ENERGY EXPENDITURE IN HUMAN MILK- VERSUS FORMULA-FED PRETERM INFANTS

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Objective We compared energy expenditure (EE) of preterm infants fed their mother's milk versus preterm infant formula.

Study design A prospective, randomized crossover study of 13 healthy, appropriate weight for gestational age, gavage-fed, preterm infants. Before the study and according to our feeding protocol, infants uniformly received alternate feeds of human milk and formula. Each infant was randomly assigned to 24 hours of formula feeding followed by 24 hours of breast milk or the reverse. Infants were studied asleep, at the end of each 24-hour period. EE was measured by indirect calorimetry 1 hour before feeding, 20 minutes during feeding, and 1 hour after feeding in a servo-controlled convective incubator. Energy content of human milk was analyzed by bomb calorimetry.

Results EE was significantly lower in breast milk–fed infants during prefeeding (52 ± 6 vs 57 ± 10 kcal/kg per 24 hours) ($P < .05$), per feeding (55 ± 6 vs 60 ± 10 kcal/kg per 24 hours) ($P < .05$), and at the postfeeding measurement (60 ± 7 vs 65 ± 7 kcal/kg per 24 hours) ($P = .059$). After correction of the results for the actual measured energy intake, all statistical differences reached the < .05 level.

Conclusions Preterm infants have lower EE when they are fed breast milk than when they are fed preterm infant formula. *(J Pediatr 2003;143:750-3)*

Several nonrandomized, cross-sectional studies suggested that breast milk-fed term[1,2] and preterm[3,4] infants have lower sleeping or resting energy expenditure (EE) (or metabolic rates) as compared with formula-fed infants. For ethical reasons, it is generally thought that infants cannot be randomly assigned to breast-feeding or formula feeding. Thus, in previous studies, it was not possible to determine if the observed differences were due to an EE-lowering effect of human milk, to feeding at the breast, or to other subtle differences between breast-fed and formula-fed infants unrelated to differences in milk composition.

During the years 1997 and 2000, human milk fortifiers were not available in our institution because of cost issues; thus, our standard feeding protocol of preterm, very low birth weight infants consisted of alternating human milk and a preterm formula in an attempt to provide infants with the benefits of human milk while preventing hypophosphatemic rickets of prematurity.[5] We took advantage of this unique feeding practice to perform a randomized, crossover study of measured EE in preterm infants fed either their mother's milk or a preterm formula. We hypothesized that preterm infants have lower EE when fed breast milk as compared with feeding by a standard preterm infant formula.

METHODS

Patients

We studied 13 healthy, growing, appropriate weight for gestational age, gavage-fed infants at the postmenstrual age of 31 to 34 weeks. All infants were clinically and thermally stable while cared for in a skin servo-controlled incubator. At the time of the study, they

EE	Energy expenditure

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Submitted for publication Mar 30, 2003; revision received July 9, 2003; accepted Aug 21, 2003.

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0022-3476/2003/$30.00 + 0
10.1067/S0022-3476(03)00532-8

were all tolerating full enteral feedings without significant gastric residuals (>5% of total feed), they were all growing steadily, and they had no electrolyte imbalance. None had any significant complication of prematurity such as intracranial hemorrhage of any grade, periventricular leukomalacia, necrotizing enterocolitis, supplemental oxygen requirements by 28 days of age or by 36 weeks of postmenstrual age, and at least 1 week before measurement, active infection, patent ductus arteriosus, or apnea of prematurity. They were all free of congenital anomalies. Before the study and according to our feeding protocol, infants were uniformly fed (by gravity drainage) every 3 hours, alternate bolus feeds of their mother's breast milk or a preterm infant formula (Similac Special Care (SSC), 67 kcal/100 mL, Ross Laboratories, Columbus, Ohio). The specific formula contents are described in Reference 6.[6] The study was approved by the local institutional review board, and written informed consent was obtained from both parents of each infant.

Design

Each infant was randomly assigned to receive 170 mL/kg per 24 hours of either breast milk or SSC. On the next day, each infant received the same amount of the alternative feeding. Metabolic studies were conducted at the end of each 24-hour feeding period while the infants were prone and asleep. Measurements were stopped during body movements (<5% of the time of measurement). Infants were fed for 20 minutes each meal through a syringe pump placed outside the incubator, with the tubing under the canopy. Care was taken not to disrupt the sealing of the canopy. Food temperature was 22.5°C (room temperature). EE was recorded for 1 hour before feeding, for 20 minutes during feeding, and for 1 hour after feeding. During the metabolic study, infants were cared for in their own convective incubator. Air temperature inside the incubator was manually changed to keep skin temperature over the back at 37°C. Expressed human milk varies in nutrient concentration from the beginning of breast pumping to the end and from one pumping to the other.[7,8] Thus, we mixed all the human milk samples collected over a 24-hour period from each mother, using a commercial blender, and stored it at 3°C after dividing it into separate equal feeding aliquots. Breast milk samples (stored at −20°C) were analyzed for caloric content with the use of a ballistic bomb calorimeter (Parr 1261 Automatic Bomb Calorimeter, Parr Instrument Company, Moline, Ill). Thus, EE measurements were expressed as such and corrected for caloric density of the milk measured (kcal/kg per day), divided by caloric density (kcal/100 mL).

Measurements

Metabolic measurements were performed by indirect calorimetry, with the use of the Deltatrac II Metabolic monitor (Datex-Ohmeda, Helsinki, Finland). This instrument uses the principle of the open circuit system that allows continuous measurements of oxygen consumption (V_{O_2}) and carbon dioxide production (V_{CO_2}), using a constant-flow generator. The measurement ranges for both O_2 consumption and CO_2 production of 5 to 2000 mL/min allow measurements in preterm infants with small tidal volumes. Before the measurement, the device performs a self-calibration, based on independently measured barometric pressure. In addition, periodic testing for accuracy was performed by alcohol burning according to the manufacturer instructions. This method is safe and allows prolonged measurements while allowing reasonable access to the infant for routine care. Validation studies have shown the technique to give results equivalent to direct measurements.[9,10] In our hands, the instrument has an intra-assay coefficient of variation of 3%.

Statistical Analysis

The sample size was determined arbitrarily in this study designed to be a pilot. Comparison of EE values between groups was performed by means of the paired Wilcoxon ranked test; comparisons of EE before, during, and after feeding were done by repeated-measures analysis of variance. Results are expressed as mean ± SD; a *P* value of $< .05$ was considered significant.

RESULTS

Clinical characteristics of the study infants were as follows: there were 3 male and 10 female infants. Mean birth weight was 1076 ± 259 g; mean gestational age was 29.0 ± 2.1 weeks; mean weight at the time of the study was 1301 ± 193 g; mean chronological age at the time of study was 30 ± 18 days; 12 infants of 13 had respiratory distress syndrome; mean rate of weight gain during the week before the study was 12.7 ± 8.9 g/kg per day; mean hematocrit was 39% ± 8%. Eight of 13 infants were treated with erythropoietin; 5 of 13 were treated with caffeine for apnea of prematurity during the study period. Formula-fed infants were fed a 67 kcal/100 mL formula. The measured (by bomb calorimetry) caloric content of breast milk was 73.1 ± 4 kcal/100 mL. Six of 13 infants were randomly assigned to receive breast milk before formula.

Energy expenditure was significantly higher in formula-fed infants for the first two measurement intervals ($P < .05$), with a *P* value of .059 after feeding (Table I). Once corrected for actual energy intake, all 3 feeding periods were statistically significant after adjustment of the *P* values for multiple comparisons (Table II). Repeated-measures analysis of variance showed that EE increased from the values measured before the feeding to the time of feeding ($P = .016$) and from the time of feeding to the time of digestion (ie, immediately after feeding) ($P < .0001$). This pilot study was stopped at this point without the recruitment of additional patients. There was no significant randomization order effect in the results observed.

DISCUSSION

Consistent with our hypothesis, we found that EE is significantly lower in metabolically and thermally stable preterm infants fed human milk, as opposed to a formula.

Table I. Comparison of mean ± SD of energy expenditure, RQ, CO_2 production, and O_2 consumption in the study infants before feeding, during feeding, and during digestion of breast milk and of preterm infant formula

	Energy expenditure kcal/kg per 24 h		Respiratory quotient		$\dot{V}CO_2$ mL/kg per min		$\dot{V}O_2$ mL/kg per min	
	Human milk fed	Formula fed	Human milk fed	Formula fed	Human milk fed	Formula fed	Human milk fed	Formula fed
Before feeding	52 ± 6*	57 ± 10	0.82 ± 0.03	0.89 ± 0.03	6.3 ± 0.6	7.2 ± 1.4	7.6 ± .09	8.1 ± 1.5
During feeding	55 ± 6*	60 ± 10	0.81 ± 0.03	0.87 ± 0.04	6.6 ± 0.7	7.5 ± 1.2	8.0 ± 0.8	8.5 ± 1.9
After feeding	60 ± 7	65 ± 7	0.90 ± 0.00	0.87 ± 0.04	7.7 ± 0.9	8.0 ± 0.9	8.6 ± 1.0	9.3 ± 1.0

*Energy expenditure was significantly lower in the human milk–fed group before and during feeding ($P < .05$); after feeding, the difference in energy expenditure was 0.059 (paired Wilcoxon ranked test).

Table II. Comparison of mean ± SD of energy expenditure (kcal/kg per 24 h per calories ingested), corrected for actual calories consumed by infants before feeding, during feeding, and during digestion of breast milk and of preterm infant formula (paired Wilcoxon ranked tests)

	Human milk fed	Formula fed	*P* value
Before feeding	0.71 ± 1.1	0.85 ± 1.6	.004
During feeding	0.76 ± 1.0	0.89 ± 1.5	.006
After feeding	0.83 ± 1.2	0.97 ± 1.1	.004

These results are consistent with those of Butte et al[1,2] in term infants or of Putet et al[3] and Whyte et al[4] in preterm infants. However, our study is a randomized study that did not make assumptions about breast milk energy content.

As suggested by Butte et al,[1,2] differences in EE between human milk-fed and formula-fed infants may be very difficult to interpret because of factors not related to the type of feeding. In the Butte et al study, nursing mothers were older, with a higher level of education than mothers of formula-fed infants. Breast-fed infants had lower birth weight and they were younger and had significant anthropometric differences (head, chest, and arm circumferences) compared with the formula-fed infants. Moreover, the technique of feeding (at the breast vs from a bottle) is different, and there are many differences in milk composition between the two groups in terms of macronutrients, minerals, vitamins, specific proteins, and so forth. Thus, Butte et al concluded that "because of the marked differences in the composition of human milk and formula, inferences regarding a cause and effect relationship between energy intake and energy utilization cannot be made."[1]

Our study provides new information because of the unique aspects of the study design: (1) Each infant served as its own control, which eliminates variables related to differences inherent between groups, for example, differences in birth weight, socioeconomic factors, anthropometric measurements, or use of caffeine. (2) The random assignment to human milk or formula was feasible in our institution. Thus, the differences that we observed can more securely be attributed to differences in the composition of milk. (3) The fact that all infants, regardless of what they were fed, were fed by gavage eliminates feeding practice factors, which may affect the results. (4) In the Butte et al study, breast-fed infants had a lower energy intake than formula-fed infants, suggesting that the decrease in EE in breast-fed infants was an adaptation to a lower level of energy. From our study, this was not the case, since the differences observed became even more significant after correction for differences in energy intake (higher when fed breast milk). Nevertheless, it is not possible to determine from our study what in human milk causes the decrease in EE. Breast milk is composed of protein, lipids, and carbohydrates similar in concentration to what is present in the formula studied, but with very different composition. For example, human milk whey and casein content differ from those of the formula we used. The carbohydrates in human milk are mainly lactose, whereas in formula, 50% are dextromaltose and 50% lactose. The lipids in the formula are of vegetal origin only, with 50% medium chain triglycerides, and, compared with human milk, are nearly devoid of long-chain polyunsaturated fatty acids. Moreover, human milk is strikingly different from the formula used in terms of minerals, metals, and other trace elements. It contains enzymes and hormones or growth factors which all, in theory, may affect the way nutrients are digested, absorbed, or utilized. A potential limitation of our study is that the composition of "preterm" human milk is somewhat different from that of term human milk, with higher protein and sodium content.[11] However, differences between "preterm" human milk and term human milk decrease over time of lactation, and, on average, our infants were studied at 30 ± 18 days of age. Nevertheless, regardless of the mechanism, the results indicate that preterm infants have a lower EE when fed their mother's milk than when they are fed a standard preterm infant formula with a similar energy content.

We also found that there was a feeding-induced increase in EE, also known as the thermic effect of feeding. This increase was already measurable during the feeding period and was the highest during the immediate postprandial period of one hour.

In summary, we conclude from our study that feeding preterm infants with human milk results in lower EE as compared with feeding with formula. The components of human milk that may trigger the metabolic difference remain to be identified.

We are indebted to Ofra Kaidar for technical support.

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