# The Metabolic Effects of Oral L-Carnitine Administration in Infants Receiving Total Parenteral Nutrition With Fat

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● β-Oxidation, an important pathway in the metabolism of free fatty acids, occurs within the mitochondria in mammals. L-Carnitine is an essential cofactor in the transfer of long-chain fatty acids across the inner mitochondrial membrane. Maintenance of normal carnitine concentrations in whole blood and tissues, either through diet or biosynthesis, would appear necessary for adequate utilization of fat as an energy source. Infants, especially premature ones, without an exogenous dietary source of carnitine, have decreased plasma carnitine levels compared with infants receiving carnitine-supplemented feedings. To determine the importance of carnitine supplementation in a total parenteral nutrition program in infants in which a fat emulsion serves as a major calorie source, the following study was undertaken. Twelve infants receiving total parenteral nutrition (TPN) with fat for seven days were divided into two treatment groups. Group 1 was orally supplemented for seven days with carnitine (70 umol/L/kg/24 h in 24 mL of 5% dextrose), while the second group received seven days of placebo supplementation (dextrose 5%, 24 cc/24 h). Plasma carnitine levels in the carnitine-supplemented group were significantly higher (29 ± 8 nmol/mL) than in the control group (12.4 ± 3.5 nmol/mL) after seven days of treatment. However, clearance of serum triglycerides and free fatty acids was not significantly different between the two groups. Baseline triglyceride levels in the carnitine-supplemented group were 96 ± 42 mg/dL, increased to 242 ± 101 mg/dL after the lipid challenge and decreased to 121 ± 47 mg/dL two hours after the lipid infusion. In the control group, baseline triglyceride levels were 93 ± 16 mg/dL, increased to 206 ± 101 mg/dL after the lipid infusion and decreased to 118 ± 54 mg/dL after two hours. In addition, ketone body production, a measure of fatty acid mobilization and clearance, was not significantly different between the two study groups. In conclusion, although carnitine is essential in the metabolism of free fatty acids, carnitine supplementation did not appear to improve triglyceride or free fatty acid clearance during TPN with fat. However, clearance in itself does not indicate whether the fatty acids are stored as triglycerides in the fat depots or are utilized as an energy source. Additionally, higher serum levels of carnitine, which could be achieved through intravenous supplementation, could have a significant effect on fat clearance.


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INFANTS UNDERGO a significant metabolic shift from utilizing glucose as a major energy source in utero to using fat as the major energy fuel postnatally.[1–3] Supporting this concept are observations that levels of free fatty acids and ketone bodies increase dramatically after birth.[1,4] Carnitine (β-hydroxy-γ-N-trimethylammonium butyrate) is required for the transport of long chain fatty acid esters through mitochondrial membranes, where energy conversion via β-oxidation occurs.[5]

In man and other mammals, carnitine is synthesized in the liver from lysine and methionine and/or is supplied from the diet. The carnitine content of breast milk increases from 39 to 63 nmol/mL during the first week postpartum,[6,7] so that infants who are breast feeding maintain normal carnitine levels as do infants receiving carnitine-supplemented formulas. Babies fed carnitine-free commercial preparations with adequate lysine and methionine concentrations become carnitine deficient, implying that adequate synthesis of carnitine from these amino acids in neonates is insufficient to maintain normal carnitine levels. Various investigators have documented significantly decreased plasma carnitine levels in neonates lacking an exogenous source of carnitine.[8,9]

Plasma carnitine deficiency has also been documented in newborn infants receiving carnitine-free total parenteral nutrition (TPN).[10–12] Lipids are a major component of TPN regimens[13–15]; however, carnitine is not currently included in TPN solutions. Therefore, the question arises as to whether or not neonates receiving TPN are able adequately to metabolize fat as an energy source. This study was undertaken to compare plasma carnitine levels, serum triglyceride and free fatty acid clearance, and ketone body generation in infants administered TPN with fat, one half of whom were supplemented 2ith exogenous carnitine.

## MATERIALS AND METHODS

Twelve neonates requiring TPN for a minimum of one week were included in this study, following approval of the experimental protocol by the Committee for Investigation Involving Human Beings and after obtaining parental informed consent. All infants underwent major surgery within the first few days of life and were subsequently randomly assigned to either a carnitine-supplemented or nonsupplemented treatment group.

**Table 1. Clinical Data**

| Carnitine-Supplemented Infant Group | | | | | Nonsupplemented Infant Group | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient No. | Gestational Age (wk) | Initial Weight (kg) | Final Weight (kg) | Diagnosis | Patient No. | Gestational Age (wk) | Initial Weight (kg) | Final Weight (kg) | Diagnosis |
| 1 | 36 | 2.50 | 2.58 | Gastroschisis | 1 | 36 | 2.26 | 2.27 | Gastroschisis |
| 2 | 34 | 1.92 | 2.00 | Esophageal atresia | 2 | 37 | 3.28 | 3.54 | Omphalocele |
| 3 | 37 | 3.58 | 3.46 | Duodenal atresia | 3 | 38 | 3.03 | 2.98 | Ileal atresia |
| 4 | 42 | 2.87 | 3.09 | Esophageal atresia | 4 | 32 | 1.60 | 1.36 | Gastroschisis |
| 5 | 36 | 4.28 | 4.00 | Omphalocele | 5 | 39 | 3.30 | 3.54 | Diaphragmatic hernia |
| 6 | 36 | 2.01 | 2.05 | Gastroschisis | 6 | 37 | 3.36 | 3.40 | Duodenal atresia |
| Mean | 36.8 | 2.86 | 2.86 | | | 36.5 | 2.81 | 2.85 | |
| + SD | 2.71 | 0.92 | 0.80 | | | 2.43 | 0.71 | 0.88 | |

Infants received standard peripheral intravenous TPN during the study period consisting of 12.5% dextrose, 2.5% amino acids, and a lipid emulsion (Liposyn 20%; Abbott Laboratories, North Chicago, Ill). Each neonate received a lipid challenge of 0.5 g/kg (Liposyn 20%) over two hours on day one and day eight of the study. Sixteen hours prior to each challenge, lipid infusions were discontinued to allow for adequate fat clearance and utilization. Additionally, one hour prior to each lipid bolus the carbohydrate concentration of the TPN solutions was changed to 10% to encourage ketone body production. Blood samples were obtained prior to the lipid challenge (time 0 hour), immediately after the lipid bolus (time 2 hours), and at time four hours on day one; and, similarly, at 0, 2, 4, 6, and 8 hours on day eight. Blood samples were analyzed for free fatty acids, triglycerides, ketone bodies, plasma carnitine, and red blood cell carnitine concentration. Complete hematologic analysis was obtained prior to both lipid challenges.

Infants received either 70 umol/L carnitine/kg/24 h in 24 mL of 5% dextrose or 5% dextrose, 24 mL/24 h, during the study period. Carnitine or placebo administration began on day one following the last blood sample (time 4 hours) and terminated on day eight prior to the lipid challenge. Infants received the appropriate (carnitine or placebo) solution in eight doses (every three hours) of three mL per dose via nasogastric, orogastric, or gastrostomy tube. Following each administration, the tube was clamped for one hour to allow for absorption.

L-Carnitine, investigational drug number 21-710, (Sigma Chemical Company, St Louis, Mo) was formulated in the University of Michigan Hospital Pharmacy to 70 umol/mL with 5% dextrose according to United States Pharmacopeia standards.

Student's t test and linear regression analyses were used to evaluate the data with $P$ values less than 0.05 considered significant.

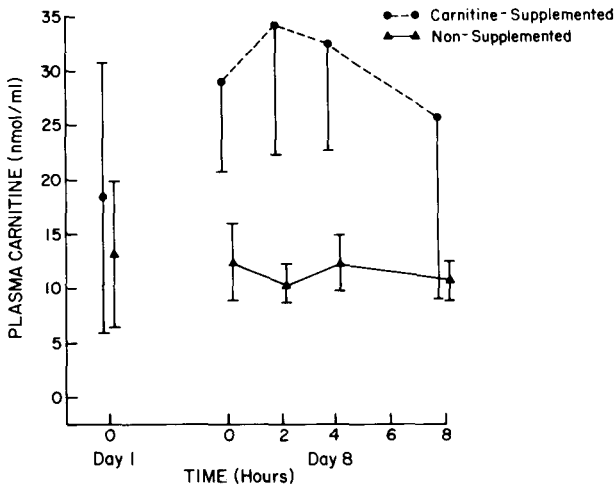


**Fig 1. Plasma carnitine levels in carnitine-supplemented *v* nonsupplemented infants.**

## RESULTS

The clinical data is summarized in Table 1. There was no significant difference in gestational age between the carnitine-supplemented (36.8 ± 2.7 weeks) and nonsupplemented (36.5 ± 2.4 weeks) infant groups. Similarly, there were no significant differences in body weight between the groups at either the beginning or conclusion of the study.

Plasma carnitine levels in the carnitine-supplemented group were significantly increased compared with the nonsupplemented group (Fig 1). Baseline plasma carnitine levels (day one) were not significantly different in the two groups (18 ± 12 nmol/mL in the carnitine-supplemented group, versus 13 ± 6.7 nmol/mL in the nonsupplemented group). However, day eight plasma carnitine levels were significantly increased to 29 ± 8 nmol/mL and remained near 30 nmol/mL through the remainder of the sampling period in the carnitine-supplemented neonates, in contrast to the nonsupplemented infants whose carnitine levels remained below baseline levels (13 nmol/mL).

Baseline and day eight red blood cell carnitine concentration was slightly higher in the carnitine-supplemented infants (0.125 nmol/mg hemoglobin) compared to the nonsupplemented neonates (0.10 nmol/mg hemoglobin; Fig 2). The day-eight red blood cell carnitine levels in both groups were decreased compared to the baseline levels.

The red blood cell carnitine to plasma carnitine ratio was lower in the carnitine-supplemented group (1.91 ± 0.89 *v* 3.42 ± 1.13), and was significantly lower at the two- and four-hour time period compared to the nonsupplemented neonates (Fig 3).

Serum triglyceride levels in both groups are depicted in Fig 4. There were no significant differences in baseline triglyceride levels, peak triglyceride levels

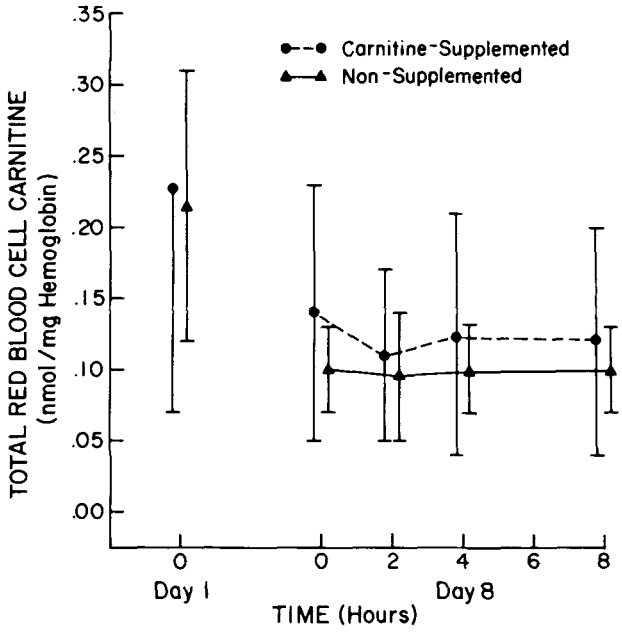


Fig 2. Total red blood cell carnitine levels in carnitine-supplemented *v* nonsupplemented infants.

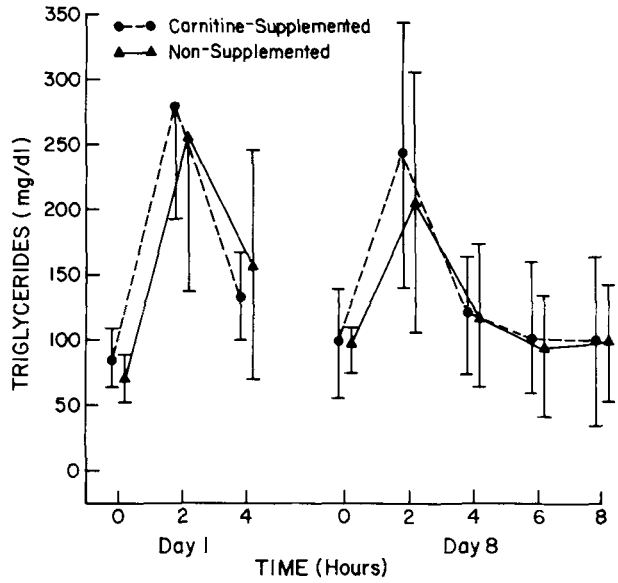


Fig 4. Serum triglyceride levels in carnitine-supplemented *v* nonsupplemented infants.

post lipid challenge, or clearance rate of the serum triglycerides in the two infant groups at the time of either the day one or the day eight lipid challenge.

Likewise, serum-free fatty acid levels mimicked the serum triglyceride profiles. Free fatty acid clearance rates post lipid challenge were not significantly different in either the carnitine-supplemented or nonsupplemented infants (Fig 5).

Total ketone body production (acetoacetic acid and β-hydroxybutyrate) are shown in Fig 6. No significant differences were evident in total ketone levels in either the carnitine or non-carnitine-supplemented infants. The day eight serum ketone levels were lower in both groups compared with the day one levels, but the differences were not significant.

The free fatty acid to ketone body ratio is presented in Fig 7. No significant differences were evident between the supplemented and nonsupplemented neonates, although the ratio was higher in the carnitine-supplemented infant group.

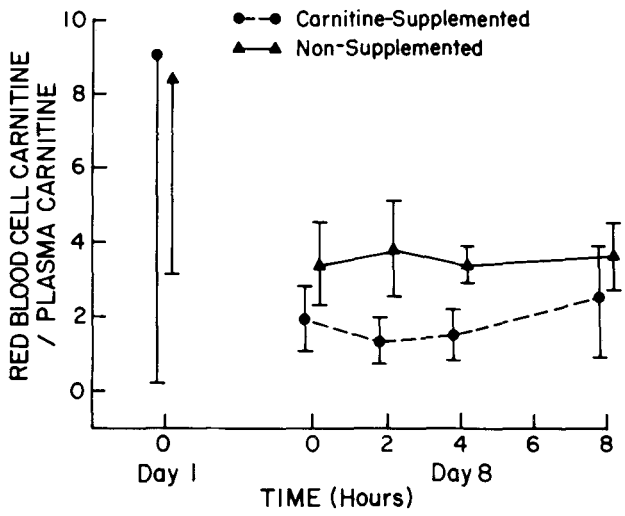


Fig 3. Red blood cell carnitine to plasma carnitine ratio in carnitine-supplemented *v* nonsupplemented infants.

## DISCUSSION

Fatty acids, an important energy substrate in mammals, are metabolized via the β-oxidation metabolic pathway. The following sequence of events summarizes the activation and transportation of free fatty acids into the mitochondria prior to entering the β-oxidation metabolic pathway (Fig 8). Triglycerides undergo hydrolysis by lipases to glycerol and free fatty acids. Free fatty acids are then activated to their coenzyme A (a pantothenic acid-containing compound with a free sulfhydryl group) esters by thiokinase. These activated fatty acid acyl-coA esters are impermeable to the mitochondrial membrane and must be transported into the mitochondria for oxidation to occur. L-Carnitine has a major function in the transport of the activated fatty acyl-coenzyme A esters from the sites of activation in the cytoplasm to the sites of β-oxidation within the mitochondria. The activated long-chain fatty acids are transesterified to acylcarnitine by carnitine acyl-transferase I, an enzyme located on the inner mitochondrial membrane. The transfer of fatty acylcarnitine esters across the inner

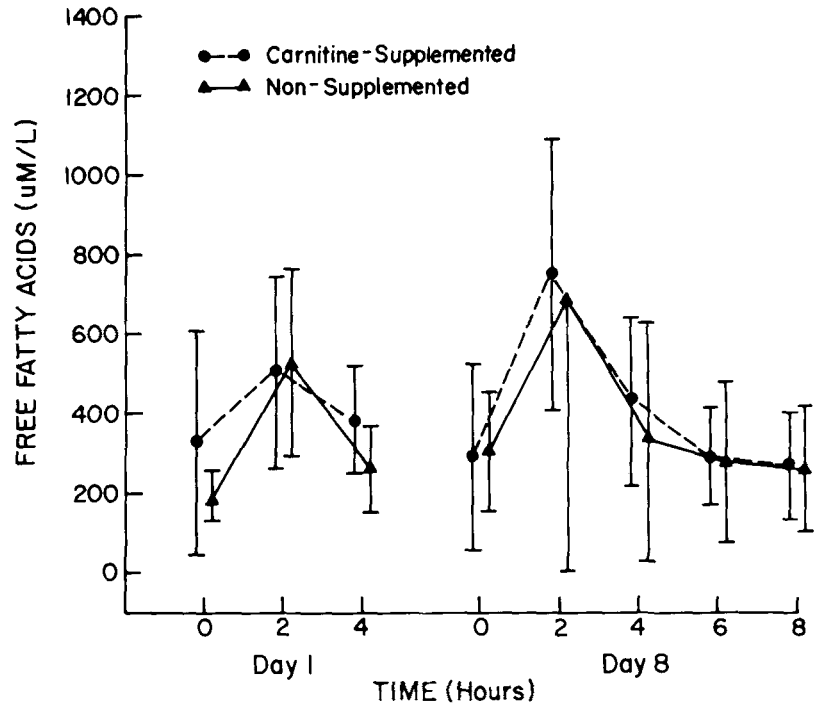


Fig 5. Serum free fatty acid levels in carnitine-supplemented *v* nonsupplemented infants.

mitochondrial membrane is then mediated by carnitine-acylcarnitine translocase. Next, the fatty acyl-carnitine ester reacts with coenzyme A on the inner mitochondrial membrane through the action of carnitine acyltransferase II to form fatty acyl-coenzyme A plus carnitine, which is translocated in the reverse direction.[1,16]

Following this sequence of events, the fatty acyl-coenzyme A can undergo $\beta$-oxidation with the subsequent formation of acetyl-coenzyme A plus a fatty acyl group, which is two carbons shorter in chain length after each turn of the cycle.[17]

Carnitine is, therefore, essential for fat metabolism in mammals. Adults are capable of meeting carnitine requirements through either diet or synthesis from lysine and methionine. It has been documented that neonates are not able to maintain normal plasma carnitine levels with carnitine-deficient diets. Thus, carnitine synthesis appears to be inadequate to maintain normal carnitine levels in the neonate.

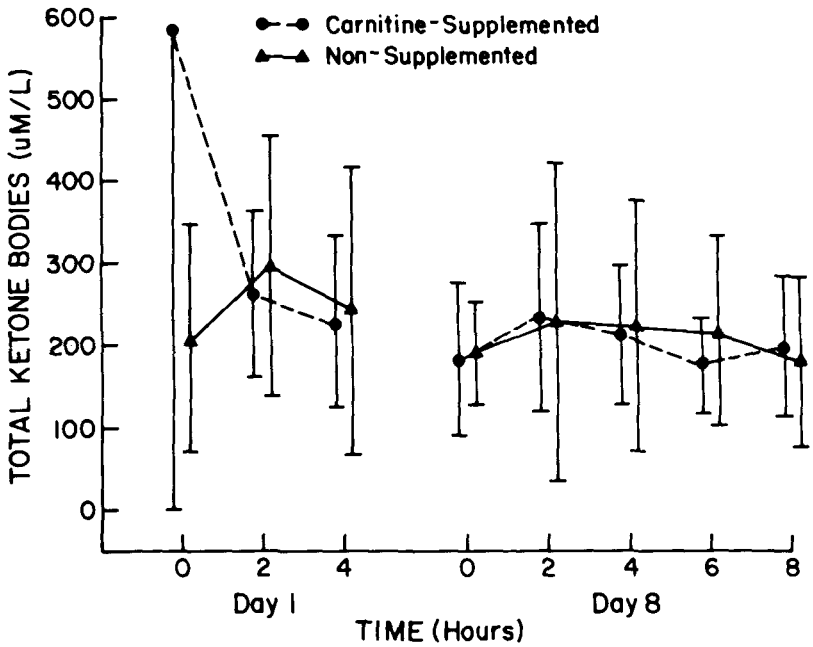


Fig 6. Total ketone bodies in carnitine-supplemented *v* nonsupplemented infants.

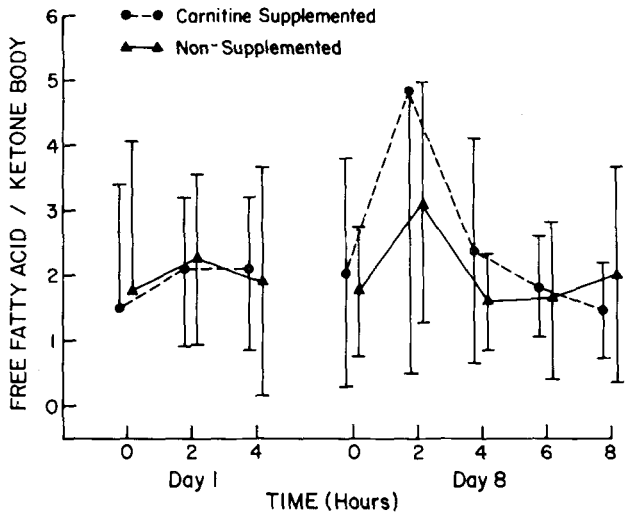


**Fig 7. Free fatty acid to ketone body ratio in carnitine-supplemented *v* nonsupplemented infants.**

Interest in the role of carnitine in infant nutrition has increased dramatically with the advent of TPN, since a significant proportion of the TPN solutions consists of a lipid emulsion in the form of triglycerides. Numerous investigators have shown decreases in plasma carnitine levels as well as delayed lipid and fatty acid clearance in various neonatal populations receiving TPN. Penn, Schmidt-Sommerfeld, and Wolf[10] compared infants receiving either TPN or a carnitine-containing formula and showed that the TPN-treated infants had decreased total carnitine levels (20 nmol/mL) compared to the infants fed the carnitine-containing formula (40 nmol/mL). Schiff, Chan, Seccombe, et al[12] monitored total plasma carnitine levels in 33 infants on TPN and continued to follow these infants when switched to oral feedings. During intravenous therapy, total carnitine was 15.9 ± 5 umol/L, compared to 29.1 ± 8.7 umol/L during the period of oral feedings. Schmidt-Sommerfeld, Penn, and Wolf[11] reported total plasma carnitine values of 25 to 70 umol/L in infants receiving intravenously supplemented carnitine (62 umol/kg) compared to levels of 13 to 16 umol/L in nonsupplemented, intravenously fed infants.

The plasma carnitine levels achieved in our carnitine-supplemented infants (30 nmol/mL) and nonsupplemented infants (13 nmol/mL) after seven days of TPN agree closely with the data of other investigators.

Triglyceride clearance was virtually identical in the two groups. Likewise, the free fatty acid clearance was not significantly different in the two groups of infants; however, the free fatty acid levels during the second lipid challenge were higher when compared with the day one lipid challenge in both groups.

Ketone body production was not significantly different in the two groups. Andrew, Chan, and Schiff,[18]

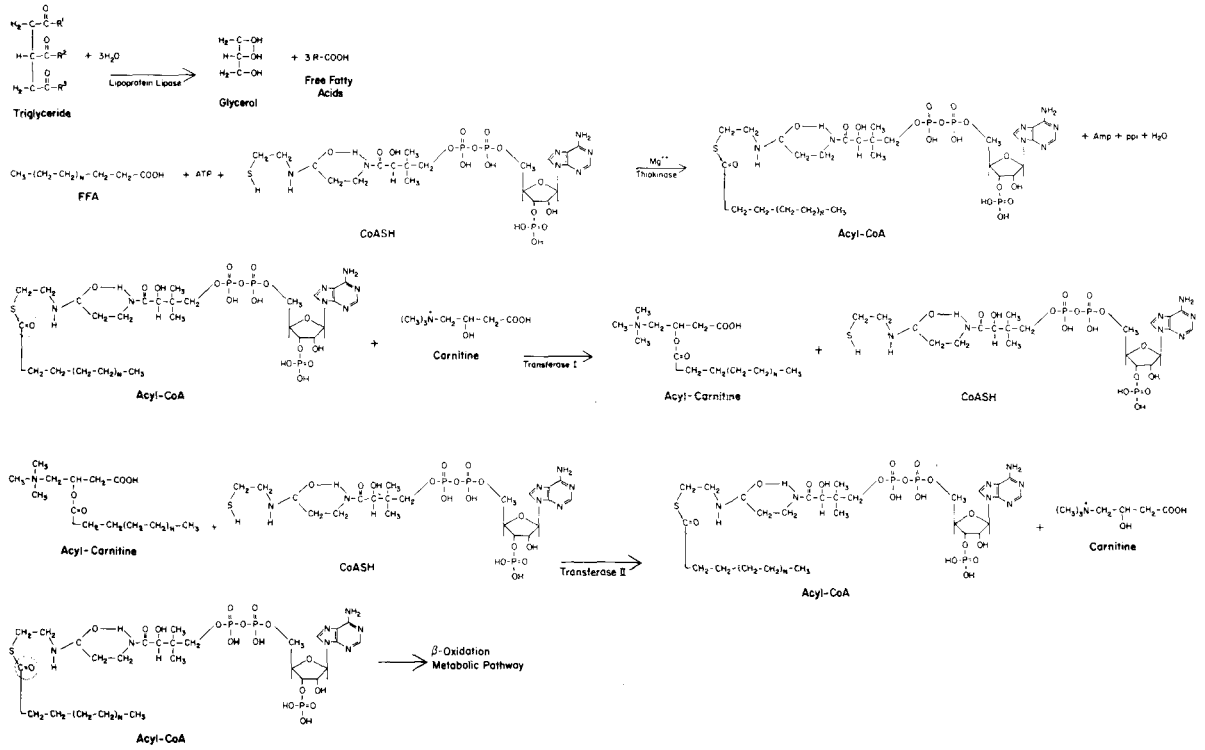


**Fig 8. Metabolic pathway of fatty acids.**

and Schmidt-Sommerfeld, Penn, and Wolf[19] all described a significant ketogenic effect from a lipid infusion, an effect not observed in our infants. A likely explanation is that the glucose concentration of the infused TPN solutions was not sufficiently lowered in these infants to promote fat utilization. The observation that free fatty acids were cleared quickly in the nonsupplemented group may indicate that these infants have sufficient tissue carnitine stores, even though the plasma carnitine levels were low.

Red blood cell carnitine levels were slightly higher in the carnitine-supplemented infants compared to the nonsupplemented group. In addition, the day eight red blood cell carnitine levels were lower when compared to the initial baseline levels on day one. If red blood cell carnitine is a reflection of tissue carnitine levels, then this could represent a shift of the available carnitine pool from the tissues to the plasma. Regardless of the relationship of red blood cell carnitine levels to total tissue carnitine, these infants were able adequately to clear the free fatty acids. Presumably, the decreased plasma carnitine levels in the nonsupplemented infant group were above threshold levels, or the infants were able to utilize tissue stores, with the shift from tissue depots not being immediately reflected in the plasma levels of carnitine.

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# Discussion

*Robert Filler (Toronto)*: The mechanisms of fat metabolism in neonates are of great interest to all of us, because we rely on the infant's ability to utilize fat in so many of the special intravenous feeding programs that we have designed for the neonates with inadequate gastrointestinal function. It has been intimated by some that low serum levels of carnitine—the enzyme necessary for the oxidation of fat—adversely affects the infant's ability to utilize the IV fat emulsions as a source of energy. This very nice paper basically shoots a hole in that hypothesis, at least at the plasma levels that we see here in this paper, of which the lowest ones are in the range of 10 nmol/mL.

Dr Coran and his colleagues have clearly shown that the serum carnitine level per se is not an index of the infant's ability to utilize fat. Despite doubling or tripling these plasma levels, by the administration of supplementary carnitine, fat metabolism was not really affected.

Carnitine does not act in the plasma but in the intracellular oxidation of fat. Therefore, it is not surprising that plasma levels are not an index of

carnitine activity. An intracellular carnitine deficiency, if that were present, would, of course, be expected to cause a decrease in oxidation of fat; but we have never seen that—certainly not in his infants. Ten of the 12 children in this study had a gestational age of 36 weeks or greater. We know that the very lowest birthweight infants tolerate fat poorly, and it would be very interesting to know if Dr Coran has extended these studies to lower weight infants.

*John Seashore* (*New Haven*): This study was designed, as so many fat clearance studies are, with a bolus of fat over several hours. It has always bothered me that this doesn't reflect the clinical practice that we use, which is, more like 2 to 3 g/kg/d over the course of 24 hours. Do you think you might have seen some differences if you had a steady state of infusion of fat for 24 hours?

*Marc Rowe* (*Pittsburgh*): A simple question about methodology. It's interesting that if you look at some of the recent work on vitamin E in preventing retrolental fibroplasia, when they check back on giving this orally, they found two interesting things: There was a very high incidence of necrotizing enterocolitis, and the osmolality of the substrate for the vitamin E was enormous. They made a very strong correlation between small doses of a medication orally, high osmolalities and high incidence of NEC. What is the concentration of this solution?

*Arnold Coran* (*closing*): With regard to Bob Filler's questions, clearly we deal with the problem of tissue levels of any supplement, *v* plasma levels. We obviously measure plasma levels for most things, because they're simpler to measure; tissue levels are harder to get at. What we did do in this study to get a handle on what the tissue levels were, was to measure the red blood cell carnitine levels that were, again, easier to measure than, for instance, liver or muscle carnitine levels; there were not any significant differences in the red cell levels. The question of prematures is a very good one, and that is certainly the group to study next. In response to Dr Seashore's question, the babies, in a sense, were being chronically administered fat. They did not just receive a bolus of fat; the babies were on continuous TPN feedings during the period of study, and then got boluses on day 1 and day 8.

Dr Rowe's question: I don't know what the osmolality of a solution of carnitine in 5% dextrose is; we didn't measure it.