Effects of high carnitine supplementation on substrate utilization in low-birth-weight infants receiving total parenteral nutrition[1-3]

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ABSTRACT Parenterally fed preterm neonates are known to be at risk for carnitine deficiency. We studied substrate utilization in low-birth-weight infants receiving total parenteral nutrition (TPN) with (A) and without (B) supplementation of 48 mg carnitine·kg^{-1}·d^{-1} on days 4–7 (birth weights 1334 ± 282 vs 1318 ± 248 g, gestational age 32 ± 2 vs 32 ± 2 wk, A vs B, respectively). TPN consisted of 11 g glucose·kg^{-1}·d^{-1} and 2.4 g·kg^{-1}·d^{-1} of both protein and fat. Plasma carnitine concentrations at day 7 were for free carnitine 11.8 ± 5.0 vs 164 ± 56 μmol/L and for acyl carnitine 3.8 ± 2.0 vs 33.9 ± 15.4 μmol/L, respectively. Indirect calorimetry at day 7 showed a higher fat oxidation (0.21, −0.31 to +0.60 vs 1.18, 0.70 to 1.95 g·kg^{-1}·d^{-1}, respectively, $P < 0.02$, median and interquartile range) in group B and a higher protein oxidation (0.37, 0.30–0.43 vs 0.63, 0.53–0.88 g·kg^{-1}·d^{-1}, $P < 0.001$). The time to regain birth weight was also higher in group B (7, 5.5–9 vs 9, 7–14 d, $P < 0.05$). Carnitine supplementation and calorie intake were the best explanatory variables for metabolic rate ($R^2 = 0.45$, $P < 0.002$). We conclude that carnitine supplementation of TPN in this dosage does not seem advisable. *Am J Clin Nutr* 1990;52:889–94.

KEY WORDS Carnitine, low-birth-weight infants, total parenteral nutrition, indirect calorimetry

Introduction

Carnitine, β-OH-τ-trimethyl amino-butyric acid, is an essential cofactor in the transport of long-chain fatty acids across the mitochondrial membrane. Plasma carnitine deficiency was documented in newborn infants receiving carnitine-free total parenteral nutrition (TPN) (1, 2). Carnitine deficiency may have a negative effect on fat clearance, ketogenesis, and thermogenesis.

Studies on the effects of carnitine on use of fatty acids in neonates were based on concentrations of triglycerides, free fatty acids, and ketone bodies as indices of fat oxidation (1, 3–5). However, clearance rates of fat emulsions are not equivalent to oxidation rates.

The aim of the study was to assess the effects of carnitine supplementation on fat oxidation, other substrate oxidation rates, and growth.

Carnitine tissue stores are lowest in small premature infants (6) even though their plasma carnitine concentrations at birth are higher than those in more mature infants (7), and it was suggested that this might reflect immaturity of mechanisms for carnitine uptake and storage in the tissues (7). For this reason a relatively high carnitine dosage was chosen.

Subjects and methods

Subjects

Twenty-four infants entered the study protocol; 12 infants received carnitine-free TPN and 12 infants received TPN with carnitine supplementation. Each group comprised six appropriate-for-gestational-age (AGA) and six small-for-gestational-age (SGA) infants. AGA was defined as a birth weight ≤ 2 SDs of the mean for gestation, according to the growth curves of Usher and McLean (8). SGA was defined as a birth weight > 2 SDs below the mean. For each patient, an individual SDS (SD score) was determined, defined as the actual birth weight of the infant minus the mean birth weight for gestational age, and divided by the SD for that gestational age according to the growth curves of Usher and McLean. Gestational age was determined by medical history and score according to Ballard et al (9).

All infants were initially admitted to the Neonatal Intensive Care Unit (NICU) of the Academic Hospital Rotterdam/Sophia Children's Hospital. Infants could enter the study if they were clinically stable and breathing room air at day 7 and not receiving phototherapy, antibiotics, or any other medication except for caffeine, which was administered to all infants in a dosage adapted to keep plasma concentrations between 100 and 200 μg/L.

Infants were only included after informed consent was ob-

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tained from at least one of the parents. The study protocol was approved by the medical ethics committee of the hospital.

Study groups

During the study period it was not logistically possible to perform a randomized trial of carnitine supplementation. Therefore, five children were measured during the first study period in which the routine parenteral feeding did not contain carnitine. Thereafter carnitine supplementation was given to all patients admitted to the NICU until measurements could be performed on six AGA and six SGA very-low-birth-weight infants who were stable on day 7. After this, seven more infants were studied during carnitine-free TPN. During both periods (with or without carnitine supplementation) ~20% of the infants with a birth weight < 2000 g admitted to the NICU fulfilled the study criteria on day 7. The groups were comparable in their mean birth weight, gestational age, and energy and substrate intakes.

In our neonatal unit, all infants with a birth weight < 2000 g routinely receive TPN for 1 wk after which oral feedings are gradually introduced. This protocol was shown to be an important tool in the prevention of necrotizing enterocolitis (10). The only premixed solution of a fat emulsion, mixed with carnitine that was commercially available (11) contained 2 g L-carnitine/L fat emulsion, hence this dosage was chosen. Although this implies a fairly high level of carnitine administration, it was not considered to be too high because no adverse effects of a high carnitine dosage have been described and equally high dosages were used in studies in preterm infants (5) and in pediatric routine TPN (12). During the first day of life, only dextrose 10% is given intravenously at a rate of 60–80 $mL \cdot kg^{-1} \cdot d^{-1}$. On the second day 0.5 $mL \cdot kg^{-1} \cdot d^{-1}$ of both an amino acid solution (Aminovenös 10%, Fresenius, Bad Homburg, FRG) and a fat emulsion (Intralipid 10%, Kabi Vitrum, Sweden) is added to the feeding regimen. On the third day fat and protein infusions are doubled. The glucose infusion is gradually increased to provide a total of 150–160 $mL \cdot kg^{-1} \cdot d^{-1}$ at day four. L-Carnitine (Sigma Tau, Rome) was added to the fat emulsion of group B in a concentration of 2 g/L. All substrates were continuously perfused for 24 h/d by a peripheral vein.

Methods

All studies were performed on postnatal day 7. Metabolic rate and substrate utilization were measured for 6–8 h by a closed-circuit indirect calorimeter at a thermoneutral temperature determined as described (13). Measurements were performed as previously described (14). Briefly, an air mixture devoid of carbon dioxide entered the research incubator. The carbon dioxide concentration was measured in a sample of the air leaving the incubator, after which all carbon dioxide was filtered out. Carbon dioxide is then injected again into the airflow by a mass-flow injector system until the same concentration of carbon dioxide is measured by the infrared meter (Unor 6N, Maihak, Hamburg, FRG). The amount of carbon dioxide injected into the system equals the carbon dioxide production of the infant. Thereafter all carbon dioxide is filtered out by a second soda-lime filter. The amount of oxygen consumed by the infant is equal to the amount of oxygen that has to be injected into the system to keep the oxygen tension constant, as measured by two polarographic oxygen cells (type 6223771 Beckman) in the system and in a reference vessel. To compensate for changes in air pressure, the reference vessel is connected to the flow circuit by means of a capillary.

Oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) are measured with an accuracy of 0.2 mL/min; the respiratory quotient (RQ) during calibration with butane was within 2% of the theoretical value.

Urine was collected in adhesive plastic bags for 3 d. Urinary nitrogen concentration of a pooled sample was determined by combustion in an automatic nitrogen analyzer (ANA 1400; Carlo Elba, Milano, Italy).

Nonprotein $\dot{V}O_2$ and nonprotein $\dot{V}CO_2$ were derived from $\dot{V}O_2$ and $\dot{V}CO_2$ by correcting the values for the protein oxidation, calculated as the timed urinary nitrogen excretion multiplied by 6.25. Metabolic rate and partition of the nonprotein macronutrients were calculated by established methods (15).

Energy retention was calculated as calorie intake minus metabolic rate because all calories were administered intravenously. Fat accretion was calculated analogously as fat intake minus fat oxidation as determined by indirect calorimetry.

Time to regain birth weight was assessed from the daily routine measurements of body weight; measurements on three infants were excluded because their weight curves were ambiguous. The characteristics of these infants were not different from the whole study group.

Total body fat was estimated by the method of Dauncey et al (16).

A 100-μL blood sample was collected in a heparin-treated tube. After separation, plasma samples were stored at −80 °C until assayed. Plasma total and free carnitine were measured by a radioenzyme assay in the laboratory of HR Scholte by the method of Barth et al (17); acyl carnitine was calculated as the difference between these two values.

Routine monitoring of Intralipid clearance was performed daily when infusion rate of lipids was increased and twice a week thereafter by using a nephelometric method (18).

Statistics

Results are presented as mean ± SD or median with interquartile range where necessary. Wilcoxon's two-sample rank test was used to compare the measured variables in the treatment groups. Multiple-linear-regression analysis with stepwise selection of variables was performed to assess the best explanatory variables for metabolic rate and body fat. The following independent variables were included: gestational age, birth weight, calorie intake, and SDS; carnitine supplementation was a dummy variable. Models were only accepted if their R^2 value was significantly greater than the value obtained with a model with fewer variables. Procedures were carried out on a standard statistical software package (*Stata 2.0,* Computing Resource Centre, Los Angeles). Correlation between fat oxidation and growth indices was calculated by using the Spearman rank correlation coefficient.

Results

Clinical characteristics of infant groups are presented in **Table 1.** Because infants were matched for birth weight, gestational age, and energy intake, these variables were similar in groups A and B. Carnitine concentrations are shown in **Table**

TABLE 1
Clinical characteristics of infants without (A) and with (B) L-carnitine supplementation*

	A (n = 12)	B (n = 12)
Birth weight (g)	1334 ± 282 (820–1740)	1318 ± 248 (975–1780)
Study weight (g)	1330 ± 263 (860–1650)	1265 ± 207 (900–1560)
Gestational age (wk)	32 ± 2 (28–36)	32 ± 2 (31–35)
Energy intake (kcal·kg^{-1}·d^{-1})	75.7 ± 3.6 (70–80)	74.7 ± 2.8 (71–79)
SD score	−1.5 ± 1.9 (−4.6–1.2)	−1.8 ± 1.6 (−4.3–1.6)

* $\bar{x}$ ± 1 SD; range given in parentheses. No significant differences between groups at $P < 0.05$.

2. All values in the nonsupplemented group A were low compared with reference values from preterm infants maintained on human milk feeding (2). There is no correlation present after 1 wk of TPN between plasma values of carnitine and the gestational age at birth (**Fig 1**). In group B total carnitine plasma concentrations were well above normal concentrations, even for adults (25–70 μmol/L).

The results of the indirect calorimetric measurements are shown in **Table 3.** Because of apparent nonnormality, the data are presented as median with the interquartile range. The RQ was lower ($P < 0.05$) and the fat oxidation was higher ($P < 0.02$) in the carnitine-supplemented group. The difference in metabolic rate was not statistically significant ($P = 0.15$) when the two groups were compared. However with multiple-linear-regression analysis the best explanatory variables for metabolic rate were energy intake and carnitine supplementation, with a coefficient of +0.50 ± 0.15 for calorie intake and +2.60 ± 0.90 kcal·kg^{-1}·d^{-1} for carnitine supplementation, (R^2 = 0.45, $P < 0.002$). Both coefficients were significantly different from zero, $P < 0.005$ and $P < 0.01$, respectively.

Protein oxidation, derived from nitrogen excretion in urine, was higher in group B ($P < 0.001$). Nitrogen intake was not different (386 ± 15 vs 352 ± 85 mg N·kg^{-1}·d^{-1}) and nitrogen balance was less positive in the supplemented group (+321 ± 37 vs +231 ± 96 mg N·kg^{-1}·d^{-1}, $P < 0.001$).

The concentrations of fat emulsion showed no significant differences between groups A and B (90 ± 39 vs 1.05 ± 0.30 g/L, respectively).

The time to regain birth weight, as a measure of weight gain (**Fig 2**), was significantly different ($P < 0.05$) between groups (7, 5.5–9 vs 9, 7–14 d for A and B, respectively).

Data on only 18 body-fat measurements were available because these measurements were not performed on the first six infants. The other characteristics of these six infants were not different from the whole study group. Mean total body-fat percentage was lower in group B, although not significant at $P < 0.05$: 5.3%, 2.8–7.3% vs 2.3%, 1.5–3.3%, $P = 0.052$, for A and B, respectively; **Fig 3**). In the stepwise selection of variables for a multiple-regression model, SDS alone was the best explanatory variable for the percentage of body fat at day 7.

Time to regain birth weight as an index of growth was correlated with fat oxidation (r_s = +0.64, $P < 0.001$; **Fig 4**) and with protein oxidation (r_s = +0.71, $P < 0.001$).

Discussion

Plasma concentrations of carnitine in the nonsupplemented group in this study were low and in the range found in earlier studies on parenterally fed, small preterm neonates (1, 2). The reported negative correlation between gestational age and carnitine concentrations at birth (9, 19) was not found in this study after 1 wk, when plasma concentrations were low over the whole range of maturity covered.

This study is the first to show that supplementing low-birth-weight infants on TPN with L-carnitine increases the oxidation of fat, as measured by indirect calorimetry. Without carnitine supplementation fat oxidation was very low in this patient group; a negative fat oxidation was calculated for 4 of 12 patients in the nonsupplemented group, as shown by an RQ > 1. Frayn (20) showed that the negative value obtained for fat oxidation still quantitatively represents net fat oxidation and equals total fat oxidation minus lipogenesis. In the supplemented group net fat oxidation always was positive and significantly higher than in the nonsupplemented group.

Consistent with the higher fat oxidation are the higher acyl carnitine concentrations in the carnitine-supplemented group, indicating that more acylation takes place although there is a lower acyl-free ratio. Previous studies of carnitine supplementation in very-low-birth-weight infants after ~1 wk of TPN indicated that a better clearance of fat could be achieved after supplementation and suggested that fat oxidation was also increased, as was concluded from a lower ratio of free fatty acids to D-β-hydroxybutyrate (1). Other studies in more mature neonates undergoing surgery showed an increase in ketone-body concentrations (4) or no effects (3, 5) in the carnitine-supplemented group. These previous studies are not quite comparable with ours, because all other studies were performed by using an intravenous lipid-tolerance test during which lipids were infused at a relatively high rate over a short time. This is not representative of the normal clinical situation because it is advised that fat emulsions should be infused continuously (21). Furthermore, in all but one study (5) lower dosages of carnitine were used.

Multiple-regression analysis indicates that carnitine supple-

TABLE 2
Levels of free-, acyl-, and total carnitine and acyl-free ratio in plasma at day 7 in infants without (A) and with (B) L-carnitine supplementation*

	A (n = 12)	B (n = 12)
Free carnitine (μmol/L)	11.8 ± 5.0	164 ± 56.6†
Acyl carnitine (μmol/L)	3.8 ± 2.0	33.9 ± 15.4†
Total carnitine (μmol/L)	15.6 ± 6.2	197 ± 59.9†
Acyl-free ratio	0.36 ± 0.16	0.23 ± 0.13‡

* $\bar{x}$ ± 1 SD. Normal values for free and acyl carnitine are 19.4 ± 6.9 and 7.5 ± 3.1 μmol/L, respectively, in milk-fed preterm infants (2). For term infants normal values for acyl and free carnitine are 19.8 ± 1.9 and 11.1 ± 2.3 μmol/L (from our laboratory).

†‡ Significantly different from A: †$P < 0.001$, ‡$P < 0.05$.

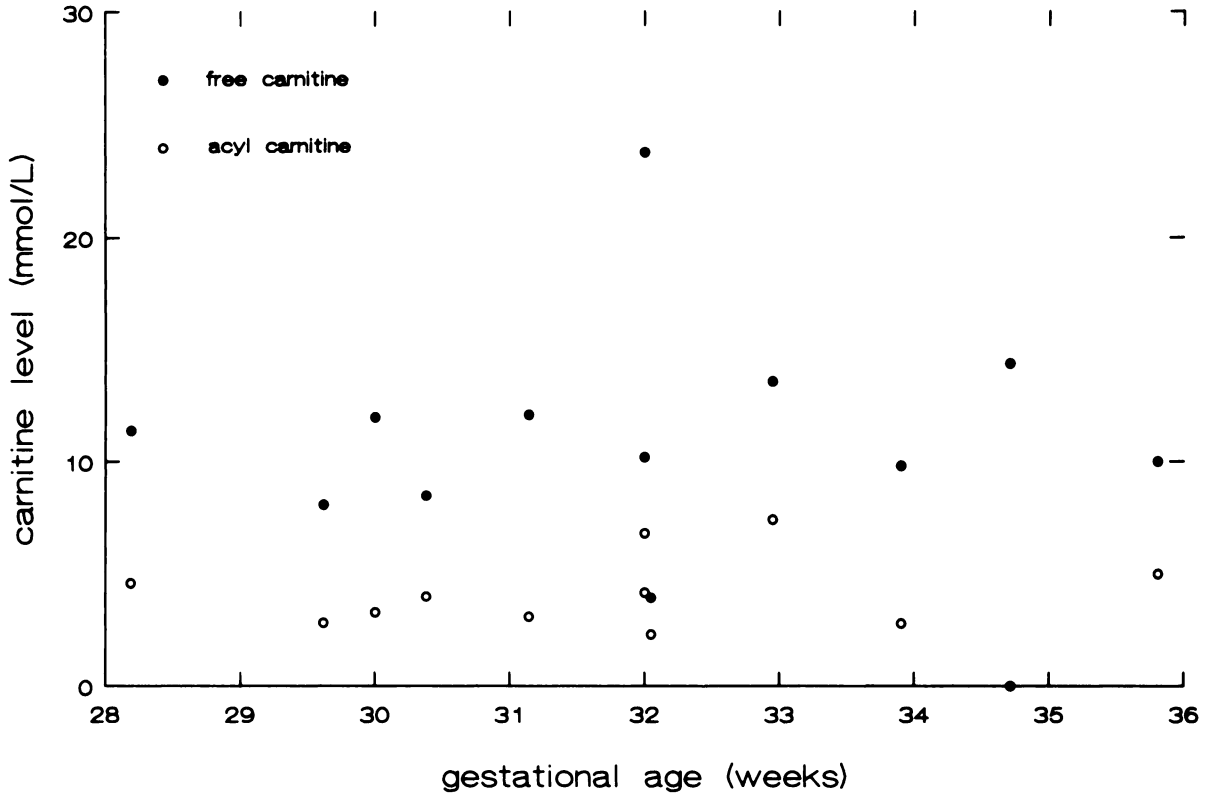

FIG 1. Relation between gestational age and free and acyl carnitine concentrations in plasma at day 7, after 1 wk of parenteral nutrition without carnitine supplementation.

mentation increases metabolic rate by 2.6 kcal·kg^{-1}·d^{-1}. Moreover, protein oxidation is also higher in the carnitine-supplemented group. Some preliminary results indicate that carnitine in group B was excreted virtually completely as free carnitine and that the concentrations were ~1 mmol/L (unpublished observations, 1990). From this it can be calculated that urinary carnitine excretion does not contribute significantly to the measured total urinary nitrogen excretion. Recently a similar decrease in nitrogen retention was noticed in adult postoperative patients receiving a relatively high carnitine dosage (22).

TABLE 3
Results of indirect calorimetry measurements in infants without (A) and with (B) L-carnitine supplementation*

	A (n = 12)	B (n = 12)
Protein oxidation (g·kg^{-1}·d^{-1})	0.37 (0.30–0.43)	0.63† (0.53–0.88)
Glucose oxidation (g·kg^{-1}·d^{-1})	10.31 (7.93–11.78)	8.48 (6.60–9.72)
Fat oxidation (g·kg^{-1}·d^{-1})	0.21 (−0.31–0.60)	1.18‡ (0.70–1.95)
Metabolic rate (kcal·kg^{-1}·d^{-1})	44.2 (41.1–45.3)	44.9 (44.2–47.0)
RQ	0.98 (0.94–1.01)	0.93§ (0.90–0.95)

* Median, with interquartile range given in parentheses. RQ, respiratory quotient.
†‡§ Significantly different from A: †$P < 0.001$, ‡$P < 0.02$, §$P < 0.05$.

Once it is known that carnitine may increase nitrogen excretion, the beneficial effects of the increased fat oxidation that can be attained by this dosage of carnitine must be weighed carefully. In the patient group studied here, intolerance of intravenous fat emulsions is not an important issue: the children

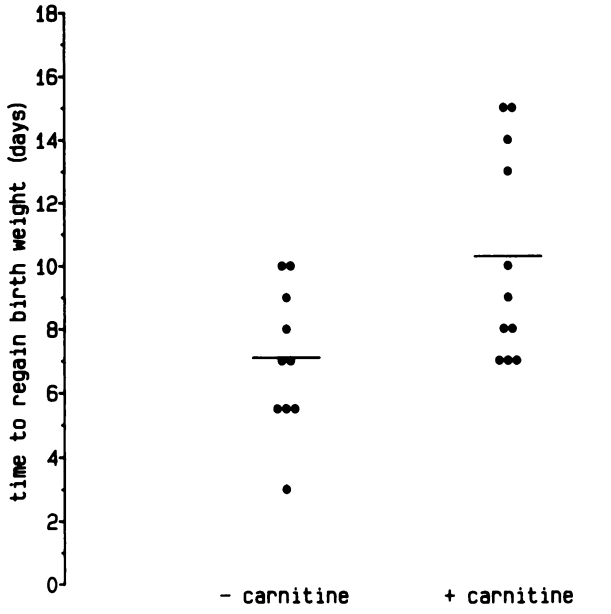

FIG 2. Time to regain birth weight in the nonsupplemented vs the carnitine-supplemented study group.

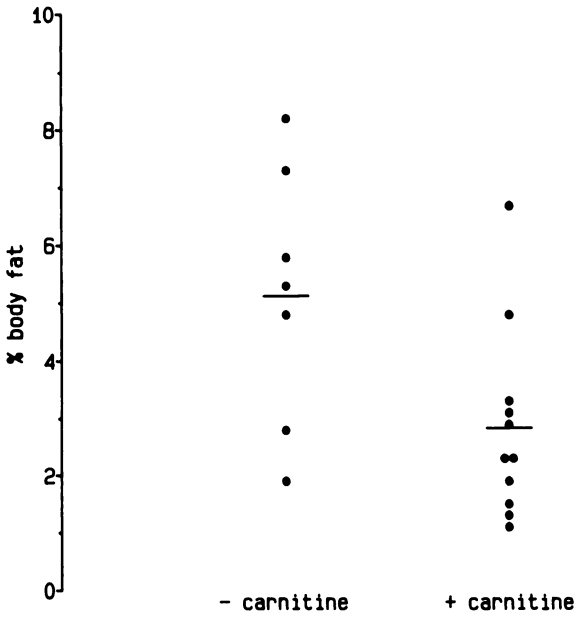

FIG 3. Percentage body fat according to Dauncey et al (16) in the nonsupplemented vs the carnitine-supplemented study group.

who fulfilled the requirements for study at day 7 form the relatively healthy part of the neonatal-intensive-care population, and none had to be excluded from the study for hypertriglyceridemia, defined as an "Intralipid level" > 1.50 g/L, while receiving 2.4 g fat·kg^{-1}·d^{-1}. Moreover, no difference in Intralipid concentration was observed between groups. We did not test to see whether a higher rate of fat infusion was better tolerated by the carnitine-supplemented infants.

In addition to achieving a better clearance rate, thus allowing an increase in the amount of calories delivered to these patients, another beneficial effect could be increased fat oxidation, resulting in increased ketone body formation and better adaptation to cold stress. Yeh and Sheehan (23) indicated that a moderately high ketone concentration provides an alternative fuel to the brain and a supply of substrates for brain myelinization, which is very active in the preterm neonate. Ketone bodies can only be formed when there is active fat oxidation. The supply of ketone bodies to the brain as an alternative substrate could be of special importance in the absence of a continuous supply of glucose, when the patient temporarily has to rely on his own production of glucose. This situation, however, should be the exception in neonatal intensive care. The concept of the necessity of a high rate of fat oxidation to provide ketone bodies as a precursor for brain myelinization is attractive, but there is insufficient clinical evidence for this. Presently there is no reason to advise that fat oxidation should be stimulated to promote ketosis in these patients, certainly not when the price is a higher protein oxidation.

Stave et al (24) indicated that carnitine supplementation at 50 mg/kg in newborn rabbits increases oxygen consumption and promotes adaptation to cold. There is a possibility that infants with carnitine might have a better tolerance to cold stress, but this was not tested. However, it remains to be seen whether this is theoretically or practically advantageous when it coincides with an increased metabolic rate and decreased protein and fat accretion. The slower attainment of birth weight in the carnitine group is in agreement with the lesser protein and fat

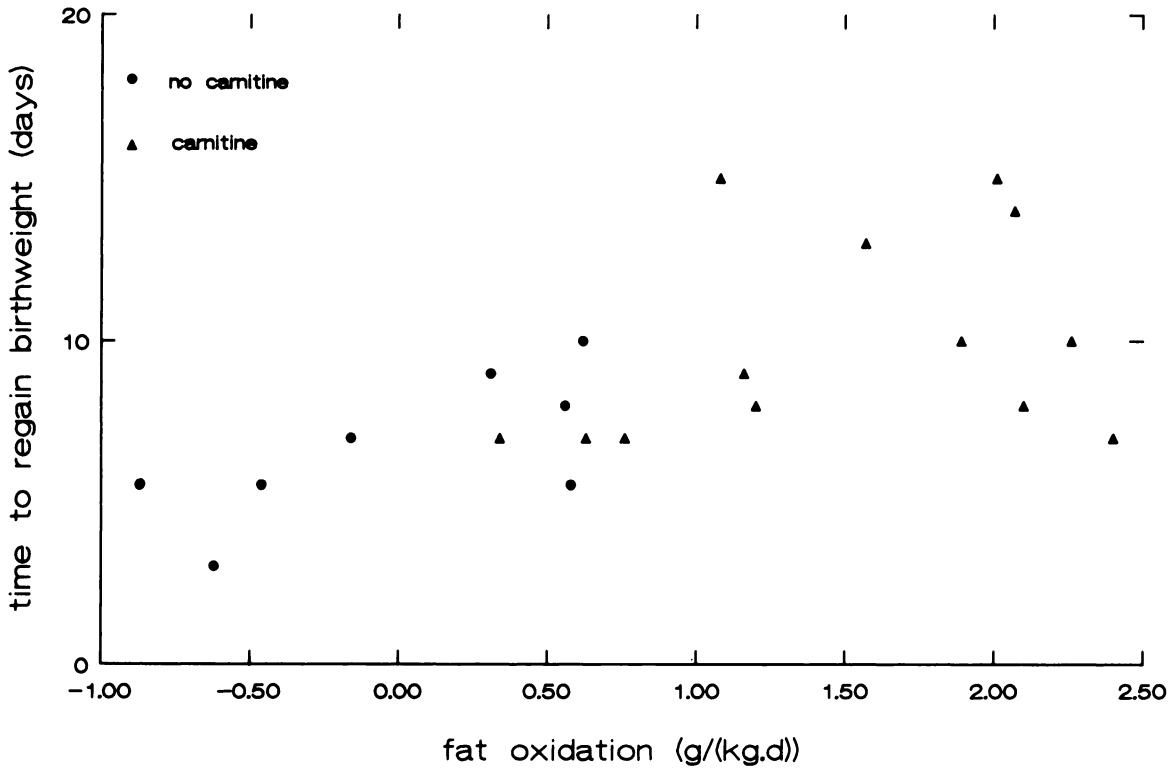

FIG 4. Relationship between time to regain birth weight and fat oxidation as measured with indirect calorimetry.

deposition. There is no consensus about the optimal fat content of a premature infant, but we can state with more certainty that the increased protein oxidation and decreased nitrogen balance in the carnitine-supplemented group can be considered an adverse effect of the carnitine administration.

Although carnitine administration in equally high doses has been described in preterm infants (5), children (11), and adults (25) without any discernable adverse effects, it could be that the higher metabolic rate and nitrogen excretion and the lower weight gain found in this study are dose-related effects. Further investigations have to focus on the question of whether lower doses of carnitine can increase fat oxidation without the changes in metabolic rate, protein oxidation, and growth found in this study.

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