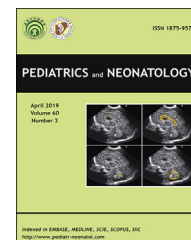


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Original Article

Does type of feeding affect body composition in very low birth weight infants? – A prospective cohort study



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Key Words

body composition;
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formula feeding;
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Abstract *Background:* The aim of the study was to analyse body composition of preterm infants fed with either breast milk or formula compared to a control group of full-term newborns.

Methods: Fifty-three newborns were enrolled: a group of 34 very low birth weight (VLBW) preterm newborns subdivided into a formula-fed ($n = 23$; group A) and breast milk-fed ($n = 11$; group B) group, and a control group of 19 full-term infants (group C). Their body composition was assessed by a bioelectrical impedance analysis (BIA) either at the estimated time of birth in the VLBW group or during the 1st week of life in the full-term group.

Results: There was no difference in body weight or length between any of the three studied groups. However, we discovered that fat free mass (% FFM) was lower (83.5% vs. 85.5%; $p < 0.01$), while fat mass (% FM) was higher (16.4% vs. 14.5%; $p < 0.01$) in group A compared to full-term newborns. There were no such differences in FFM (84.3% vs. 85.5%; $p = 0.13$) or FM (15.7% vs. 14.5%; $p = 0.13$) between group B and control.

Conclusion: To sum up, the VLBW infants fed with breast milk shared similar body composition with the full-term infants, while the formula-fed VLBW developed higher amounts of adipose tissue and lower amounts of fat-free mass. This is the first study to expose differences in fat tissue content attributed to type of provided nutrition, which has become significant as early as estimated time of birth despite the comparable weight.

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1. Introduction

In the recent years, there is a noticeable increase in the survival rate of premature infants due to improvements in perinatal health care, use of antenatal steroids, pulmonary surfactant treatment, advances in respiratory and nutritional management.^{1,2} It appears that both prematurity and treatment provided after birth affect future development of those children. On one hand, preterm newborns are more susceptible to malnutrition and extrauterine growth retardation compared to their full-term counterparts, especially early in life.³ On the other hand, they might face increased risk of obesity as it is observed in general population, where uncontrollable weight gain in children has become an important public health problem leading to numerous complications.⁴ There are reports that body composition abnormalities in infants modulate risk of variety of health disorders in the future, including hypertension, stroke, type 2 diabetes, and obesity,^{5,6} although there are no studies on increased obesity risk in former VLBW infants. Energy balance and nutritional status are of vital importance in early infancy, in particular in preterm babies. The newest guidelines recommended breast milk as a preferable way of feeding for the VLBW.^{7,8}

Routine methods used in the clinical settings to assess body composition in infants and children are based on anthropometric measurements (such as body length and weight, skinfold thickness), dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) techniques.⁹ In studies about fat mass and fat distribution, low birth weight has been associated with a more central pattern of fat distribution^{10,11} and lower BMI, mostly because of a lower lean body mass and not a lower fat mass.^{12,13} The aim of the study was to evaluate whether there was any difference in body composition of the VLBW preterm infants fed with either breast milk or formula compared to the control group of full-term newborns.

2. Methods

2.1. Study design and area

The study included newborns admitted to the Neonatal Intensive Care Unit, Department of Paediatrics, Jagiellonian University Medical College, Krakow, Poland between February 2014 and June 2016. Two groups of children were enrolled: preterm newborns with birth weight of 1000–1500 g, and term newborns with birth weight of 2500 g–4000 g (served as the control group, group C). We evaluated initial neonatal risk for the preterm infants using Clinical Risk Index for Babies (CRIB)¹⁴ and Score for Neonatal Acute Physiology II (SNAPPE II, <http://www.sfar.org/scores/snap2.php>) scales. The infants received parenteral solutions of glucose, lipids and amino acids from the time of their admission until their oral feeding reached adequate volumes. All studied infants started oral feeding within 24–48 h with either breast milk, which was supplemented a standard dose of human milk fortifier when the feeding portion >140 ml/kg/day (Bebilon HMF, Nutricia), or formula specially adapted for the preterm infant (PreNAN, Nestle, or Bebilon Nenatal,

Nutricia). The infants were fed by nasogastric tube or by nipple when possible. Each mother was encouraged to provide milk for her own infant; we did not use human milk from a milk bank. Based on type of feeding, the preterm group was divided into two subgroups: formula-fed (group A) and breast milk-fed (group B). Exclusion criteria for all the groups were as follows: severe congenital malformations, chromosomal aberrations, asphyxia (5th minute Apgar Score < 3 points), intraventricular haemorrhage grade IV, and severe infections. All the neonates admitted to the hospital who fulfilled the inclusion criteria (birth weight between 1001 and 1500 g, admission before 5th day of life, and feeding started within first 48 h of life) were included in the study. Only 2 children were not included due to lack of parental consent.

2.2. Ethical issues

The study protocol was approved by the Jagiellonian University Medical College Ethical Committee (issue No KBET/58/B/2013 from 4.04.2013). Written and informed consents were obtained from the parents.

2.3. Anthropometric measurements

All infants were weighed naked to the nearest 10 g on an electronic baby scale (RADWAG 2006). Crown-heel length and occipito-frontal circumference were measured to the nearest 0.5 cm by a standard measuring tape. A single investigator made all the measurements.

2.4. Body composition measurements

Body composition was measured with a multi-frequency impedance body composition monitor (BCM; Fresenius Medical Care, Bad Homburg, Germany), and four special disposable electrodes BCM-FMC (<25 kg). The BCM instrument measured resistance and reactance between 5 and 1000 kHz at 200 Hz increments (50 measurements). The amplitude of the electric current was 0.8 mA. Examined newborns were placed in supine positions with their arms and legs extended. Two electrodes were attached to a dorsal surface of a hand, and the other two to a dorsal surface of a foot on the same side. Measurements were made 2 min after attachment of the electrodes to their respective sites.

The BIA analysis to determine body composition was carried out either at estimated time of birth in the VLBW groups or during the 1st week of life in the control group.

2.5. Statistical analysis

Statistical analysis was conducted using JMP 9.0.0, 2010 SAS Institute Inc. The detected differences were considered statistically significant in case of $p < 0.05$. Our null hypothesis was that there was no difference in the body composition between VLBW preterm infants fed with human milk or formula at estimated time of birth and full-term newborns. Demographic and clinical data comparisons between the study and control groups were performed using Student's *t*-test, Mann–Whitney *U* test, chi-square

test, or ANOVA, depending on the data character and their distribution. Comparisons between formula-fed, human milk-fed VLBW preterm infants and full-term newborns were performed using Tukey test.

2.6. Justification of sample size

Our study hypothesis was based on data indicating a difference in body composition of the VLBW preterm infants compared to full term newborns. Analysis of the available publications^{15,16} and results of our own pilot study¹⁷ suggested that prematurity could increase the amount of fat mass and decrease the amount of fat free mass in preterm infants. The minimal number of patients required to be enrolled to each study group was calculated using an online sample size calculator at www.stat.ubc.ca. Based on the published data, we estimated mean fat mass to be 0.4 kg in term-born neonates, while it would be about 35% higher in preterm babies corresponding to 0.54 kg with the standard deviation of 0.15 kg in each group. We determined a required sample size for each group to be 19 patients based on the two-sided test with $\alpha = 0.05$, power = 0.8. Therefore, we recruited eligible patients until we reached 19 patients in the smaller (control) group.

3. Results

Fifty-three newborns (34 preterm infants and 19 full-term infants) were included in the study. Baseline characteristics of the studied groups are listed in Table 1. There were no statistically significant differences in the birth weight, body length or head circumference between exclusively breast-fed and exclusively formula-fed preterm infants at their time of birth. The median length of hospitalization was 47 days ($p = 0.81$), and this was comparable in the two groups of preterm babies. The neonatal risks as measured by CRIB and SNAPPE II scales were similar. Median CRIB was 2 points in both groups ($p = 0.8$), median SNAPPE II scale was 12 points in group A and 17.5 points in group B ($p = 0.24$). We found no significant differences in the maternal status (as reflected in maternal weight gain during pregnancy and education level), which might have affected the wellbeing of the babies. Mothers from group A presented median 10 kg (8–14 kg) weight gain, mothers from group B presented median 9 kg (8–12 kg) weight gain during pregnancy ($p = 0.46$). There were no statistically significant differences in the maternal level of education ($p = 0.177$). The total number of days of mechanical ventilation, nasal continuous positive airway pressure (nCPAP) and oxygen supplementation were similar in formula-fed and human

Table 1 Baseline characteristics of the study population. The p-values were calculated as indicated: ^C - p-value for chi-square test, ^T - p-value for *t*-test, ^W - p-value for Wilcoxon test. The p-values were significant in case of $p < 0.05$.

	Preterm group A	Preterm group B	p-value (A vs. B)	Full-term group C
Gestational age [week], Me ^a (IQR) ^b	29 (28–31.75)	29 (28–32)	NS ^W	39 (37–40)
Birth weight [g], mean (SD) ^d	1240 (180)	1210 (161)	NS ^T	3320 (399)
Birth weight [Z-SCORE], mean (SD)	0.18 (0.92)	−0.45 (1.1)	NS ^T	0.09 (0.88)
Birth length [cm], mean (SD)	39.8 (2.8)	40.3 (3.0)	NS ^T	52.1 (3.5)
Birth length [Z-SCORE], mean (SD)	0.56 (1.38)	0.56 (1.31)	NS ^T	54 (3)
Head circumference at birth [cm], mean (SD)	26.9 (1.7)	27 (1.7)	NS ^T	34.5 (1.3)
Head circumference at birth [Z-SCORE], mean (SD)	0.09 (1.63)	−0.20 (1.07)	NS ^T	0.08 (0.88)
Weight gain during pregnancy [kg], Me (IQR)	10 (8–14)	9 (8–12)	NS ^W	13 (9–16)
Maternal level of education, n (%)				
Primary	4 (19)	0 (0)	NS ^C	0 (0)
Secondary	11 (52.4)	5 (45.5)		7 (36.8)
High/College	6 (28.6)	6 (54.5)		12 (63.2)
SIMV [days], Me (IQR)	1 (0–3)	0 (0–7)	NS ^W	0 (0)
nCPAP [days], Me (IQR)	5 (2–9)	8 (0–15)	NS ^W	0 (0)
Oxygen supplementation nasal cannulas [days], Me (IQR)	4 (0–12)	15 (3–23)	NS ^W	0 (0–2)
Oxygen supplementation – TOTAL [days], Me (IQR)	12 (7–29)	28 (10–38)	NS ^W	0 (0–4)
CRIB ^e scale, Me (IQR)	2 (1–3)	2 (2–2)	NS ^W	NA ^g
SNAPPE II ^f scale, Me (IQR)	12 (0–27)	17.5 (15–23)	NS ^W	NA
Apgar Score 5th min of life, Me (IQR)	7 (6–8)	6.5 (5–8.25)	NS ^W	10 (9–10)
Surfactant administration, n (%)	12 (52.2)	5 (45.5)	NS ^C	0 (0)
Length of hospitalization [days], Me (IQR)	47 (39–73)	47 (35.5–64.25)	0.8141 ^W	8 (6–11)

^a Median.

^b Interquartile range.

^c Not significant.

^d Standard deviation.

^e Clinical Risk Index for Babies.

^f Score for Neonatal Acute Physiology II.

^g Not analysed.

milk-fed VLBWs. The results of anthropometric measurements during BIA examination are summarized in Table 2. At the estimated time of birth, we observed that formula-fed preterm infants were heavier (3683 [SD 690] g vs. 3336 [SD 385] g; $p = 0.022$; z-score: 0.81 [SD 1.12] vs. -1.02 [SD 0.88]; $p = 0.019$) and they had increased head circumference (36.1 [SD 1.8] cm vs. 34.6 [SD 1.0] cm; $p = 0.02$; z-score: 0.39 [SD 1.26] vs. -0.81 [SD 0.84]; $p = 0.013$) compared to the breast milk-fed preterm group. We also analysed selected independent growth deficit risk factors, such as bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhages grade III and IV, retinopathy of prematurity requiring laser coagulation, episodes of sepsis and necrotizing enterocolitis. The incidence of the premature birth complications above was similar in groups A and B, as outlined in Table 3.

Once we analysed selected anthropometric parameters, we noted that there were some statistically significant differences in fat-free mass (FFM) and fat mass (FM) between group A of VLBW preterm infants fed with formula

and the full-term control group C. The formula-fed group showed decreased percentage of FFM (83.554 [SD 1.74] vs. 85.488 [SD 1.3]; $p = 0.001$) and increased FM mass and percentage (respectively, 0.617 [SD 0.18] vs. 0.494 [SD 0.1]; $p = 0.02$; and 16.446 [SD 1.74] vs. 14.511 [SD 1.31]; $p = 0.001$). We found no differences in FFM or FM between group B and the control group (Table 4).

4. Discussion

We present results of a study of the preterm infants' group, which showed very early differences in the body composition once they reached their estimated time of birth. Our gold standard of body composition represented full-term newborns at birth, which constituted our control group C. We determined that VLBW preterm infants fed with formula, but not with breast milk, had significantly lower amounts of fat-free mass and increased fat mass compared to the control group. Our study is one of few to evaluate the

Table 2 Anthropometric characteristics of the study preterm infants at the 40th week of postmenstrual age. The parameters are presented as means \pm SD. The compared parameters were analysed with one-way ANOVA. The p-values were significant in case of $p < 0.05$.

	Preterm group A	Preterm group B	p-value
Weight at study BIA ^a (g)	3683 (690)	3336 (385)	0.022
Weight at study BIA (Z-SCORE)	-0.81 (1.12)	-1.02 (0.88)	0.019
Length at study BIA (cm)	52 (3)	50 (2)	0.4
Length at study BIA (Z-SCORE)	0.78 (1.1)	-0.93 (0.83)	<0.05
Head circumference at study BIA (cm)	36.1 (1.8)	34.6 (1.0)	0.002
Head circumference at study BIA (Z-SCORE)	0.39 (1.26)	-0.81 (0.84)	0.013

^a bioelectrical impedance analysis.

Table 3 Incidence of selected independent risk factors for growth deficits in the Very Low Birth Weight group. Statistical significance was determined with ^C - chi-square analysis and ^W - Wilcoxon test. The p-values were significant in case of $p < 0.05$.

	Group A	Group B	TOTAL	p-value
Bronchopulmonary dysplasia, n (%)	6 (26.1%)	6 (54.5%)	12 (35.3%)	0.12 ^C
Necrotizing enterocolitis, n (%)	4 (17.4%)	2 (18.2%)	6 (17.6%)	0.96 ^C
Patent ductus arteriosus, n (%)	11 (47.8%)	4 (36.4%)	15 (44%)	0.53 ^C
Sepsis, n (%)	8 (34.8%)	3 (27.3%)	11 (32.4%)	0.66 ^C
Intraventricular haemorrhage $\geq 3^\circ$, n (%)	1 (4.4%)	2 (18.2%)	3 (8.8%)	0.38 ^C
Retinopathy of prematurity requiring laser coagulation, n (%)	2 (8.7%)	0 (0%)	2 (5.9%)	0.31 ^C

Table 4 Characteristics of the study populations either at their estimated time of birth (A, B), or at birth (C). The parameters are presented as means \pm SD. The p-values were significant in case of $p < 0.05$.

	GROUP A Mean (SD)	GROUP B Mean (SD)	GROUP C Mean (SD)	A vs. B p-value	A vs. C p-value	B vs. C p-value
Weight (kg)	3.683 (0.69)	3.336 (0.39)	3.396 (0.42)	0.022	0.197	0.978
Length (cm)	52 (3.0)	50 (2.0)	54 (3.0)	0.4	0.149	0.23
FFM ^a (kg)	3.066 (0.52)	2.808 (0.28)	2.885 (0.35)	0.226	0.356	0.88
FFM%	83.554 (1.74)	84.3 (1.64)	85.488 (1.3)	0.405	0.001	0.126
FM ^b (kg)	0.617 (0.18)	0.529 (0.11)	0.494 (0.1)	0.217	0.02	0.797
FM%	16.446 (1.74)	15.698 (1.64)	14.511 (1.31)	0.405	0.001	0.126

^a fat-free mass.

^b fat mass.

role of the type of feeding on body composition in the preterm infants at such an early period of their life, namely at term-corrected age. Amesh et al. compared preterm infants fed with fortified human milk or preterm formula until term. At term, infants were randomized to a nutrient-enriched formula without extra energy or standard formula until 6 months corrected age. Twenty-six infants received unfortified human milk after term. At term and 6 months corrected age, anthropometry and a dual-energy x-ray absorptiometry (DEXA) scan were performed. There were no differences in growth or body size between the feeding groups. Infants fed the enriched formula gained less FM and had lower FM corrected for body size at 6 months corrected age than infants fed standard formula. Infants fed human milk had lower lean mass and higher FM corrected for body size at 6 months corrected age than formula-fed infants.¹⁸

Our findings are significant and very interesting despite certain limitations of our study, such as small sample size, use of bioimpedance analysis instead of dual-energy X-ray absorptiometry, typically a reference method for assessing body composition.

The American Academy of Paediatrics (AAP) recommends human milk as a preferred type of feeding for all infants.¹⁹ Exclusive breastfeeding early in life is associated with a slower rate of weight gain and about 20% reduction in odds of being overweight in childhood and adolescence compared to formula feeding.²⁰ However, certain subpopulations might demonstrate additional nutritional needs, as it is true in premature newborns who often require supplementation with human milk fortifiers.¹⁹ The influence of birth weight and type of feeding on growth and body composition in very low birth weight infants (VLBW) has gained growing interest. Infants born prematurely appear to accumulate fat in greater amounts during the period of time between their actual birth and estimated time of birth compared to a foetus in the last trimester of pregnancy. At the same time, the majority of infants with an extremely low birth weight (<1000 g) demonstrate severe growth restriction and significantly decreased body mass at their hospital discharge compared to infants born at term.²¹ Premature infants also face a number of other challenges, such as bronchopulmonary dysplasia that increases their risk of future growth deficits^{22,23} due to the very low birth weight, treatment with the systemic steroids to shorten time of mechanical ventilation and intolerance of appropriate volumes of milk feeding.²⁴ Despite the recommendations of the AAP, premature infants do not appear to reach growth and body composition similar to term-born infants.¹⁹ Kwinta et al. demonstrated that there were differences in body composition between VLBW preterm infants and their term counterparts even at school age.¹⁷ The authors examined the children at the age of 7 years with BIA method to show significantly lower amount of the adipose tissue in the group born prematurely with extremely low birth weight in comparison with their school mates born at full term. In our previous study, we showed differences in body composition between preterm and term infants at 3 months. We recorded lower amount of fat tissue, greater amount of fat-free mass and increased total body water in the group of infants born prematurely.²⁵ Atkinson et al. found that LBW infants at term-adjusted age were lighter and shorter than term-born infants but had a higher percent of fat mass.²⁶

Our study demonstrates that formula-based diet in contrast to breastfeeding is associated with alterations in baby's body composition that occurs in the time period between preterm birth and the time of the originally estimated birth. Quigley et al. performed a meta-analysis to assess potential differences between infants fed with either formula or donor breast milk in a population of preterm or low birth weight infants (between 1500 and 2500 g). Formula-fed infants were bigger and they demonstrated greater increase in weight, length and head circumference compared to the breast-milk group when analysed during their hospital stay. Despite better growth on formula, it appeared that formula feeding increased risk of necrotising enterocolitis. The authors did not find any evidence that post-discharge growth rates of either study group affected their neurodevelopmental outcomes.²⁷ Corpeleijn et al. determined that supplementation with either donor human milk or formula yielded similar short-term outcomes during first 10 days of life of VLBW infants. Regardless of whether pasteurized donor human milk or special preterm formula was provided in case of insufficiency of mother's milk, the rates on incidence of serious infection, necrotizing enterocolitis, and mortality were comparable.²⁸

To summarize, we showed that nutrition with human breast milk in contrast to formula allowed the premature VLBW infants to develop body composition similar to our gold standard, babies born full-term. It is still difficult to predict whether differences in body composition so early in life may affect programming growth in later years. Future investigations should verify whether changes in body composition can be attributed only to type of nutrition or whether they represent a combined result of nutrition, genetics and other environmental factors. Regardless of the ultimate aetiology, these children may require regular monitoring to see whether altered fat content might affect future neuro-psychological development and physical activity. We believe that more studies investigating longer use of human donor milk on short-term and long-term outcomes are necessary.

5. Conclusions

1. The VLBW infants fed with breast milk shared similar body composition with the full-term infants at estimated term of birth, while the formula-fed VLBW infants developed higher amounts of adipose tissue and lower amounts of fat-free mass.
2. These differences between breast milk and formula-fed infants were noted very early despite their comparable weights. Also, the observed disparity in fat content became significant over the short period of time between birth and estimated time of birth.
3. In light of these results, our study supports promotion of breastfeeding as preferable method of providing nutrition at NICU and other paediatric settings.

Conflicts of interest statement

The authors declare no potential conflicts of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.pedneo.2018.04.010>.