Body Composition and Circulating High-Molecular-Weight Adiponectin and IGF-I in Infants Born Small for Gestational Age

Breast- Versus Formula-Feeding

Francis de Zegher,[1] Giorgia Sebastiani,[2,3] Marta Diaz,[2,3] David Sánchez-Infantes,[2,3] Abel Lopez-Bermejo,[4,5] and Lourdes Ibáñez[2,3]

Prenatal growth restraint, if followed by postnatal overweight, confers risk for adult disease including diabetes. The mechanisms whereby neonatal nutrition may modulate such risk are poorly understood. We studied the effects of nutrition (breast-feeding [BRF] vs. formula-feeding [FOF]) on weight partitioning and endocrine state (as judged by high-molecular-weight [HMW] adiponectin and IGF-I) of infants born small for gestational age (SGA). Body composition (by absorptiometry), HMW adiponectin, and IGF-I were assessed at birth and 4 months in BRF infants born appropriate for gestational age (AGA; n = 72) and SGA infants receiving BRF (n = 46) or FOF (n = 56), the latter being randomized to receive a standard (FOF1) or protein-rich formula (FOF2). Compared with AGA-BRF infants, the catchup growth of SGA infants was confined to lean mass, independently of nutrition. Compared with AGA-BRF infants, SGA-BRF infants had normal HMW adiponectin and IGF-I levels at 4 months, whereas SGA-FOF infants had elevated levels of HMW adiponectin (particularly SGA-FOF1) and IGF-I (particularly SGA-FOF2). In conclusion, neonatal nutrition seems to influence endocrinology more readily than body composition of SGA infants. Follow-up will disclose whether the endocrine abnormalities in SGA-FOF infants can serve as early markers of an unfavorable metabolic course and whether they may contribute to design early interventions that prevent subsequent disease, including diabetes. ***Diabetes*** **61:1969–1973, 2012**

Yearly, millions of human infants are born small for gestational age (SGA), and these infants are at higher risk for later diseases such as diabetes and hypertension (1), particularly if their weight gain is excessive in early infancy (2,3) and if they receive protein-enriched formula-feeding (FOF) instead of breast-feeding (BRF) (4–6). The mechanisms underpinning this risk are poorly understood, but evidence starts to indicate that fetal-neonatal anomalies in adipogenesis and circulating adipokines and hormones are among the contributors (7–9).

From the [1]Department of Pediatrics, University of Leuven, Leuven, Belgium; the [2]Hospital Sant Joan de Déu, University of Barcelona, Barcelona, Spain; the [3]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain; the [4]Department of Pediatrics, Dr. Josep Trueta Hospital, Girona, Spain; and the [5]Girona Institute for Biomedical Research, Girona, Spain.
Corresponding author: Lourdes Ibáñez, libanez@hsjdbcn.org.
Received 20 December 2011 and accepted 9 March 2012.
DOI: 10.2337/db11-1797
This article contains Supplementary Data online at http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db11-1797/-/DC1.

In 2005 to 2006, we designed a study that aimed to yield evidence that could point toward mechanisms whereby nutrition in early infancy may modulate the long-term course of SGA children. Between birth and 4 months, we studied how SGA-BRF and SGA-FOF infants distribute their weight gain as compared with BRF controls born appropriate for gestational age (AGA). SGA-FOF infants were randomized to receive a standard formula or a protein-enriched formula that is still recommended for low-birth-weight infants. In parallel, we assessed circulating IGF-I, a prime endocrine marker for which levels are known to be lower in AGA infants receiving BRF than in those receiving FOF (10–12). Finally, we measured the circulating levels of high-molecular-weight (HMW) adiponectin, an adipokine that is abundantly present in the fetus (13,14) and is a sensitive marker of SGA-related features from early childhood onwards (15–17).

RESEARCH DESIGN AND METHODS

Study population. The study cohort consists of 174 infants (88 girls and 86 boys) recruited (Fig. 1) into a longitudinal study that assesses the body composition and endocrine-metabolic state of SGA infants, as compared with AGA-BRF controls, in the first years after birth (9,13,18). The present substudy focused on weight partitioning and circulating HMW adiponectin and IGF-I between birth and age 4 months. Accordingly, the specific inclusion criteria were

- Birth at Hospital Sant Joan de Déu, Barcelona, after an uncomplicated, term (37–42 weeks), singleton pregnancy (no maternal hypertension, gestational diabetes, alcohol abuse, or drug addiction)
- Birth weight between 2.9 and 3.9 kg for AGA and between 1.9 and 2.6 kg for SGA infants
- Exclusive breastfeeding for 4 months in AGA controls; either exclusive breastfeeding for 4 months or exclusive feeding with the randomly assigned formula in SGA infants (see below)
- Body composition assessment at ages 2 weeks and 4 months
- Enough cord serum available (at birth) and enough serum available in pre-feeding state (at age 4 months) to enable measurement of circulating HMW adiponectin and IGF-I (there were logistic restraints, mainly for nighttime collection of cord blood; see Step 1 in Fig. 1)
- Written, informed consent in Spanish/Catalan language (as expected, the parental consent rate was higher for SGA than for AGA infants; see Step 2 in Fig. 1)

Exclusion criteria were complications at birth (need for resuscitation or for parenteral nutrition) and congenital malformations.

The fraction of infants with complete follow-up was higher in the SGA than in the AGA subpopulation (68 vs. 26%; see Step 3 in Fig. 1). No differences were detected in the baseline features of infants who completed versus those who did not complete the 4-month follow-up (data not shown).

Mothers of SGA infants were recommended to give BRF, but a substantial fraction preferred nevertheless to give FOF. Among the 102 SGA infants with complete follow-up, 46 infants were exclusively BRF, and 56 were exclusively FOF (see Step 4 in Fig. 1).

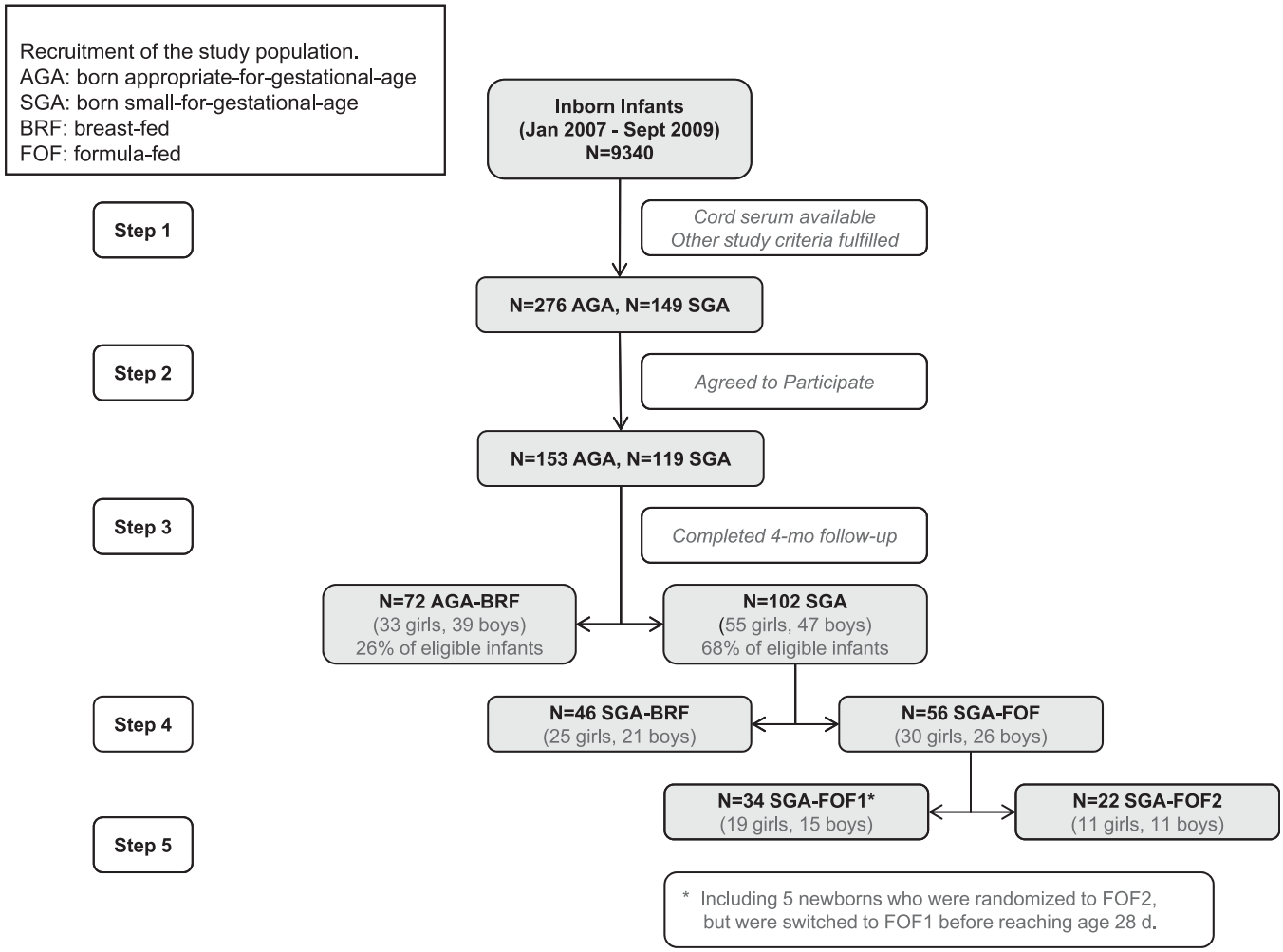

FIG. 1. Recruitment of the study population.

Shortly after birth, SGA-FOF infants were randomly assigned (1:1) to receive either FOF1 (Enfalac 1; Mead Johnson) or FOF2 (Enfalac Premature for premature and low-birth-weight infants; Mead Johnson). The milk concentration was 12.9%, and the recommended volume was 150 mL/kg/day. FOF2 contains less fat and more protein than human milk; FOF1 has an intermediate composition and is rich in energy (Supplementary Table 1). Five newborns (two girls and three boys), who were originally randomized to receive FOF2, did not seem to tolerate this formula well and were switched to FOF1 prior to age 28 days (see Step 5 in Fig. 1); their results were pooled with those of FOF1 infants.

Gestational age was calculated according to the last menses and confirmed by first-trimester ultrasound (~10 weeks). The delivery rate by caesarean section was 22%. A total of 39 mothers reported smoking during pregnancy; they delivered 9 AGA and 30 SGA infants. Endocrine and body-composition results from 21 out of 72 AGA-BRF infants and 18 out of 46 SGA-BRF infants were part of earlier reports (9,18); no results from the 56 SGA-FOF infants have hitherto been reported.

Assessments. Weight and length were measured by the same investigator (G.S.) at birth and 4 months (132 ± 1 day [mean ± SEM]). Weight was measured with a beam balance (Seca, Hamburg, Germany) and length with a length board, the mean of three measurements being used for analysis.

Body composition was assessed by absorptiometry at ages 2 weeks and 4 months with a Lunar Prodigy, coupled to Lunar software (version 3.4/3.5; Lunar Corp, Madison, WI), adapted for assessment of infants (9,13). All body-composition studies were performed during spontaneous sleep prior to feeding. Body fat, lean mass, and bone mineral content (BMC) were assessed. Coefficients of variation (CVs) were <3% for fat and lean mass (9,13).

Circulating levels of HMW adiponectin and IGF-I were measured in cord serum and prefeeding/morning serum samples obtained at age 4 months. HMW adiponectin was assessed with an ELISA kit (Linco Research, St. Charles, MO) with intra- and interassay CVs <9%. IGF-I was measured by immunochemiluminiscence (IMMULITE 2000; Diagnostic Products, Los Angeles, CA), the detection limit being 25 ng/mL; intra- and interassay CVs were <10%.

Statistics. Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL). Skewed data were log-transformed before comparison. General lineal models for repeated measurements were used to detect differences in baseline and 4-month data and in 4-month increments between groups.

The study had 80% power to detect a difference of 0.6 SD between SGA-BRF and SGA-FOF infants for the major variables in the study (fat and lean mass, IGF-I, and HMW adiponectin). The detectable difference was 0.8 SD for comparisons of the same variables between SGA-FOF1 and SGA-FOF2.

A P value <0.05 was considered significant for nominal associations. A Bonferroni correction by a factor of 10 (product of five independent outcomes and two independent groups) is recommended to account for multiple comparisons of major variables, so that only conventional P values <0.005 yield Bonferroni-corrected P values <0.05.

The study was approved by the Institutional Review Board of Barcelona University, Hospital of Sant Joan de Déu; informed written consent was an inclusion criterion.

RESULTS

Body composition. SGA infants receiving FOF1 or FOF2 developed similar gains of weight, length, lean mass, fat mass, and BMC (Table 1), and their results were therefore pooled into an SGA-FOF group. In turn, SGA-FOF and SGA-BRF infants developed similar gains of weight, length, lean mass, fat mass, and BMC (Table 2 shows data at 2 weeks and 4 months; Table 3, right, shows the gains), and their results were also pooled into a total SGA group. Compared with

TABLE 2
Results in infants born either AGA or SGA

	At age 2 weeks*					At age 4 months†				
	AGA	SGA	*P* value‡	SGA-BRF§	SGA-FOF§	AGA	SGA	*P* value‡	SGA-BRF	SGA-FOF
n	72	102		46	56	72	102		46	56
Weight (kg)	3.9 (3.0–4.0)	2.9 (2.8–3.0)	<0.0001	2.9 (2.8–3.1)	2.9 (2.8–3.0)	7.2 (7.0–7.4)	6.4 (6.2–6.5)	<0.0001	6.3 (6.1–6.6)	6.4 (6.2–6.6)
Weight Z-score‖	0.0 (−0.1 to 0.2)	−2.2 (−2.3 to −2.1)	<0.0001	−2.2 (−2.4 to −2.2)	−2.1 (−2.3 to −2.0)	0.5 (0.3–0.8)	−1.2 (−1.4 to −1.0)	<0.0001	−1.2 (−1.5 to −1.0)	−1.1 (−1.4 to −0.9)
Length (cm)	51 (51–52)	47 (47–48)	<0.0001	47 (47–48)	47 (47–48)	63 (63–64)	60 (60–61)	<0.0001	60 (60–61)	60 (60–61)
Length Z-score‖	−0.1 (−0.2 to 0.1)	−1.7 (−1.9 to −1.6)	<0.0001	−1.7 (−1.9 to −1.5)	−1.8 (−1.9 to −1.6)	0.1 (−0.1 to 0.4)	−0.8 (−1.0 to −0.6)	<0.0001	−0.9 (−1.1 to −0.6)	−0.8 (−1.0 to −0.5)
BMC (kg)	0.11 (0.11–0.12)	0.08 (0.07–0.08)	<0.0001	0.08 (0.08–0.09)	0.08 (0.07–0.08)	0.19 (0.18–0.21)	0.17 (0.17–0.18)	<0.0001	0.17 (0.16–0.17)	0.18 (0.17–0.19)[a]
Fat mass (kg)	0.79 (0.73–0.85)	0.43 (0.39–0.47)	<0.0001	0.46 (0.41–0.53)	0.40 (0.35–0.45)	2.8 (2.7–3.0)	2.3 (2.2–2.4)	<0.0001	2.3 (2.2–2.5)	2.3 (2.2–2.4)
Lean mass (kg)	3.0 (2.9–3.1)	2.4 (2.3–2.5)	<0.0001	2.4 (2.3–2.5)	2.4 (2.3–2.5)	4.2 (4.0–4.3)	3.9 (3.8–4.0)	0.003	3.8 (3.7–4.0)	3.9 (3.8–4.1)
IGF-I (ng/mL)‖	55 (49–62)	46 (40–52)	0.04	48 (37–60)	44 (38–50)	51 (45–56)	69 (61–76)	<0.0001	54 (46–61)	81 (69–93)[b]
HMW adiponectin (μg/mL)‖	33 (30–36)	26 (23–29)	0.001	27 (23–32)	25 (21–28)	27 (25–30)	34 (31–37)	0.001	29 (26–33)	38 (34–43)[c]

Data are mean (95% CI) unless otherwise indicated. All AGA infants were BRF, whereas SGA infants were either BRF or FOF. Differences remaining significant after Bonferroni correction are those with a *P* value <0.005 (see STATISTICS). *Age: AGA, 16 ± 1 day; SGA, 17 ± 1 day. †Age: AGA, 129 ± 1 day; SGA, 128 ± 1 day. ‡*P* values for comparisons between AGA and SGA infants. §No significant differences between SGA-BRF and SGA-FOF at age 2 weeks. ‖At birth instead of at age 2 weeks. [a]$P < 0.05$, [b]$P < 0.001$, and [c]$P < 0.005$ vs. SGA-BRF at age 4 months.

TABLE 1
Results in infants born SGA and receiving FOF1 or FOF2

	At age 2 weeks			At age 4 months			0- to 4-month change		
	FOF1	FOF2	*P* value	FOF1	FOF2	*P* value	FOF1	FOF2	*P* value
n	31	25		31	25		31	25	
Weight (kg)	2.9 (2.7–3.1)	2.8 (2.8–3.0)	ns	6.4 (6.1–6.6)	6.4 (6.1–6.7)	ns	3.5 (3.2–3.7)	3.5 (3.2–3.8)	ns
Length (cm)	47 (46–48)	47 (47–48)	ns	60 (59–61)	61 (60–62)	ns	15 (14–16)	15 (14–16)	ns
BMC (kg)	0.08 (0.07–0.08)	0.08 (0.07–0.09)	ns	0.18 (0.17–0.19)	0.18 (0.16–0.20)	ns	0.10 (0.09–0.12)	0.10 (0.09–0.11)	ns
Fat mass (kg)	0.39 (0.32–0.46)	0.41 (0.35–0.48)	ns	2.3 (2.1–2.4)	2.3 (2.2–2.5)	ns	1.9 (1.7–2.0)	1.9 (1.8–2.0)	ns
Lean mass (kg)	2.4 (2.3–2.5)	2.4 (2.3–2.5)	ns	3.9 (3.7–4.2)	3.9 (3.7–4.2)	ns	1.5 (1.2–1.8)	1.5 (1.3–1.8)	ns
IGF-I (ng/mL)*	44 (35–52)	44 (37–52)	ns	71 (63–79)	94 (70–119)	<0.05	27 (18–37)	50 (26–74)	<0.05
HMW adiponectin (μg/mL)*	23 (18–28)	27 (21–33)	ns	42 (36–48)	33 (27–39)	<0.05	20 (12–27)	6 (−1 to 14)	<0.05

Data are mean (95% CI) unless otherwise indicated. For formula composition, see Supplementary Table 1. None of the differences in this table remained significant after Bonferroni correction (see STATISTICS). *Values at birth instead of at age 2 weeks.

TABLE 3
Changes (0–4 months) in weight, length, and body composition in infants born either AGA or SGA

	0- to 4-month change				
	AGA	SGA	*P* value*	SGA-BRF†	SGA-FOF†
n	72	102		46	56
Δ Weight (kg)	3.3 (3.1–3.5)	3.4 (3.3–3.6)	ns	3.4 (3.2–3.6)	3.5 (3.3–3.7)
Δ Length (cm)	13 (13–14)	15 (14–15)	<0.0005	14 (14–15)	15 (14–16)
Δ BMC (kg)	0.09 (0.08–0.10)	0.09 (0.09–0.10)	ns	0.09 (0.08–0.09)	0.10 (0.09–0.11)
Δ Fat mass (kg)	2.0 (1.9–2.2)	1.9 (1.8–2.0)	<0.05	1.9 (1.7–2.0)	1.9 (1.8–2.0)
Δ Lean mass (kg)	1.2 (1.1–1.3)	1.5 (1.4–1.6)	<0.0005	1.5 (1.3–1.6)	1.5 (1.3–1.7)
Δ Fat mass − Δ Lean mass (kg)	0.9 (0.7–1.0)	0.4 (0.2–0.6)	<0.0001	0.4 (0.2–0.7)	0.4 (0.1–0.6)

Data are mean (95% CI) unless otherwise indicated. All AGA infants were BRF, whereas SGA were either BRF or FOF. Differences remaining significant after Bonferroni correction are those with a *P* value <0.005 (see STATISTICS). Δ, change. **P* values for comparisons between AGA and pooled SGA infants (adjusted for sex). †No significant differences between BRF-SGA and FOF-SGA.

AGA controls, the SGA infants caught up in length but confined their weight catchup to lean mass, thereby aggravating their low adiposity versus AGA controls (Table 3, left). All of the differences between AGA and SGA infants were independent of sex, gestational age, and maternal smoking.

HMW adiponectin and IGF-I. In cord serum, the levels of HMW adiponectin and IGF-I were lower in SGA than AGA infants (Table 2). At 4 months, circulating HMW adiponectin and IGF-I seemed to be influenced by nutrition, the levels in SGA-FOF being higher than in SGA-BRF infants (Table 2); in addition, HMW adiponectin levels were higher in SGA-FOF1 than in -FOF2 infants, whereas IGF-I levels were higher in SGA-FOF2 than in -FOF1 infants (Table 1 and Fig. 2, *left*). Accordingly, the longitudinal dynamics of HMW adiponectin and IGF-I differed markedly among the study subgroups (Fig. 2, *right*); these differences were independent of sex, gestational age, and maternal smoking.

Correlation analyses. Across the study population (but not within SGA subgroups), 4-month changes in HMW adiponectin and IGF-I associated to each other ($r = 0.316$; $P < 0.0001$), and both predicted percent lean mass at 4 months ($r = 0.231$; $P < 0.001$ and $r = 0.223$; $P < 0.005$, respectively).

DISCUSSION

In the first months after birth, SGA infants prioritize the recovery of lean mass above that of fat mass, thereby further lowering their body-fat fraction relative to AGA controls. This prioritization does not appear to be readily influenced by nutrition in early infancy. In contrast, circulating HMW adiponectin and IGF-I seem sensitive to nutritional influences in SGA infants, because FOF was associated with higher HMW adiponectin and IGF-I levels than BRF, and protein enrichment of FOF had opposite effects on HMW adiponectin and IGF-I levels. Therefore,

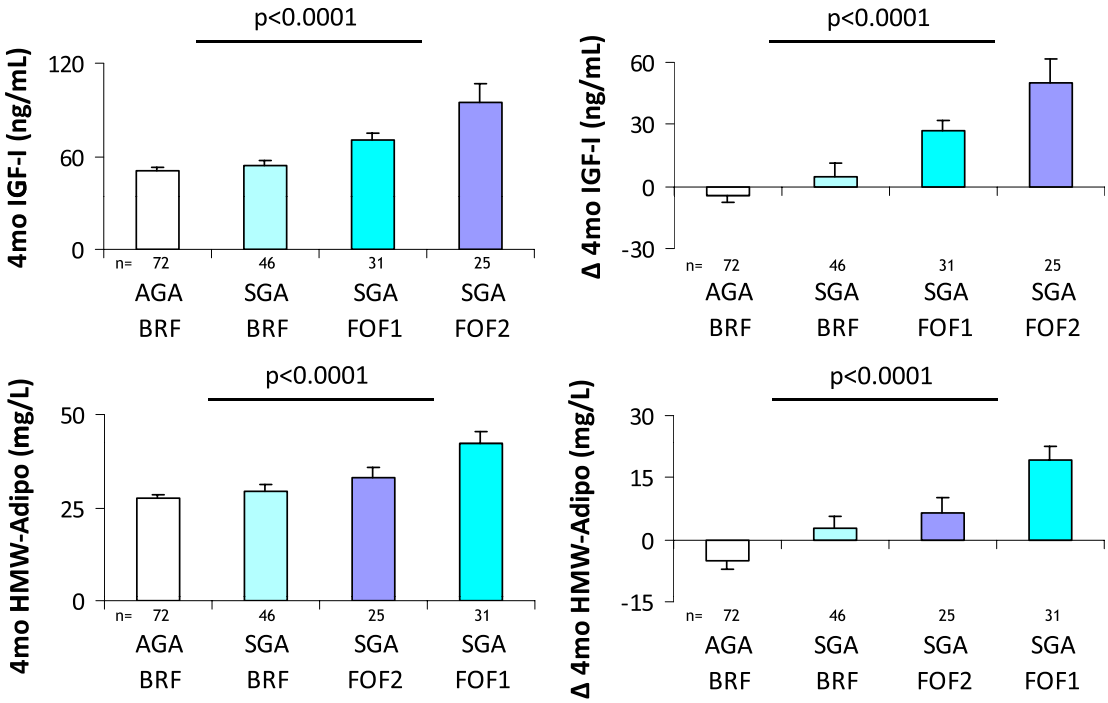

FIG. 2. Results of circulating IGF-I and HMW adiponectin at age 4 months (*left*) and changes thereof between birth and age 4 months (*right*) in BRF infants born AGA and in infants born SGA who were either BRF or FOF with FOF1 or FOF2. Mean and SEM are shown. *P* values are from general lineal models.

the swift recovery of lean mass in SGA infants is unlikely to be mediated by circulating HMW adiponectin or IGF-I.

In the first 4 months after birth, AGA and SGA infants gain more fat than lean mass, and both groups thus increase their body fat fraction. However, the surplus in fat increment is more than twice higher in AGA than in SGA infants (Table 3, bottom row). If it is correct that less energy is required to gain 1 kg of lean mass than to gain 1 kg of fat mass (19), then SGA infants need fewer calories than AGA infants to gain the same amount of body weight. One of the implications of this reasoning is that there may be no strict need to give a calorie-enriched formula to SGA infants.

At age 4 months, the circulating levels of HMW adiponectin and IGF-I in SGA-BRF infants compared with those in AGA-BRF controls, but they were elevated in SGA-FOF infants, with the highest levels of HMW adiponectin and IGF-I being observed, respectively, in SGA-FOF1 and SGA-FOF2 infants. Our longitudinal results of HMW adiponectin confirm that the circulating levels of this adipokine are essentially stable in AGA-BRF infants (20), and they seem to be the first indication that HMW adiponectinemia may rise markedly in SGA-FOF infants. Our IGF-I results align well with the reports that AGA-FOF infants have higher IGF-I levels than AGA-BRF infants, particularly when receiving protein-enriched FOF (10–12).

The weaknesses of our study include that neither visceral fat nor hepatic lipid content was assessed; the strengths include the presence of two parallel and longitudinal control groups for SGA-FOF infants, namely the AGA-BRF (golden standard) and SGA-BRF infants.

In conclusion, SGA infants receiving protein-enriched FOF are known to be at higher risk for later cardiovascular and metabolic disease (4–6) and are in this study shown to have elevated serum concentrations of HMW adiponectin and IGF-I in early infancy. Breastfeeding is known to attenuate the risk of SGA infants for subsequent disease (4–6) and is shown to be accompanied by normal serum concentrations of HMW adiponectin and IGF-I in SGA infants. Follow-up will disclose whether endocrine anomalies in SGA-FOF infants can serve as early markers of an unfavorable metabolic course and whether they may thus contribute to design fetal-neonatal interventions that prevent adult disease. Such interventions would be of particular relevance for public health in countries like India, where the sequence from fetal growth restraint to adult diabetes is highly prevalent.

ACKNOWLEDGMENTS

This study was supported by the Ministerio de Ciencia e Innovación, Instituto de Salud Carlos III, Madrid, Spain (PI08/0443). F.d.Z. is a Clinical Investigator supported by the Clinical Research Council of the University Hospital Leuven. G.S., M.D., D.S.-I., and L.I. are Clinical Investigators of Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas, Instituto de Salud Carlos III, Madrid, Spain. A.L.-B. is an Investigator of the I3 Fund for Scientific Research (Ministry of Education and Science, Spain).

No potential conflicts of interest relevant to this article were reported.

F.d.Z. contributed to study design, wrote the manuscript, and reviewed/edited the manuscript. G.S., M.D., and D.S.-I. researched data. A.L.-B. contributed to study design and discussion and reviewed/edited the manuscript. L.I. contributed to study design, wrote the manuscript, and reviewed/edited the manuscript. L.I. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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