

Body Composition Assessment in Children Born Small for Gestational Age and Its Correlation with Early Nutrition Type: Observational Study

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Abstract

Small for gestational age (SGA) refers to an infant born at term with a birth weight less than the 10th percentile. Several studies associate this condition with an increased risk of developing endocrine-metabolic diseases later in life either childhood and adulthood. The aim of this study was to assess body composition in children born SGA depending of the type of nourishment followed in early life. Herein we evaluated Breast-Fed (which include one or two milk integration with formula during the day), Exclusive Breast-Fed and Formula-fed as three types of nutrition in early life, highlighting differences in body composition. The obtained results revealed that female have a tendency to have the worst physical condition depending on the early nutrition followed. This result could mean that growth hormone (GH) has very different action or sensitivity in male and female.

Keywords: SGA, Obesity, BMI, Anthropometric

Introduction

In the last few years, many studies on children born Small for Gestational Age (SGA) were carried out [1-6]. The definition of SGA is not straightforward as it requires an accurate knowledge of gestational age (ideally based on first-trimester ultrasound exam), an accurate measurement at the birth of weight, length and head circumference. Several definitions have been used for SGA, ranging from a birth weight and/or length below the 10th to 3rd percentile or -2 SD for gestational age [1]. In 2007, the consensus statement published by the European Society of Pediatric Endocrinology (ESPE), the

Growth Hormone Research Society (GRS) and the Lawson Wilkins Pediatric Endocrine Society (LWPES), recommends that SGA should be defined as a weight and/or length less than below -2 Standard Deviations (SD) for gestational age because this will identify the majority of those in whom ongoing growth assessment is required [2]. Often, the acronym SGA is confused with the acronym IURG, but they have different meanings. Intrauterine Growth Retardation (IUGR) refers to the fetal growth pattern and assumes that at least 2 intrauterine growth assessments are performed indicating a low growth velocity in the fetus. The term SGA does not refer to fetal growth but to the size of the infant at birth [3]. Although SGA is often

related to IUGR, not all SGA infants have suffered from IUGR and infants who are born after a short period of IUGR are not necessarily SGA. Equally, SGA and/or IUGR babies have an increased risk for prenatal morbidity, associated health problems, persistent short stature and metabolic alterations in later life [5]. Likewise, IUGR the factors contributing to SGA can be classified as fetal or maternal placental causes. The first ones include chromosomal abnormalities, genetic defects, metabolic problems, and congenital malformations while the second ones are associated with the inadequate supply of nutrients and/or oxygen, preeclampsia or placental insufficiency. Maternal age, weight and race and the presence of medical a condition such as chronic systemic diseases (hypertension, nephropathy, diabetes mellitus), infections (toxoplasmosis, rubella, cytomegalovirus, herpes virus), or the use of illicit substances are other important factors that have to be considered. When SGA does not deal with such causes as frequently observed in the clinical practice the condition is considered idiopathic [6]. Several studies relate SGA with the endocrine-metabolic disorders in both childhood and adulthood, such as insulin resistance, type 2 diabetes mellitus, overweight and obesity, dyslipidemia and metabolic syndrome [7-9]. Several theories have been proposed, including the thrifty phenotype hypothesis that epidemiologically correlates poor fetal and infant growth and the subsequent development of obesity and the metabolic syndrome with the type of nutrition in early life [9]. In this the study we evaluated in children born SGA, the impact of the different neonatal nutritional patterns, herein indicated ad Breastfed (with one or two milk integrations with formula during the day), Exclusive Breastfed and Formula-fed on children 6-7 years older. Our results highlight that human milk nutrient-integrated with formula one or two times per day is somewhat better than the others two nutrient patterns. Surprisingly we found that only SGA female children have a tendency to have worst body composition depending on the early nutrition followed during the neonatal period.

Methods

Type of study

We performed an open-label, retrospective and observational study that is part of a monocentric Italian Project between the University of Calabria and the Neonatal Intensive Care Unit (NICU) of Annunziata Hospital of Cosenza, Italy approved by the local ethics committee on 16th July 2014, protocol number 39/2014. The study was in agreement with the Declaration of

Helsinki and the Guidelines for Good Clinical Practice criteria. Informed consent was obtained from parents before to carry out the study.

Protocol

The study was conducted in two phases. The first phase started in September 2014 and ended in December 2015. In this phase, we performed a retrospective study on the clinical records of NICU and we collected general data (initials, age, sex, height, weight, born year) as well as the type of nutrition (i.e. breastfed (BF), exclusive breastfed (EBF) or formula-fed (F)). After the analysis of the data, from February, 2016 to September, 2017 started the second phase of the study where the (identified with a birth weight between 1.800-2.300 g) were recalled and recruited to evaluate weight, height and data concerning, foods, diseases and drugs used (e.g. corticosteroids) and to perform bioelectrical impedance analysis.

Body mass index and Bio-impedance analysis (BIA)

Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters. National and international BMI-for-age reference standards are available [8]. In addition, Bio Impedance Analysis (BIA) was performed using a single-frequency BIA analyzer (ImpediMED DF50), which applies a 50 kHz oscillating current. The most clinically established impedance parameters, FDA approved, are the Phase Angle (PA) in a range of 0° to 90° with 0,1° of resolution and with an accuracy of +/-0,5% and the Body Cell Mass (BCM) [9-11]. ImpediMED DF50 is a device has specifics algorithms, which consent to investigate also children.

Ethical approval and funding

This study is part of an Italian Project, called "Progettobebè: dallanascitaall'etàprepuberale" (approved in 16th July 2014, protocol C.E. N°39); the partners of the project are the University of Calabria and the NICU of Annunziata Hospital of Cosenza. All the recruited subjects for this study are participants of the cited project. Such subjects participated freely, with informed consent and all the prescriptions of privacy law were respected.

Statistical analysis

The cohort analyzed comprise of 248 SGA eligible children (6-7 years old), 131 females (44 breastfed, 22 exclusive breastfed and 71 formula-fed) and 117 males (24 breastfed, 59 exclusive breastfed and 31 formula-

fed). BMI, PA, and BCM values were plotted as whiskers and analyzed through Tukey's Multiple Comparison Test following one-way ANOVA. The threshold of statistical significance was set at $P < 0.05$.

Results

Body mass index in prepuberal SGA female subjects

Figure 1, panel A show that prepuberal SGA female children, BF and EBF were associated with a slightly lower mean BMI than F $BMIBF = 15.84 \pm 2.23$; $BMIEBF = 15.51 \pm 1.95$; $BMIF = 17.80 \pm 2.66$; ($***p < 0.0001$ $BMIBF$ vs $BMIF$; $**p < 0.05$ $BMIEBF$ vs $BMIF$). The mean difference in BMI appeared larger in the female children with a percentile in the range values of 75-90% for children formula-fed is shown in Cacciari's graph in figure 2, panel A. This range is indicative for these children as the upper limit of normal weight. No differences in BMI mean were highlighted in breastfed and exclusive breastfed children.

Body mass index in prepuberal SGA male subjects

Figure 1, panel B show that in the BF and EBF or F infant SGA male children, no difference in BMI was evidenced ($BMIBF = 16.52 \pm 2.84$; $BMIEBF = 16.51 \pm 3.53$; $BMIF = 16.50 \pm 3.12$). The overall data percentile was in the range values of 50-75% indicating normal weight as it shows in Cacciari's graph Figure 2, panel B. This range is indicative for these children as the upper limit of normal weight. No differences in BMI mean were highlighted in breastfed and exclusive breastfed subjects, which show a percentile range values of 50-75% indicating normal weight.

BCM value in prepuberal SGA female subjects

Figure 3 panels a show BCM value in prepuberal SGA female subjects of 19.23 ± 5.34 for $BCMIBF$; 18.39 ± 3.66 for $BCMIEBF$ and 17.58 ± 3.45 for $BCMIF$ and in panel B PA value of 6.13 ± 0.87 $PABF$; 5.29 ± 0.76 $PAEBF$ and 5.43 ± 0.65 PAF .

BCM value in prepuberal SGA male subjects

Figure 4 panels a show BCM value in prepuberal SGA male subjects of 39.30 ± 8.25 for $BCMIBF$; 38.71 ± 8.55 for $BCMIEBF$ and 40.02 ± 7.07 for $BCMIF$ and in panel B PA value of 5.92 ± 1.12 $PABF$; 5.80 ± 1.09 $PAEBF$ and 5.87 ± 1.21 PAF .

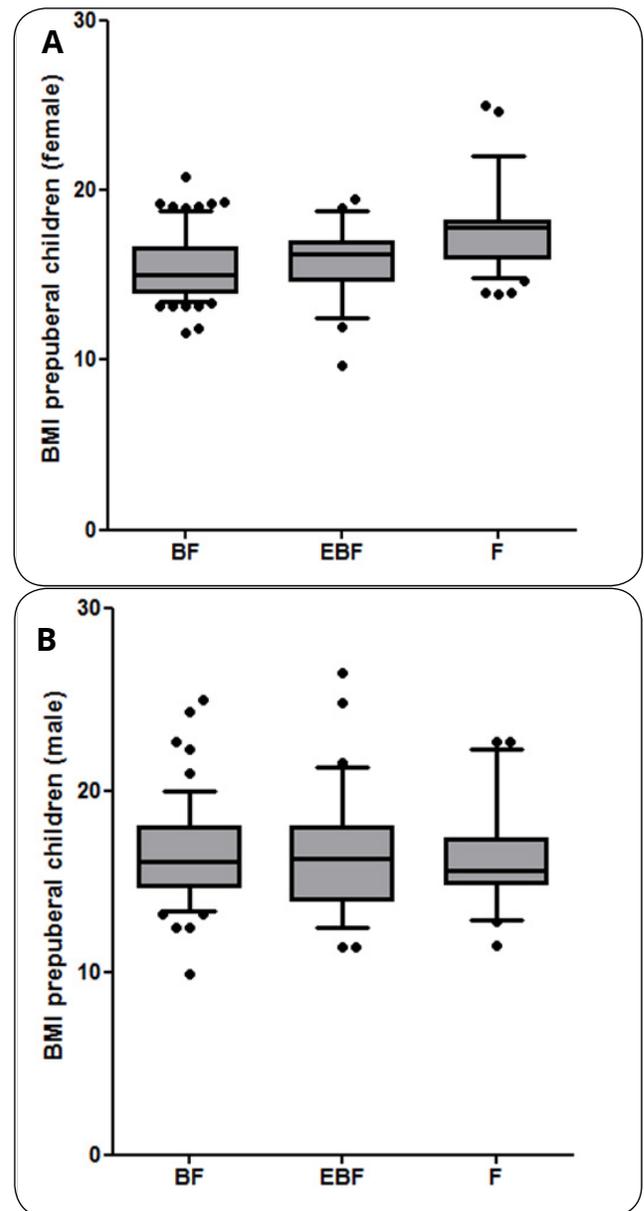


Figure 1: The data are plotted as a Wiskers 10-90 percentile graph. Panel A: BMI prepuberal female . BF, EBF, and F feeding. Panel B: prepuberal SGA male children. BF, EBF, and F feeding

Comparison of BCM and PA value in prepuberal SGA subjects

In figure 5 A and B, it is possible to observe the difference between BCM and PA values for male SGA vs female.

Discussion

Breast milk is undoubtedly a unique source of nutrients and immune modulating agents and new is the discovery of immune-related microRNAs and protect children against obesity later in life [10,11,15]. The aim of this

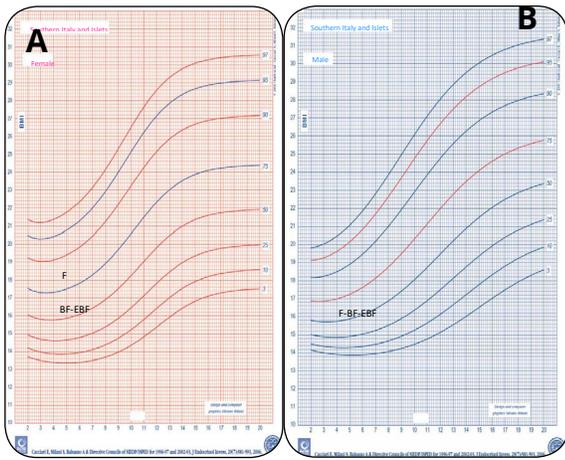


Figure 2: Data representation by Cacciari's graph. The mean difference in BMI appeared larger in the female SGA subjects with a percentile in the range values of 75-90% for children formula-fed (panel A) respect to male SGA subjects where the overall data percentile was in the range values of 50-75% indicating normal weight (panel B).

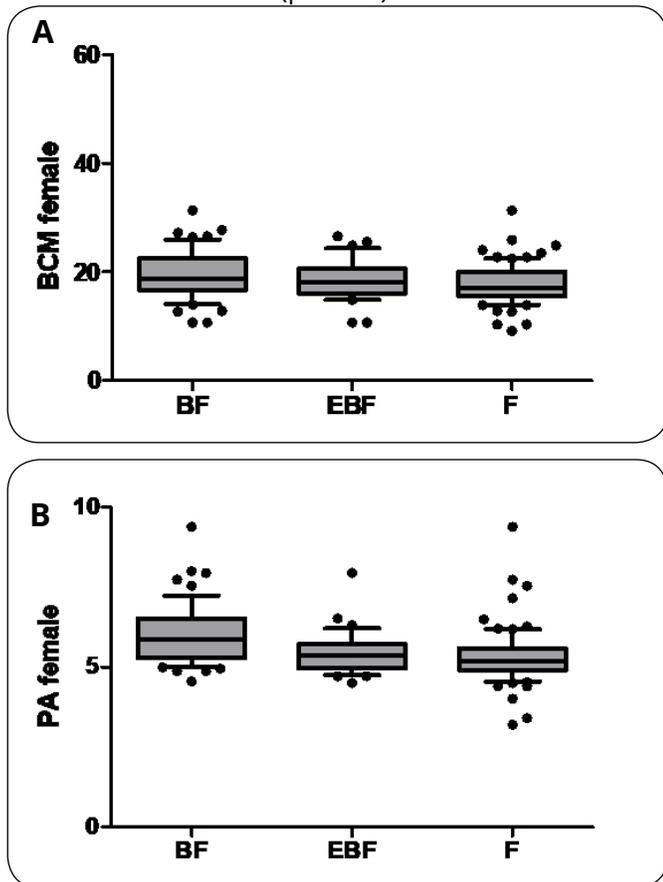


Figure 3: The data are plotted as a Wiskers graph. Panel A: Body Cell Mass (BCM) prepuberal female SGA subjects. BF, EBF, and F feeding. Panel B: Phase Angle (PA) of female subjects prepuberal SGA subject. BF, EBF, and F feeding.

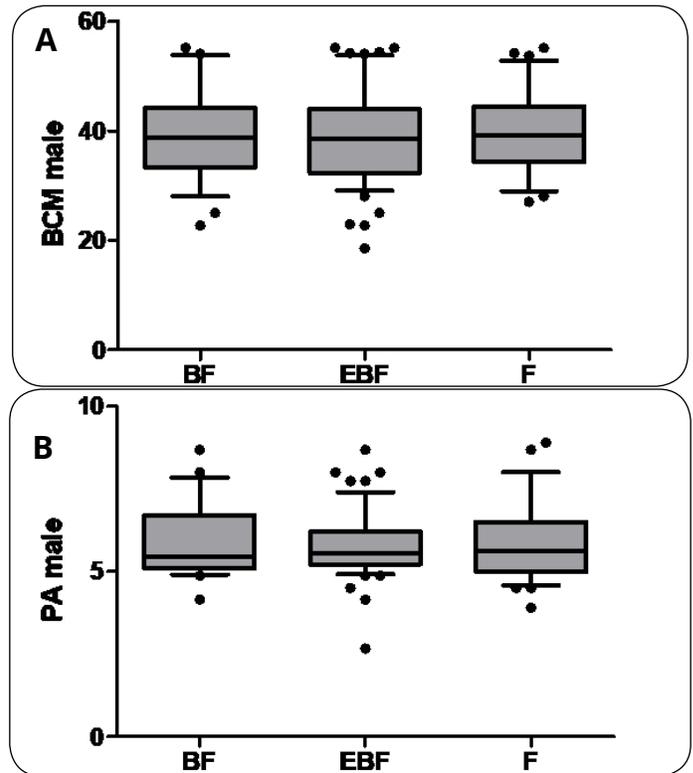


Figure 4: The data are plotted as a Wiskers 10-90 percentile graph. Panel A: Body Cell Mass (BCM) prepuberal male SGA children. BF, EBF, and F feeding. Panel B: Phase Angle (PA) of male subjects prepuberal SGA children. BF, EBF, and F feeding.

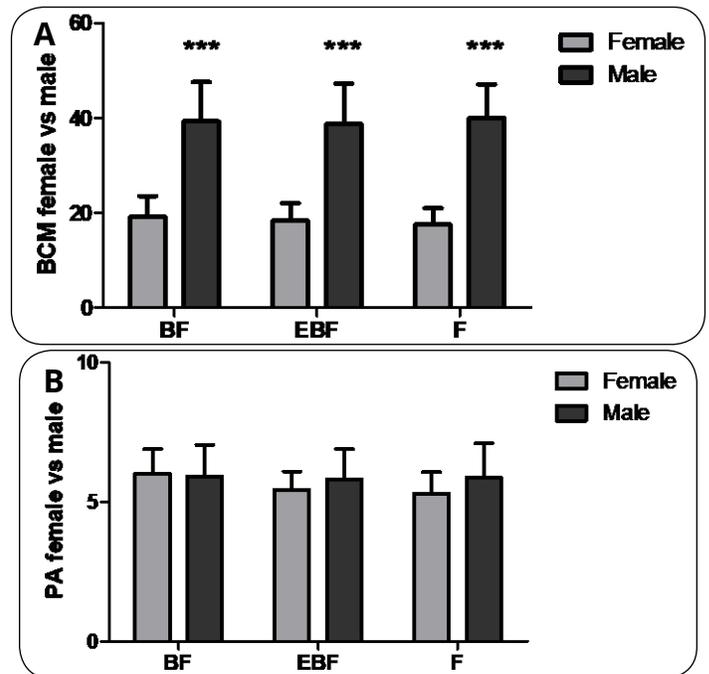


Figure 5: Panel A: The Body Cell Mass (BCM) value in prepuberal SGA female vs male children BF, EBF, and F feeding. Panel B: The Phase Angle (PA) value in prepuberal SGA female vs male children BF, EBF, and F feeding.

study was to evaluate if the type of nutrition (TN) received early in the life in a children population born SGA were linked to overweight development. Herein TN is indicated as BreastFed (one or two milk integration with formula during the day), Exclusive Breast Fed and Formula-fed. We observed that SGA subjects showed in term of Body Mass Index (BMI) Phase Angle (PA) and the Body Cell Mass (BCM) from Bio Impedance Analysis (BIA) no difference among groups (Figure 1 and 2, panels A and B; Figure 4 panel A and B). Instead, BMI measurement showed that female SGA subjects fed with formula early in the life could be prone to be overweight as shown in Cacciari's graph (Figure 1 and 2, panel A) where the mean difference in BMI appeared larger in the SGA female subjects with a percentile in the range values of 75-90% for children formula-fed. Such differences in BMI are consistent with previous studies [8,9]. In addition, BIA parameters such as Phase Angle (PA) and the Body Cell Mass (BCM) values evidenced the worst condition outcome for female SGA subjects fed with formula (Figure 3 panel A and B). Surprisingly, when BCM values of male SGA subjects are compared to female SGA subjects a huge difference is highlighted among the group and between sex (Figure 5 panel A), although PA values do not show a significant difference (Figure 5 panel B) as it also evidenced in table 1 by statistical analysis. BCM and PA are often but not always correlated between them. Both parameters have been suggested to be indicators of cellular health and high values of them reflect cell membrane integrity and better cell function indicating an overall good health condition [12]. In healthy subjects, PA usually ranges between 5° and 10°, correlating with various indices of functional and nutritional status [13]. PA is a marker of amount and

quality of soft tissue mass as well as hydration status it has been considered a useful marker of nutritional status by many authors [14-19]. Our study highlights for the first time that male and female, SGA subjects independently by early nutrition followed in the neonatal period, exhibited a relevant difference of BCM values but not of PA and BMI. This result could mean that growth hormone (GH) has very different action or sensitivity in regarding the sex.

Conclusions

For some of the investigated parameters difference among groups are not always significant. Maybe, differences in terms of body composition could arise in later life. However, diverse values of BCM were found comparing male versus female revealing that this latter group has a tendency to have the worst physical condition depending by the early nutrition (when formula was used) followed during the neonatal period. This result could mean that growth hormone (GH) has very different action and sensitivity depending by sex, male and female suggesting that "gender nutritional-medicine" should be applied after born.

Acknowledgment

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Table 1: t-test analysis of BCM and PA in male and female SGA children.

Table Analyzed	BCM female vs male	PA female vs male
Column A Vs Column B	Female vs Male	Female vs Male
Unpaired t test		
P value	P < 0.0001	0.270
P value summary	***	ns
Are means signif. Different? (P < 0.05)	Yes	No
One- or two-tailed P value?	Two-tailed	Two-tailed
t, df	t=34.37 df=4	t=1.280 df=4
How big is the difference?		
Mean ± SEM of column A	18.40 ± 0.4765 N=3	5.583 ± 0.2188 N=3
Mean ± SEM of column B	39.35 ± 0.3799 N=3	5.866 ± 0.03470 N=3
Difference between means	-20.95 ± 0.6094	-0.2837 ± 0.2216
95% confidence interval	-22.64 to 19.26	-0.8988 to 0.3314
R squared	0.997	0.291

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20. https://www.who.int/elena/titles/bbc/breastfeeding_childhood_obesity/en/



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