High Beta-Palmitate Formula and Bone Strength in Term Infants: A Randomized, Double-Blind, Controlled Trial

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Abstract We aimed to compare the effect of 12-week feeding of commercially available infant formulas with different percentages of palmitic acid at \( sn-2 \) (beta-palmitate) on anthropometric measures and bone strength of term infants. It was hypothesized that feeding infants with high beta-palmitate (HBP) formula will enhance their bone speed of sound (SOS). Eighty-three infants appropriate for gestational age participated in the study; of these, 58 were formula-fed and 25 breast-fed infants, serving as a reference group. The formula-fed infants were randomly assigned to receive HBP formula (43 % of the palmitic acid is esterified to the middle position of the glycerol backbone, study group; \( n = 30 \)) or regular formula with low-beta palmitate (LBP, 14 % of the palmitic acid is esterified to the middle position of the glycerol backbone, \( n = 28 \)). Sixty-six infants completed the 12-week study. Anthropometric and quantitative ultrasound measurements of bone SOS for assessment of bone strength were performed at randomization and at 6 and 12 weeks postnatal age. At randomization, gestational age, birth weight, and bone SOS were comparable between the three groups. At 12 weeks postnatal age, the mean bone SOS of the HBP group was significantly higher than that of the LBP group (2,896 ± 133 vs. 2,825 ± 79 m/s respectively, \( P = 0.049 \)) and comparable with that of the breast-fed group (2,875 ± 85 m/s). We concluded that infants consuming HBP formula had changes in bone SOS that were comparable to those of infants consuming breast milk and favorable compared to infants consuming LBP formula.

Keywords Beta-palmitate · Bone speed of sound · Infant formula · Quantitative ultrasound

Introduction

During the last decade, substantial efforts were made to determine the factors that influence bone mineral accretion in healthy children. This arises from the notion that osteoporosis originates in childhood [1]. Providing optimal nutrition in childhood may be essential in our effort to reach the highest possible peak bone mass. The absorption of nutrients, such as minerals, fats, carbohydrates, and proteins, is significantly important for normal infant growth and development and may contribute to early bone mineral accretion [2].

In human breast milk (BM) and in most infant formulas, about 50 % of the dietary calories are supplied as fat [3, 4]. Palmitic acid, comprises 17–25 % of fatty acids in BM, of which 70–75 % is esterified to the \( sn-2 \) (\( \beta \)) position of the triglyceride [3]. Previous studies have shown that to assure
optimal fat absorption, palmitic acid is best absorbed from human milk as sn-2 monoacylglycerol [5, 6] and is conserved as such through digestion, absorption, and chylo-
micron triacylglycerol synthesis [7]. In contrast, the free palmitic acid originating from the -1 and -3 positions of vegetable oils, commonly used in manufactured infant formulas [8], has high tendency to create complexes with dietary minerals such as calcium to form fatty acid soaps [9, 10], resulting in loss of both calcium and fatty acids in the stool. Beta-palmitate is a fat ingredient that mimics the fatty acids positioned in BM. Previous studies have shown that its use in both term and preterm infant formulas may enhance fatty acids and calcium absorption [8, 11–14].

Quantitative ultrasound (QUS) measurements of bone speed of sound (SOS) is now considered an important tool for the diagnosis and follow-up of bone strength in term and preterm infants [15]. QUS measurements of bone are noninvasive, painless, portable, and relatively inexpensive, involving no ionizing radiation and posing no known adverse effects. In addition to bone mineral density (BMD), it measures bone cortical thickness, elasticity, and microarchitecture and provides a more complete picture of bone strength in adults, children, and newborns [16–25].

The aim of the present study was to assess the short term effect of consuming high-beta-palmitate (HBP) formula compared with regular infant formula, comprising low-beta-palmitate (LBP), on bone strength of term newborns as the primary outcome and on anthropometric measures as the secondary outcome. We hypothesized that compared with LBP formula, feeding term newborns with HBP formula will enhance their bone strength.

Methods

Study Design and Participants

Healthy term (>37 weeks) infants, appropriate for gesta-
tional age and younger than 14 days of age, were eligible for entry to this randomized, double-blind controlled, longitudinal trial. Infants were excluded if they had congenital or chromosomal disorder or if noncompliance with the trial feeding regimen was expected of their parents. Infants were enrolled only if their mother unequivocally decided to formula feed within the first 2 weeks of the baby’s life. By means of an automatic randomization system, infants were randomly assigned to receiving HBP formula (forming the study group) or LBP formula (regular infant formula; forming the control group). Formulas were packed in identical and unmarked boxes, with the personnel caring for the infants and mothers being blinded to their content.

Infant and maternal demographic characteristics for the HBP and LBP formula groups are listed in Table 1. Included was also a gestational age matched reference group of term infants consuming BM. Twins were initially assigned to the same group; however, to avoid possible genetic or intrauterine effects, only the twin with the larger birth weight was included in the analysis. The infants were followed up twice, at 6 and 12 weeks.

The study was conducted according to the principles of the Declaration of Helsinki and good clinical practice. The protocol was approved by the ethics committee of Meir Medical Center, Kfar Saba, Israel, and by the Israeli Ministry of Health. Before enrollment, all parents signed a written informed consent.

Formula-Feeding Regimen

We used currently available commercial formulas. Both HBP and LBP formulas were produced by the same manu-
ufacturing company (Materna Laboratories, Kibbutz Maabarot, Israel) and under the same conditions using ingredients such as minerals and vitamins from the same batches, thus resulting in identical commercial formulas (standard vegetable oil mix of palm kernel oil, rapeseed oil, sunflower oil, and palm oil or structured palm oil) that differ mainly in the palmitic structural distribution (14 and 43 % of the palmitic acid esterified to the midpoint position of the glycerol backbone, respectively) (InFat® Advanced Lipids AB, Migdal HaEmeq, Israel; Table 2). Infants were fed ad libitum; no supplementary feeding was provided. All infants, including BM infants, received 400 IU/day of vitamin D during the study intervention period.

Anthropometric Measurements

Measurements of growth and bone SOS were done at random-
ization and at 6 and 12 weeks postnatal age by a single trained technician, who was blinded to the study group assignment. The measurements covered the following variables: body weight (the mean of three measurements; Model 20 Tabletop Infant Scale, Olympic Medical, Seattle, WA), body length (the mean of two measurements of recumbent crown–heel length to the nearest 0.1 cm; O’Leary Preemie LengthBoard, Ellard Instrumentation Ltd., Monroe, WA), and fronto-occipital head circumference (standard 1-cm wide measuring tape to the nearest 0.1 cm).

QUS Measurements of Bone SOS

The left tibial SOS was measured by the QUS (Sunlight Premier Software, Omnisense 7000/8000, BeamMed Ltd., Petah Tikva, Israel), a method designed to measure SOS at multiple skeletal sites by axial transmission. The measure-
ment is based on the fact that ultrasound waves propagate faster through bone than through soft tissue. A standardized
procedure was followed, and the probe was placed on the left tibia at half the measured distance between the apex of the heel and the distal patellar apex. After calibrating the machine with a standard phantom, three measurements were obtained from the same site and the mean value calculated.

Measurement accuracy was 0.25–0.5 % with a root mean square coefficient of variation of 0.4–0.8 %.

The measurements were performed by the same technician, who was blinded to group assignment. Formula consumption before each visit was based on a structured diary completed by the parents, calculating the mean total amount of formula feeds per kilogram of body weight over a 3-day period.

### Statistical Analysis

Baseline characteristics of mothers and infants of the HBP and LBP formula groups were compared by pairwise $t$ test for scale outcomes and pairwise $\chi^2$ test for nominal outcomes. The mean SOS and primary study endpoint of the groups was tested with the analysis of covariance (ANCOVA) adjusted for infant birth weight. The model was run for baseline, 6-, and 12-week SOS measurements, once for available observations at each time point and once restricted to the subset of newborns, thus resulting in a complete set of SOS measurements. Serving as a reference group, all parameters of the BM group were also compared with that of the two formula groups. The similarity of the SOS measurements of the HBP formula group with those of the BM group was demonstrated by showing that the mean difference and the 95 % confidence interval (CI) of both groups were close to zero.

Statistical analysis was conducted by SPSS software, version 17.0 (SPSS Inc., Chicago, IL). Data were expressed as mean ± SEM. Statistical significance was inferred at 2 tails $P < 0.05$. Power calculation indicated that a sample of about 20 infants in each arm could detect statistical significance, showing a difference of 80 m/s in the SOS measurements with an 80 % value for power.

### Table 1 Demographic characteristics of infants and mothers

| Characteristic          | Formula   | BM (n = 25) |
|-------------------------|-----------|-------------|
|                         | HBP (n = 26) | LBP (n = 25) |
| Infant                  |           |             |
| Gestational age (weeks) | 39.4 ± 0.2 | 39.2 ± 0.2  |
| Type of delivery (vaginal, %) | 76.0     | 64.0        |
| Twins (%)               | 15.4*     | 12.0        |
| Gender (male, %)        | 57.7      | 40.0*       |
| Birth weight (kg)       | 3.28 ± 0.1| 3.26 ± 0.1  |
| Age at inclusion (days) | 3.3 ± 0.5 | 3.5 ± 0.6   |
| Mother                  |           |             |
| Maternal age (years)    | 32.3 ± 0.7| 33.3 ± 0.8  |
| Maternal education (>12 years) (%) | 65.4* | 56.0*       |
| Primigravida (%)        | 15.4      | 16.0        |
| Maternal smoking (%)    | 15.4*     | 32.0*       |

Data are presented as mean ± SEM

HBP high beta-palmitate, LBP low-beta palmitate, BM human breast milk, SEM standard error of the mean

* $P < 0.05$ compared with the BM group

### Table 2 Composition of HBP and LBP formulas

| Composition | Per 100 g powder of: | HBP | LBP |
|-------------|----------------------|-----|-----|
|             |                      |     |     |
| Energy (kcal) |                     | 510 | 510 |
| Protein (lactalbumin/casein, 60/40) (g) | 12 | 12 |
| Carbohydrate (g) |                 | 55 | 55.7 |
| Fat (g) |                     | 26 | 26 |
| Calcium (mg)* |                   | 430| 420 |
| Vitamin D (IU)* |                 | 372| 404 |
| Percentage by weight of total fatty acids b |     |     |
| 8:0 | 0.9 | 3 |
| 10:0 | 0.8 | 2.2 |
| 12:0 | 10.4 | 9.4 |
| 14:0 | 4.3 | 4.2 |
| 16:0 | 22 | 19 |
| 18:0 | 4.4 | 6.4 |
| 18:1 n−9 | 38.5 | 34.4 |
| 18:2 n−6 | 14 | 15.1 |
| 18:3 n−3 | 1.5 | 1.5 |
| 20:4 | 0.42 | 0.53 |
| 22:6 | 0.22 | 0.29 |
| Other fatty acids | 2.9 | 5.1 |
| 16:0 in sn-2 position c | 44 | 14 |

HBP high beta-palmitate, LBP low-beta palmitate

* Value differences between the formulas are within analytical method deviation

b Included vegetable oil mix

c The ratio is normalized per position and calculated as percentage of sn-2 palmitic/3: % total palmitic acid × 100
Results

A total of 83 term infants were enrolled. Twenty-five were exclusively breast-fed. Of the 58 formula-fed infants, 30 were randomly assigned to receive HBP formula and 28 LBP formula. The attrition rate by the end of the study period was 21% and was equally distributed between the three groups (Fig. 1). The sample of 21% of those who did not complete the study was matched with those who did according to gestational age and birth weight (data not shown).

Infant characteristics are presented in Table 1. No significant differences were observed between the two formula groups. The BM group had a higher incidence of males than the LBP group (68 and 40%, respectively) and included no twins. Infant growth for weight, length, weight gain, and head circumference are listed in Table 3.

Maternal characteristics of the two formula groups were comparable. Breast-feeding mothers had a significantly higher education level (>12 years) and lower smoking rate during pregnancy compared with the mothers of the HBP and LBP formula groups (Table 1). However, the differences in maternal smoking did not significantly affect the infants’ birth anthropometric measures and/or baseline SOS.

Anthropometric data during study visits at baseline and at 6 and 12 postnatal weeks showed no significant differences between the two formula groups. There was also no significant difference in formula consumption between these groups at 6 weeks (177 vs. 178 ml/kg/day, respectively) and 12 weeks (143 vs. 139 ml/kg/day) (P > 0.05 for all).

At randomization, bone SOS was comparable for all three groups of the study. When compared with baseline, it was shown that bone SOS decreased significantly at 6 and 12 weeks postnatal age (P < 0.001). Although there were no significant differences between the groups at 6 weeks postnatal age, at 12 weeks postnatal age, the mean SOS of

Fig. 1 Participant flow diagram

| Time point | Formula | Weight (kg) | Length (cm) | Weight gain (g/day)* | Head circumference (cm) |
|------------|---------|-------------|-------------|----------------------|-------------------------|
| Baseline   | HBP     | 3.2 ± 0.1   | 49.9 ± 0.5  | NA                   | 34.3 ± 0.3              |
|            | LBP     | 3.1 ± 0.1   | 49.2 ± 0.4  | NA                   | 34.2 ± 0.3              |
|            | BM      | 3.2 ± 0.1   | 50.3 ± 0.5  | NA                   | 34.9 ± 0.3              |
| 6 weeks    | HBP     | 4.7 ± 0.1   | 55.7 ± 0.4  | 37.2 ± 1.8           | 37.6 ± 0.3*             |
|            | LBP     | 4.7 ± 0.1   | 55.2 ± 0.5* | 36.7 ± 1.7           | 37.4 ± 0.4*             |
|            | BM      | 5.0 ± 0.1   | 56.7 ± 0.6  | 37.2 ± 1.8           | 38.3 ± 1.0              |
| 12 weeks   | HBP     | 6.0 ± 0.2   | 60.1 ± 0.7  | 29.3 ± 1.8           | 39.6 ± 0.4              |
|            | LBP     | 5.9 ± 0.2   | 59.9 ± 0.5  | 26.8 ± 1.6           | 40.1 ± 0.3              |
|            | BM      | 6.2 ± 0.2   | 60.9 ± 0.4  | 27.2 ± 1.4           | 39.9 ± 0.4              |

Data are presented as mean ± SEM

HBP high beta-palmitate, LBP low-beta palmitate, BM human breast milk, NA not applicable

* P < 0.05 compared with the BM group

a Baseline to 6 weeks and 6–12 weeks
the HBP group was significantly higher than that of the LBP group (2,896 ± 133 vs. 2,825 ± 194 m/s, respectively, \( P = 0.049 \)) and similar to that of the BM group (2,875 ± 85 m/s, \( P = 0.3 \); Table 4; Fig. 2). The difference between the HBP and the LBP groups remained statistically significant when weight at each visit was used as a covariate in the ANCOVA (\( P < 0.05 \)).

There was a twofold difference in maternal smoking between the two formula groups. This difference did not reach statistical significance. Further analysis with maternal smoking used as a covariant was not found to affect the change in bone SOS.

### Discussion

As hypothesized in this randomized, controlled, double-blind study, bone SOS of term newborns fed HBP formula was significantly higher than that of newborns fed LBP and comparable with that of term newborns fed BM. These data are consistent with two other studies that used dual-energy X-ray absorptiometry (DEXA) that assessed bone mineralization [8, 26]. Kennedy et al. [8] showed in their randomized controlled trial that infants fed a greater proportion of palmitate in the \( sn-2 \) position have higher body bone mass at 12 weeks. In a complementary longitudinal study, term infants ingesting formula with palmitate in the \( sn-1 \) and \( sn-3 \) positions, developed reduced total body bone mineral content (BMC) compared with infants ingesting infant formula without palm oils [26]. Clearly, bone QUS and DEXA modalities are based on different measuring principles. Although DEXA mainly measures quantitative aspects of BMD, QUS relates to qualitative factors, such as bone elasticity, microarchitecture, geometry, and porosity of cortical bone that contribute to bone strength. We found that bone SOS of the HBP group was comparable with that of the BM group, again consistent with Kennedy et al. [8]. Studies in the 1990s published conflicting data regarding BMC of breast-fed versus formula-fed infants. Specker et al. [27] reported lower total body BMC in exclusively breast-fed infants compared with formula-fed infants. In contrast, others found comparable BMC with different types of feeding [28, 29]. However, the composition of other nutrients, especially fat composition, was not addressed in these early studies.

Our SOS measurements show a decrease in SOS in the first 12 weeks postnatal age for all infants regardless of the type of feeding. This is in agreement with studies in both preterm infants [21, 22] and term infants demonstrating a decrease in SOS [30] and DEXA [31]. The reasons for this phenomenon are not clear. It was suggested that the decline in BMD in healthy newborns is associated with a relative physiological decrease of the cortical area and the redistribution of bone tissue from the endocortical to the periosteal surface rather than with bone loss [30]. It is also possible that this decrease represents a delay between rapid bone linear growth and mineralization. In a nonrandomized clinical study, Zuccotti et al. [32] showed that at 4 months there is already increase in SOS, with no significant differences between exclusive breast-fed or formula-fed

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**Table 4** Bone SOS measurements at baseline, 6, and 12 weeks postnatal age

| Time point | HBP (n = 20) | LBP (n = 18) | BM (n = 22) | HBP vs. BM difference (95 % CI) | HBP vs. LBP difference (95 % CI) |
|------------|--------------|--------------|-------------|-------------------------------|-------------------------------|
| Baseline   | 3,027 ± 20   | 3,001 ± 22   | 3,023 ± 21  | 1.3 (−72.1, 74.6)             | 21.7 (−49.2, 92.6)           |
| 6 weeks    | 2,920 ± 24   | 2,852 ± 24   | 2,915 ± 26  | 13.4 (−65.1, 92.0)            | 68.6 (−5.9, 149.1)           |
| 12 weeks   | 2,896 ± 30** | 2,825 ± 19   | 2,875 ± 18  | 33.2 (−36.6, 103)             | 74.7 (0.33, 149)*            |

Data are presented as mean ± SEM of unadjusted SOS (m/s) or as 95 % CI for group differences according to ANCOVA adjusted for birth weight

SOS: speed of sound, HBP: high beta-palmitate, LBP: low-beta palmitate, BM: human breast milk, CI: confidence interval, SEM: standard error of the mean

* Group differences statistically significant at \( P < 0.05 \)

** Significantly different from controls according to ANCOVA adjusted for birth weight at \( P < 0.05 \)
infants after 4 and 12 months. This is in agreement with our findings that HBP infants have comparable SOS values with breast-fed infants, yet it is in contrast to our finding that BM infants have higher SOS values than control infants. Of note is that although the authors compared between formula and BM feeding, they did not differentiate between the different types of formula milk. Further, given that bone SOS was done at 4 months, it is possible that the initial decline was missed.

To our knowledge, our study is the first to demonstrate bone status by using QUS for term infants consuming HBP or LBP formula. The measurements obtained by QUS may not only be related to BMD but also to additional parameters of bone strength and quality. Nevertheless, the study has several limitations. First, we had a relatively small sample size; however, there was adequate statistical power to detect differences between the two formula arms of the trial. A second limitation is a potential noncompleters bias. In this respect, we stress that the sample of 21 % of those who did not complete the study was matched with those who did for gestational age and birth weight. Third, no longer-term follow-up after 12 weeks postnatal age was provided to examine the effect of supplementation of BM and HBP and LBP formulas on future bone strength. Thus, it is unclear whether the differences we found in bone SOS at infancy affect bone strength at older ages. Moreover, it is possible that the initial decrease in bone SOS and mineralization is a physiologic phenomenon that is necessary for bone development later in life. If this is the case, efforts to prevent this decrease are questionable. It should be emphasized that the findings of the HBP group was similar to those of the BM group and thus mimic a gold standard. Still, further studies are needed to elucidate the complex relationship between neonatal bone strength and the development of osteopenia and osteoporosis later in life.

In conclusion, at 12 weeks postnatal age, bone SOS of term infants consuming infant formula enriched with HBP was higher than that of infants consuming LBP formula, and comparable with that of the BM infants.

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