C Soy formula + 250 nmol/mL C Supplementation for 3 mo	Increased plasma free C. Greater urine concentration of free C with 250 nmol/mL.
Melegh, 1987[11]	LS	20 LBW preterm infants receiving EN Enrolled by 10–33 d PNA	Pooled HM + 300 nmol/mL C Supplementation for 7 d	Increased plasma total C, free C, acyl-C, and BOB. Decreased TG, urea and total N excretion.
Melegh, 1988[12]	LS	18 HM-fed infants Enrolled by 16–41 d PNA	Pooled HM +300 nmol/mL C Supplementation for 7 d	Increased plasma total C, free C, acyl-C, and BOB. Decreased urea and total N excretion. No difference in FFA.
Olson, 1989[13]	RCT	23 term infants Enrolled by DOL 6–9	Soy formula + 86 nmol/mL C Supplementation for 4 mo	Increased plasma total C, free C, and acyl-C. Decreased FFA. Less excretion of medium-chain dicarboxylic acids. No difference in TG or growth.
Melegh, 1990[14]	CT	29 preterm infants receiving mixed EN (pooled HM/formula)	Formula + 600 nmol/mL C Supplementation for 7 d	Decreased ammonia and urea excretion. No difference in plasma BOB.

(Continued)

Table 1
Studies of L-carnitine supplementation in parenteral and enteral nutrition (Continued)

Study	Design	Patient characteristics	Intervention	Results
Sulkers, 1990[15]	CT	24 preterm neonates receiving PN Enrolled on DOL 1	48 mg/kg/d C given with IVFE for 7 d	Increased plasma total C, free C, acyl-C, and acyl:free C ratio. Increased fat and protein oxidation. Decreased N balance, weight gain.
Larsson, 1990[16]	RCT	12 preterm neonates receiving PN Enrolled on DOL 1	10 mg/kg/d C added to IVFE infusion for 5–21 d	Increased plasma total C, free C, and BOB.
Helms, 1990[17]	RCT	43 preterm neonates receiving PN Enrolled ~2–3 wk PNA	~10 mg/kg/d C for 7 d followed by ~ 20 mg/kg/d C for another 7 d IVFE infusion pre/post supplementation (d 7 and 14)	Increased plasma total C, N balance, and weight gain. Decreased TG and FFA. Greater (BOB+ACA):FFA ratio after second wk of supplementation (~20 mg/kg/d)
Bonner, 1995[18]	RCT	43 preterm neonates initially receiving PN Enrolled ≤DOL 2	10 mg/kg/d C continuous IV infusion for 2 wk	Increased plasma total C, RBC-C (at 2 wk in infants 1001–1500 g), weight gain (first 2 wk of life), and fat tolerance. Decreased BOB in unsupplemented group.
Hirose, 1997[19]	CS	3-y-old with SBS receiving long-term PN	PN (no IVFE/no C) PN (no IVFE/oral C) PN (IVFE/no C) PN (IVFE/oral C) Regimens maintained at least 10 d before analysis C supplement = 60, 90, and 120 mg/kg/d orally in 3 divided doses	Consistently low plasma total C despite increasing dose.
Shortland, 1998[20]	RCT	86 preterm neonates receiving IVF/EN Enrolled ≤DOL 3	25 mg/kg/d C IV initially, then oral Supplemented until 40 wk GA	Increased plasma total C, free C, and acyl-C. No difference in growth or incidence of hypoglycemia.
O'Donnell, 2002[21]	RCT	41 preterm neonates initially receiving PN Enrolled ≤DOL 2	30 mg/kg/d C *via* PN initially, then oral in a single daily dose Supplemented until 34 wk adjusted age	Increased plasma total C. Increased periodic breathing on DOL 4 (no change on DOL 8 and DOL 12). No difference in apnea, time on mechanical ventilation, growth, time to regain BW, or hospital stay.
Whitfield, 2003[22]	RCT	64 preterm neonates initially receiving PN Enrolled ≤DOL 4	15 mg/kg/d C *via* PN initially, then 100 mg/kg/d *via* EN in 4 divided doses Supplemented until 36 wk PCA	Increased plasma total C, free C, and acyl-C. No difference in growth or apnea.
Pande, 2005[23]	RCT	63 preterm neonates initially receiving PN Enrolled ≤DOL 3	10 mg/kg/d C *via* PN initially, then *via* EN in 3 divided doses Supplemented until 36 wk PCA	No difference in daily weight gain, time to regain BW, or length of stay.
Crill, 2006[24]	RCT	29 preterm neonates initially receiving PN Enrolled ≤DOL 4	20 mg/kg/d C *via* PN initially, then *via* EN divided in each enteral feeding Supplemented for 8 wk	Increased plasma total C and RBC-C. More rapid return to BW and decreased percent periodic breathing.

Acyl-C, acylcarnitine; ACA, acetoacetate; BOB, β(OH)butyrate; BW, birthweight; C, carnitine; CS, case study; CT, controlled trial; DOL, day of life; EN, enteral nutrition; FFA, free fatty acid; GA, gestational age; GT, gastric tube; HM, human milk; IVF, IV fluid; IVFE, intravenous fat emulsion; LBW, low birthweight; LS, longitudinal study; N, nitrogen; NG, nasogastric; PCA, postconceptional age; PNA, postnatal age; PN, parenteral nutrition; RBC-C, red blood cell carnitine; RCT, randomized controlled trial; SBS, short bowel syndrome; SCMF, standard cow's-milk formula; TG, triglyceride; VLDL, very-low-density lipoprotein.
Adapted from: Crill CM, Wang B, Storm MC, Helm RA.
Carnitine: a conditionally essential nutrient in the neonatal population? *J Pediatr Pharmacol Ther.* 2001;6:225–236. With permission from the Pediatric Pharmacy Advocacy Group.

out supplemented carnitine had significantly higher serum free fatty acid concentrations and greater urinary excretion of medium-chain dicarboxylic acids than infants who received supplementation. These results suggest that increased metabolism of fat by carnitine-independent pathways may produce short- or medium-chain dicarboxylic acids.[13]

Several studies have found benefits of carnitine supplementation in PN and EN on nutrition markers, primarily improved IVFE tolerance, and increased nitrogen balance.[11,12,14,17,18] In addition, carnitine supplementation has been found to be important for weight gain in neonates.[17,18,24] Other studies have found no effect on growth.[20–23]

The investigators of a previously published study[15] have speculated that the use of higher doses may have negative effects. In this study, increased substrate metabolism (fat and protein) and decreased nitrogen balance and weight gain were reported in neonates receiving 48 mg/kg/d carnitine.[15] The lack of effect with carnitine supplementation in some studies may be explained by differences in study design, specifically, the dose and method of carnitine administration (ie, single doses compared with continuous therapy), time of initiation, and length of therapy.[31]

Respiratory and Gastroesophageal Morbidity

Improved respiratory and gastrointestinal symptomatology has been documented with carnitine supplementation. In one report, 2 weeks of a carnitine-supplemented diet resulted in resolution of gastrointestinal dysmotility and myopathy, as well as improved language, in a developmentally delayed child with low serum carnitine concentrations.[45] In another report, a twin infant died of Sudden Infant Death Syndrome (SIDS), which resulted in closer analysis of the family. Both twin infants and another infant sibling had abnormal acylcarnitine concentrations, and the mother was found to be carnitine deficient. The surviving infants, one fed a soy-based formula and the other fed human milk, had apnea and periodic breathing, as well as gastroesophageal reflux by pH probe study. All respiratory abnormalities resolved with carnitine supplementation.[48]

Neonatal Morbidity

The most recent work evaluating carnitine supplementation has focused on neonatal morbidity. Most of these studies have found no benefit with carnitine supplementation on growth, periodic breathing, apnea, time receiving mechanical ventilation, or hospital stay.[20–23] One study, however, documented decreased periodic breathing and more rapid return to birth weight in neonates receiving 20 mg/kg/day carnitine initially *via* PN, followed by EN supplementation (daily dose divided with each enteral feeding) once the neonates were taking sufficient enteral calories.[24] Another study, published only in abstract form, evaluated the effect of carnitine supplementation in premature neonates with apnea and found a significant decrease in the incidence of apnea and mechanical ventilation in the supplemented group.[61] The authors of a systematic review have referenced this study and stated that the authors did not submit the data for paper publication because they found the results to be incorrect.[62]

The effect of carnitine on neonatal morbidity in 1 study and the lack of effect in others may be explained by differences in dosing strategies as well as by study design. Two studies that found no difference in respiratory morbidity and weight gain gave larger carnitine doses and reported higher plasma total carnitine concentrations (up to 250 nmol/mL in 1 study and up to 343.6 nmol/mL in the other).[21,22] In addition, differences in dosing regimens when neonates were supplemented enterally may have resulted in variable carnitine concentrations across the study period. One of the studies concluded no effect with carnitine supplementation, but there was a statistical difference between groups in the initial cardiorespirogram recording on day-of-life 4 (neonates were enrolled by 48 hours of age). There was no difference between groups on the next cardiorespirogram recording 4 days later. It is possible that the carnitine-supplemented infants had greater respiratory morbidity at baseline that resolved once supplementation was initiated.[24] The neonates in this study were relatively stable from a respiratory standpoint because infants were eligible for enrollment only if they were nonintubated on nasal continuous positive airway pressure or intubated with a rate of <6 breaths per minute.[21]

Systematic Reviews

Two systematic reviews have been published evaluating the use of carnitine supplementation in PN and EN.[62,63] The first review, published in 2001, evaluated the effects of carnitine supplementation on weight gain (primary objective) and IVFE tolerance and ketogenesis (secondary objective).[63] At the time of the evaluation, 14 studies were identified and only 6 met the criteria for inclusion into the review. Studies were excluded due to lack of randomization (n = 5), the use of different IVFE products among groups (n = 2), and provision of primarily EN (n = 1). Although the authors of the systematic review concluded that there was no evidence to support the routine supplementation of parenterally fed neonates with carnitine, 4 of the evaluated trials found positive effects with respect to growth, improved fatty acid metabolism, or IVFE tolerance.[1,16–18] The design of the systematic review also excluded trials of carnitine supplementation *via* EN, which have also found positive effects.[3,8,11–14] The second systematic review, published in 2004, evaluated the effect of carnitine supplementation on

apnea of prematurity and concluded that the evidence did not support the regular use of carnitine for prevention of apnea.[62] Only 2 studies were included in this review.[21,22]

Administration and Bioavailability

The only available FDA-approved pharmaceutical product is L-carnitine inner salt or zwitterion form (Carnitor; Sigma Tau Pharmaceuticals, Inc, Gaithersburg, MD). It is available as sterile injection (200 mg/mL), oral solution (100 mg/mL), and tablet (330 mg). The sterile injection form is stable in pediatric 2-in-1 PN formulations and y-site compatible with IVFE.[64,65] Nonpharmaceutical-grade products are available; however, these products should not be considered interchangeable with the FDA-approved product.[31] Due to a lack of quality control in the manufacturing of these products, they may contain as little as 40% of the purported amount of carnitine.[31,66] Because carnitine is excreted almost completely *via* the kidneys, patients with renal dysfunction may not be able to adequately eliminate carnitine.[67,68]

Although doses of 50–100 mg/kg/d L-carnitine (maximum 3 g/d) is used for patients with carnitine deficiency syndromes,[31] studies in neonates and infants have found increased serum carnitine concentrations with 10–20 mg/kg/d.[1,8,9,16–18,20–22,24] L-Carnitine therapy has little known or observed adverse effects at doses of approximately 10–20 mg/kg/d. When using larger doses or with the oral product, gastrointestinal symptoms, specifically diarrhea, nausea, and cramping, may appear.[31,69] The labeling for L-carnitine includes an increased risk for seizure activity in patients receiving oral and IV L-carnitine who may or may not have underlying seizure disorders.[69] Communication with the manufacturer when the labeling was revised to include this risk revealed that there had been 13 reports of seizure occurrence in patients receiving L-carnitine.[31] Seizures occurred most commonly in adult and adolescents already predisposed to seizures, including patients receiving dialysis and anticonvulsants.[31] In children and infants, predisposing factors included microcephaly, metabolic acidosis, and large carnitine doses.[31] According to the available data and the fact that negative effects have been seen with doses of approximately 50 mg/kg/d,[15] the recommended dose of carnitine supplementation in pediatric nutrition patients (ie, patients with acquired secondary deficiency syndromes) should be 10–20 mg/kg/d. Other recommendations for carnitine supplementation in pediatric patients are outlined in Table 2.

Table 2
Recommendations for carnitine supplementation in pediatric nutrition patients

	Recommendation
Initiate therapy	Neonates/infants (premature/term) expected to be on PN ≥7 d
Consider therapy	PN patients with IVFE intolerance, increased TG
	Patients with SBS, diffuse IBD, or malabsorption syndrome requiring a portion of caloric intake *via* PN*
Dose	10–20 mg/kg/d; may be given IV or orally†
When to initiate therapy	Day 1 of PN
Length of therapy	No data to support continued supplementation after sufficient enteral intake achieved‡

*In patients outside of infancy, recommend carnitine assessment before supplementation.
†With enteral supplementation, recommend giving total daily dose in divided doses throughout a 24-hour period.
‡In patients at risk for malabsorption (SBS, diffuse IBD), periodic carnitine assessment may be warranted.
IBD, inflammatory bowel disease; IV, intravenous; IVFE, intravenous fat emulsion; PN, parenteral nutrition; SBS, short bowel syndrome; TG, triglyceride.

Although larger doses of oral carnitine have been used due to concerns of reduced bioavailability, studies suggest that carnitine is adequately absorbed if given in divided doses throughout the day.[8,9,20,24] Carnitine bioavailability after oral dosing has been reported to range from 5% to 18%[70–73]; however, most of these studies have evaluated bioavailability after large single oral doses of carnitine. These lower estimates of bioavailability may in part be due to a dose-dumping effect after administering single oral doses.[74] A recent study administering 20 mg/kg/d in divided doses with each enteral feeding documented stable carnitine concentrations when neonates transitioned from supplementation *via* PN to EN and an estimated oral carnitine bioavailability of approximately 80%.[74] This study and others, using similar dosage regimens, have also reported serum carnitine concentrations that have exceeded the reference range within a relatively short period of supplementation (≤7 days), which may support the use of smaller doses in the future.[8,20,74]

Because the primary mechanism for absorption of exogenous carnitine is by passive diffusion in the small intestine, certain patient populations, such as those with intestinal resections or other functional abnormalities of the gastrointestinal tract, may not be capable of adequate oral absorption of carnitine and therefore would require IV supplementation.[74] A case report has documented carnitine deficiency in a 3-year-old patient with short bowel syndrome who was receiving oral carnitine supplementation during chronic PN therapy.[19] Another study, however, found increased concentrations by giving the total daily dose over 24 hours *via* continuous nasogastric or gastric tube feedings.[9] In this study, postoperative infants with underlying disease of the bowel (eg, necrotizing enterocolitis and gastroschisis) and many with significant bowel loss had been receiving long-term carnitine-free PN. Although baseline car-

nitine status of the infants (9.4 ± 6.7 nmol/mL) suggested carnitine deficiency, they were able to achieve plasma carnitine concentrations within the 30–40 nmol/mL range after receiving 10 mg/kg/d oral carnitine for 7 days.[9]

Future Research Needs

Studies over the last several decades have suggested that pediatric patients, specifically neonates and infants, become carnitine deficient when given PN without carnitine supplementation. Carnitine supplementation has resulted in improved markers of fatty acid oxidation and nutrition; however, the data are not clear as to its benefit in neonatal morbidity and long-term clinical outcomes. Future avenues for carnitine research include studies that focus on determining the populations that benefit most from carnitine supplementation, the appropriate dose and duration of carnitine supplementation, whether or not there is a benefit in neonatal respiratory morbidity, and whether or not there is any additional benefit to carnitine supplementation once sufficient enteral feeding occurs. In addition, because red blood cell total carnitine concentrations do not correlate with plasma total carnitine concentrations, a surrogate marker for tissue carnitine stores is required to more accurately assess carnitine status.

Conclusions

Studies evaluating the use of carnitine supplementation in PN and EN have primarily shown benefit through improved markers of fatty acid oxidation, weight gain, and nitrogen balance. It is unclear whether there is any benefit of carnitine supplementation on neonatal morbidity. Recent studies suggest that enteral carnitine is well absorbed and can produce similar concentrations as IV carnitine when given in divided doses throughout a 24-hour period. Future research should focus on the potential benefit of carnitine on respiratory morbidity and the determination of an appropriate dose and length of carnitine supplementation in pediatric nutrition.

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