Journal of the Endocrine Society, 2022, **6**, 1–11
https://doi.org/10.1210/jendso/bvac028
Advance access publication 21 February 2022
Clinical Research Article

First Year Metabolic and Hormonal Behavior Define two Different Populations of SGA Newborn for Weight or Height

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Abstract

Context: Small-for-gestational-age (SGA) children have a particular metabolic and hormonal pattern at birth that changes rapidly.

Objective: To evaluate the linear and weight growth in the first year of life in SGA children.

Design: Prospective, monocentric cohort study.

Setting: Real-world data collected from April 2012 to January 2016.

Patients: SGA newborns uniformly defined by either growth or length lower than -2 SDs for gestational age.

Interventions: All children were evaluated for 1 year after birth, at 3 days of life, then 3, 6, and 12 months after birth.

Main outcome measures: Anthropometric parameters and biochemical variables, such as blood glucose, insulin, leptin, IGF-1, IGF binding protein-3 (IGFBP-3), and homeostasis model assessment - insulin resistance (HOMA-IR) index.

Results: A total of 133 SGA children were enrolled. Length significantly improved 1 month after birth, whereas weight significantly increased only at 3 months after birth. Biochemical variables increased during the first year of life, showing a prediction by IGFBP-3 and HOMA-IR index. Then, the variables were divided considering either weight, length, or both, showing a different incidence. The biochemical variable changes recorded in the first step were maintained considering SGA children for weight or length, whereas they disappeared when weight and length were considered together.

Conclusions: Our study shows a specific catchup growth for weight and length in SGA children. Moreover, we highlight that weight and length should be considered as independent parameters in SGA children, defining 2 different metabolic-hormonal populations with different conceivable predictive role in early catchup growth and in later growth and metabolic status.

Key Words: small for gestational age, IGF-1, IGFBP-3, HOMA-index, catch-up growth

Abbreviations: AGA, appropriate for gestational age; CV, coefficient of variation; HC, head circumference; HOMA-IR, homeostasis model assessment - insulin resistance; IGFBP-3, IGF binding protein-3; IUGR, intrauterine growth restriction; SGA, small for gestational age

The born small-for-gestational-age (SGA) incidence has increased in the past decades, ranging between 3.3% and 5.5% of newborns, although with relevant differences among populations evaluated [1-4]. However, the real SGA incidence remains unclear, mainly because of the challenges in SGA definition [5-9]. The interest in SGA is heterogeneous, including looking for SGA-related short- and long-term medical complications, such as the persistence of short stature [10, 11], to the detection of predictive factors influencing the catchup growth during the first 2 to 4 years of life. Indeed, although 90% of SGA children experience catchup growth and achieve a height above -2 SDs within the first 2 years of life, short stature persists in approximately 8% to 14% of these children [10, 11]. A direct correlation between the causes of length and weight deficiency at birth and catchup growth during the first 2 years of life is suggested [10, 11]. In this setting, recent studies underlined the influence of the genetic factors on SGA condition and the catchup growth behavior in early infancy [8-11].

The GH IGF axis is fundamental to mediate fetal and early postnatal growth [12]. Accordingly, lower IGF-1, IGF-2, and IGF binding protein-3 (IGFBP-3) levels are detected during fetal life in SGA compared with appropriate-for-gestational-age (AGA) children [5, 13]. In addition, SGA children who reached catchup growth show normal GH–IGF-1 axis early in postnatal, whereas GH deficiency and/or GH resistance could be detected in those children with persistent short stature [5]. Several studies evaluated IGF-1 and IGFBP-3 growth factors pre- and postnatally in SGA children, although confounding results have been reached so

Received: 7 December 2021. **Editorial Decision:** 16 February 2022. **Corrected and Typeset:** 22 March 2022

far, mainly because of the heterogeneous SGA classification and definition [13-15].

Metabolic pattern is generally altered in SGA children, related to insulin resistance in early and later life. SGA and large-for-gestational age newborns share a similar insulin sensitivity decrease, evaluated by the homeostasis model assessment - insulin resistance (HOMA-IR) index, requiring an elevated compensatory insulin secretion from the fetus to maintain euglycemia [16]. Thus, a predisposition to abnormal glucose metabolism, insulin resistance, type 2 diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease are expected in SGA children [17-19]. Indeed, SGA children with catchup growth in height and with high body mass index are prone to develop insulin resistance later in life [20]. However, this strict correlation has been suggested in older children born SGA [21, 22]. In particular, the adipose tissue seems to have a role in insulin resistance pathophysiology because adipocytes secrete several adipokines, such as leptin. Although the leptin role in controlling fetal growth is not completely understood, its serum levels are higher in AGA compared with SGA infants at birth [23, 24], reaching higher serum levels in SGA than AGA children after 1 year of age, suggesting a rapid increase in adipose tissue after a period of undernutrition [23].

This study was designed to evaluate the linear and weight growth in the first year of life in SGA children, comparing the trend and consequent role of growth factors such as insulin, leptin, IGF-1, IGFBP-3, and the HOMA-IR index among children born SGA for weight and/or height.

Materials and Methods

A prospective, monocentric cohort study was performed based on real-world data. Newborns at term (>37 weeks of gestation) were selected at birth in the Department of Pediatrics of Luigi Sacco Hospital, Milan, from April 2012 to January 2016, according to the following inclusion criteria: newborn with weight and/or length at birth < -2 SDs for gestational age [25]. Birth weight was measured within 1 hour from delivery with an electronic weighing scale (Tanita Electronic Scale). Length and head circumference (HC) were measured within 1 day from delivery with a Harpenden neonatometer and inelastic tape, respectively. Children enrolled were of different ethnic origin; thus, different classifications were used for Italian [25] and for newborns of different ethnic origins [26, 27].

Exclusion criteria were infants born after 43 weeks of gestation and born from mothers with chronic conditions such as gestational diabetes mellitus, infections, high blood pressure, and who had abused alcohol or smoked during pregnancy. Moreover, newborns with congenital malformations, neonatal infection, congenital heart disease, and respiratory, metabolic, and neurological diseases were excluded. The intrauterine growth restriction (IUGR) and preterm state were not considered exclusion criteria. IUGR is defined by clinical features of malnutrition and evidence of reduced growth regardless of an infant's birth weight percentile [28, 29].

All parents of children included in the study provided informed consent before the enrollment. The study was approved by the Ethics Committee of the Luigi Sacco Hospital.

Study Design

All children included in the analysis were evaluated 1 year after birth, in 4 consecutive visits with the following time-frame interval: baseline (visit 0, performed 3 days after birth), after 1 (visit 1), 3 (visit 2), 6 (visit 3), and 12 months (visit 4). During each visit, the children's growth was evaluated considering both anthropometrical and biochemical variables.

Anthropometrical Variables

All children were evaluated at each visit for the following anthropometrical variables: weight, length, and HC. Weight was evaluated using an electronic weighing scale (Baby Precision Chicco). For auxological evaluation, the tables of the Centers for Disease Control and Prevention were used [27].

Biochemical Variables

In the third day of life and in other study visits, a venous blood sample after 2 hours of fasting was obtained in the morning determine blood glucose, IGF-1, IGFBP-3, leptin, and insulin. Subsequently, we calculated the HOMA-IR index, using the following formula: (fasting plasma glucose basal × insulin × 0.0555)/22.5 [30].Children with a glucose value at the time of withdrawal that was > 100 mg were excluded from the study because could indicate a lack of adequate fasting.

Serum glucose was determined using a commercial kit. Serum insulin was measured using a chemiluminescence method (Roche Diagnostics GmbH, Mannheim Germania), with intra-assay coefficients of variation (CVs) of 1.1% and interassay CVs of 3.6%. Serum IGF-1 levels were determined using an ELISA method (Mediagnost, Reutingen Germania), with intra-assay CVs of 5.7% and inter-assay CVs of 5.8%. Serum IGFBP-3 levels were determined using an ELISA method (Mediagnost, Reutingen Germania), with intra-assay CVs of 1.9% and interassay CVs of 5.7%.

Statistical Analysis

The statistical analysis was performed following 2 consecutive steps. In the first phase, a cohort study was conducted, in which all children were considered as SGA according to the given definition. In the second phase, 3 different case-control studies were performed, dividing newborns into SGA and non-SGA groups, considering 3 different classifications. In particular, the first case-control study divided subjects in SGA and non-SGA groups by considering the weight at birth, the second considering the length, and the third considering both weight and length at birth [31].

Parameters distribution was evaluated by Kolmogorov-Smirnov test and a description of variable collected at each visit was provided. Considering the not-normal distribution of all parameters, differences among visits were evaluated using nonparametric tests (Wilcoxon test, followed by Tukey post hoc test) considering the entire database. A correlation analysis was performed. In particular, the correlation between anthropometrical variables and biochemical parameters was checked for each visit, assessed by Spearman correlation coefficient. Moreover, stepwise, linear, multiple regression analyses were performed, considering anthropometric variables as dependent parameters and glycemia, insulin, HOMA-IR index, IGFBP-3, IGF-1, and leptin as independent variables. All multiple regression analyses were based on a single regression analysis for each predictor independent variable that allowed identifying candidate predictive variables. During the analysis, anthropometrical variables were adjusted for gestational age.

The longitudinal analyses (difference among visits), as well as the cross-sectional analyses (difference between groups at each visit) were repeated grouping children according to the 3 different SGA definitions (weight, length, and both, respectively) in the case-control studies.

Statistical analysis was performed using the Statistical Package for the Social Sciences software for Mac (version 21.0; SPSS Inc., Chicago, IL). Significant values were considered as $P < 0.05$.

Results

Cohort Study: Cohort Description

One hundred and thirty-three children born SGA were enrolled, with a mean gestational age of 38.82 ± 1.53 weeks. A total of 120 children (90.2%) were born at term, 13 (9.8%) preterm, and 17 (12.8%) showed an IUGR.

Cohort Study

Weight, length, and HC showed a progressive significant ($P < 0.001$) increase during the first year of life (Table 1). Similarly, biochemical variables increased during the first year of life (Table 1). However, the pattern of increase was different, and glucose serum levels remained higher than baseline until the end of follow-up, whereas insulin came back to baseline value since the third visit (Table 1). Accordingly, the HOMA-IR index showed an increasing trend similar to insulin (Table 1).

IGFBP-3 started to increase 1 month after birth, when it was significantly higher than baseline ($P < 0.001$). At visit 2, it was significantly higher than at baseline and visit 1 ($P < 0.001$). At visit 3, IGFBP-3 remained higher than at baseline and visit 1 ($P < 0.001$). Finally, IGFBP-3 reached the highest value 1 year after birth (Table 1). Similarly, IGF-1 showed a rapid increase 1 month after birth, when it reached higher values compared with both baseline ($P < 0.001$) and visit 3 ($P < 0.001$) (Table 1). At visits 2 and 3, it was significantly higher than baseline ($P < 0.001$), although the highest value was reached 1 month after birth. Thus, unlike IGFBP-3, IGF-1 rapidly increased after birth, although it progressively decreased until 6 months after birth, with a new increase 1 year after birth. These results remained statistically significant although excluding children born preterm. Correlation analyses are reported in Table 2.

Considering weight as a dependent variable, 2 statistical models were created. Model 1, with IGFBP-3 as a predictor ($P < 0.001$; $R = 0.703$), generated the following equation: Weight = 2259.27 + 1765.77 (IGFBP-3). In the second model ($P < 0.001$; $R = 0.776$) the HOMA-IR index was entered as a further predictor with the following equation: Weight = 1718.39 + 1572.11 (IGFBP-3) + 621.66 (HOMA-IR index).

Considering length as a dependent variable, 2 statistical models were created. Model 1, with IGFBP-3 as a predictor ($P < 0.001$; $R = 0.711$), generated the following equation: Length = 45.30 + 7.20 (IGFBP-3). In the second model ($P < 0.001$; $R = 0.790$) the HOMA-IR index was entered as a further predictor with the following equation: Length = 43.01 + 6.38 (IGFBP-3) + 2.64 (HOMA-IR index).

Considering HC as dependent variable, 2 statistical models were created. Model 1, with IGFBP-3 as a predictor ($P < 0.001$; $R = 0.753$), generated the following equation: HC = 32.05 + 3.64 (IGFBP-3). In the second model ($P < 0.001$; $R = 0.821$), the HOMA-IR index was entered as a further predictor with the following equation: HC = 31.01 + 3.27 (IGFBP-3) + 1.19 (HOMA-IR index).

These analyses suggest that the change in anthropometrical variables is predicted primarily by IGFBP-3 and the HOMA-IR index.

Case-control Study

The case-control phase consisted of 3 comparisons considering different SGA definitions. First, newborns were divided by weight at birth, identifying 110 children (82.7%) with weight lower than -2 SDs for gestational age. The second comparison considered the length at birth, identifying 78 children (58.6%) with length lower than -2 SDs for gestational age. Finally, weight and length lower than -2 SDs for gestational age were considered, identifying 55 children (41.4%).

Case-control Study: Weight

Considering anthropometrical variables, weight was significantly lower in SGA children, compared with non-SGA at baseline ($P < 0.001$) (Table 3). HC was lower in SGA children compared with non-SGA only at baseline ($P = 0.040$), whereas length was not different between groups. Similarly, all biochemical parameters were not different between SGA and non-SGA children at each visit (Table 3). Longitudinally,

Table 1. Biochemical and anthropometrical variables at each visit of observation, considering the entire cohort of children

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
Glycemia	72.16 ± 16.11	82.81 ± 10.10[a]	87.89 ± 6.31[a]	87.91 ± 7.37[a]	84.00 ± 8.32[a]
Insulin	3.98 ± 4.22	6.54 ± 5.50[a]	7.25 ± 5.26[a]	5.91 ± 5.23	6.00 ± 5.93
HOMA-IR index	0.84 ± 1.13	1.34 ± 1.21	1.54 ± 1.08[a]	1.31 ± 1.14	1.29 ± 1.25
IGFBP-3	0.74 ± 0.22	1.78 ± 0.53[a]	2.26 ± 0.61[a]	2.38 ± 0.49[a]	2.76 ± 0.57[a]
IGF-1	23.05 ± 9.78	69.36 ± 28.21[a]	60.33 ± 28.18[a]	48.73 ± 24.44[a]	73.61 ± 41.05[a]
Leptin	0.52 ± 0.13	-	2.09 ± 1.19[a]	1.92 ± 0.42[a]	1.48 ± 0.81[a]
Weight	2398.27 ± 340.43	3606.69 ± 533.28	5352.50 ± 708.08[a]	6909.52 ± 840.95[a]	10,142.86 ± 10,106.03[a]
Length	45.83 ± 2.08	51.18 ± 2.46[a]	58.07 ± 2.36[a]	64.61 ± 2.33[a]	73.22 ± 2.42[a]
HC	32.42 ± 1.34	36.21 ± 1.31[a]	39.60 ± 1.30[a]	42.22 ± 1.39[a]	45.71 ± 3.98[a]

Data are expressed as mean ± SD.
Abbreviations: HC, head circumference; HOMA-IR, homeostasis model assessment - insulin resistance; IGFBP-3, IGF binding protein-3.
[a]$P < 0.001$ compared with baseline.

Table 2. Correlation analyses considering hormonal and anthropometrical variables at each visit

Baseline		Insulin	HOMA-IR index	IGFBP-3	Leptin	IGF-1	Weight	Length	HC
Glycemia	Rho	0.436	0.602	0.146	0.257	0.265	-0.134	-0.101	-0.043
	P	**<0.001**	**<0.001**	0.181	0.505	**0.003**	0.142	0.266	0.641
Insulin	Rho		0.885	0.193	0.065	0.269	-0.148	-0.015	-0.061
	P		**<0.001**	0.077	0.868	**0.003**	0.104	0.868	0.510
HOMA-IR index	Rho			0.078	ND	0.271	-0.158	-0.038	-0.098
	P			0.479	ND	**0.003**	0.085	0.683	0.289
IGFBP-3	Rho				ND	0.182	0.085	0.077	0.335
	P				ND	0.096	0.436	0.480	**0.002**
Leptin	Rho					ND	0.730	0.709	0.643
	P					ND	**0.025**	**0.033**	0.062
IGF-1	Rho						0.266	0.095	0.224
	P						**0.003**	0.294	**0.013**
Weight	Rho							0.623	0.630
	P							**<0.001**	**<0.001**
Length	Rho								0.465
	P								**<0.001**
Visit 1									
Glycemia	Rho	0.269	0.406	0.361		0.378	0.240	0.222	0.072
	P	**0.006**	**<0.001**	**0.008**		**<0.001**	**0.016**	**0.026**	0.483
Insulin	Rho		0.943	0.172		0.238	0.359	0.324	0.168
	P		**<0.001**	0.218		0.014	**<0.001**	**0.001**	0.092
HOMA-IR index	Rho			0.118		0.303	0.374	0.280	0.145
	P			0.404		**0.002**	**<0.001**	**0.005**	0.159
IGFBP-3	Rho					0.147	0.207	0.351	-0.081
	P					0.297	0.141	**0.011**	0.576
Leptin	Rho								
	P								
IGF-1	Rho						0.269	0.175	0.115
	P						**0.006**	0.075	0.256
Weight (g)	Rho							0.680	0.474
	P							**<0.001**	**<0.001**
Length (cm)	Rho								0.461
	P								**<0.001**
Visit 2									
Glycemia	Rho	-0.038	0.084	-0.158	-0.251	0.076	0.178	0.128	0.198
	P	0.733	0.454	0.279	0.515	0.499	0.104	0.244	0.078
Insulin	Rho		0.977	-0.043	-0.017	0.065	0.166	0.152	0.113
	P		**<0.001**	0.771	0.966	0.557	0.128	0.164	0.314
HOMA-IR index	Rho			-0.035	-0.075	0.048	0.230	0.211	0.189
	P			0.815	0.847	0.670	**0.037**	0.057	0.098
IGFBP-3	Rho				-0.033	0.530	0.217	0.027	0.042
	P				0.932	**<0.001**	0.134	0.856	0.781
Leptin	Rho					-0.017	-0.517	0.067	-0.878
	P					0.966	0.154	0.865	**0.002**
IGF-1	Rho						0.186	0.057	-0.214
	P						0.092	0.609	0.058
Weight	Rho							0.693	0.548
	P							**<0.001**	**<0.001**
Length	Rho								0.405
	P								**<0.001**
Visit 3									
Glycemia	Rho	0.028	0.144	-0.288	0.393	0.140	0.136	0.222	-0.089
	P	0.819	0.249	0.080	0.295	0.257	0.272	0.071	0.477

Table 2. Continued

Baseline		Insulin	HOMA-IR index	IGFBP-3	Leptin	IGF-1	Weight	Length	HC
Insulin	Rho		.991	-0.113	0.077	0.182	0.254	0.266	0.243
	P		**<0.001**	0.501	0.845	0.135	**0.035**	**0.027**	**0.046**
HOMA-IR index	Rho			-0.154	0.060	0.202	0.252	0.223	0.185
	P			0.363	0.878	0.104	**0.041**	0.072	0.141
IGFBP-3	Rho				-0.119	0.492	0.044	-0.137	-0.084
	P				0.760	**0.002**	0.795	0.412	0.623
Leptin	Rho					0.061	-0.359	ND	-0.221
	P					0.877	0.343	ND	0.567
IGF-1	Rho						0.301	0.065	-0.054
	P						**0.012**	0.595	0.660
Weight	Rho							0.590	0.565
	P							**<0.001**	**<0.001**
Length	Rho								0.469
	P								**<0.001**
Visit 4									
Glycemia	Rho	0.331	0.433	-0.051	0.042	0.174	-0.187	-0.227	-0.140
	P	**0.017**	**0.001**	0.778	0.915	0.217	0.176	0.099	0.313
Insulin	Rho		0.919	0.124	0.353	0.141	0.106	0.124	-0.110
	P		**<0.001**	0.499	0.352	0.311	0.440	0.366	0.425
HOMA-IR index	Rho			0.088	0.288	0.180	0.148	0.047	-0.109
	P			0.633	0.453	0.206	0.294	0.742	0.442
IGFBP-3	Rho				-0.326	0.575	-0.060	0.024	-0.155
	P				0.391	**0.001**	0.739	0.893	0.388
Leptin	Rho					-0.192	-0.343	0.345	0.204
	P					0.620	0.366	0.364	0.598
IGF-1	Rho						-0.046	-0.043	-0.269
	P						0.740	0.753	0.047
Weight	Rho							0.747	0.403
	P							**<0.001**	**0.001**
Length	Rho								0.421
	P								**<0.001**
Visit 5									
Glycemia	Rho	0.342	0.478	0.086	ND	0.233	0.129	0.189	0.027
	P	0.059	**0.007**	0.872	ND	0.207	0.490	0.308	0.884
Insulin	Rho		0.905	0.607	ND	0.237	0.060	-0.135	-0.208
	P		**<0.001**	0.148	ND	0.191	0.744	0.460	0.253
HOMA-IRindex	Rho			-0.086	ND	0.232	0.184	-0.036	-0.094
	P			0.872	ND	0.210	0.322	0.846	0.614
IGFBP-3	Rho				ND	0.321	-0.786	-0.821	-0.491
	P				ND	0.482	**0.036**	**0.023**	0.263
Leptin	Rho					ND	ND	ND	ND
	P					ND	ND	ND	ND
IGF-1	Rho						-0.021	0.037	-0.305
	P						0.910	0.843	0.090
Weight	Rho							0.720	0.606
	P							**<0.001**	**<0.001**
Length	Rho								0.498
	P								**0.001**

Data are expressed as mean ± SD. Bold values represent statistically significant values.
Abbreviations: HC, head circumference; HOMA-IR, homeostasis model assessment - insulin resistance; IGFBP-3, IGF binding protein-3; ND, not detectable.

both anthropometrical variables and biochemical parameters showed the same significant increasing pattern demonstrated considering the entire cohort of children (Table 3).

Case-control Study: Length

Considering anthropometrical variables, length was significantly lower in SGA compared with non-SGA children at birth and visit 1, whereas it was similar between groups after visit 2 (Table 4). HC was significantly lower in SGA compared with non-SGA children only at baseline ($P = 0.009$), whereas weight was not different at all visits (Table 4). Longitudinally, SGA children for length showed the same significant pattern showed by the entire group, apart from insulin ($P = 0.336$) (Fig. 1) and HOMA-IR index ($P = 0.261$) (Fig. 2) (Table 4).

Case-control Study: Weight and Length Together

Considering anthropometrical variables, length was significantly lower in SGA children compared with non-SGA at baseline and visit 1 ($P < 0.001$ and $P = 0.001$, respectively) (Table 5), according to the SGA definition. However, length was not different between groups since visit 2 (Table 5). Similarly, weight was significantly lower in SGA compared with non-SGA children only at baseline ($P < 0.001$) and visit 1 ($P = 0.001$) (Table 5). HC was significantly lower in SGA compared with non-SGA children only at baseline ($P < 0.001$) (Table 5). Considering biochemical parameters, only HOMA-IR index was significantly lower in SGA children compared with non-SGA (1.29 + 1.01 vs 1.33 + 1.31, $P = 0.050$) (Table 5).

Considering the biochemical parameters, no differences were found at baseline between SGA and non-SGA children considering the 2 different definitions (Table 5). Only IGFBP-3 was significantly lower in SGA compared with non-SGA children at visits 1 and 3, considering both weight and length for the diagnosis ($P = 0.020$ and $P = 0.032$, respectively) (Table 5).

Longitudinally, non-SGA children showed the same significantly increasing pattern in the first year of life, as did the entire cohort, of both anthropometrical and biochemical variables. On the contrary, SGA children did not show the significant change in insulin levels during the first year ($P = 0.092$) (Table 5).

Finally, children defined as SGA for weight have been compared with children defined as SGA for both weight and length. Interestingly, biochemical variables were not different between groups, apart from IGFBP-3, which was significantly higher in children SGA for weight compared with SGA for both weight and length (1.96 ± 1.03 vs 1.63 ± 0.82, $P = 0.006$).

Discussion

Here, we give a snapshot of the first year of life of a large group of SGA children, uniformly defined by either length or weight lower than -2 SDs for gestational age at birth, using real-world data collected in a single Italian Center. The definition of SGA children according to either weight or length or both clearly recognizes different categories of children, with different metabolic (ie, insulin and HOMA-IR index) and hormonal (GH/IGF-1 axis) patterns. Moreover, we describe that SGA children showed a catchup growth in both weight and length at different time point during the first year of life. Catchup growth length was recorded 1 month after birth, whereas catchup growth in weight occurs at the third month of life.

Table 3. Biochemical and anthropometrical variables at each visit, dividing children in SGA (when weight at birth was lower than -2 SDs for gestational age, n = 110) and non-SGA (when weight was higher than -2 SDs for gestational age, n = 23) groups

		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	*P*
Glycemia	SGA	72.24 ± 15.96	82.82 ± 10.42	87.69 ± 6.03	87.85 ± 7.63	83.21 ± 8.24[a]	**<0.001**
	Non-SGA	71.79 ± 17.22	82.79 ± 8.73	38.72 ± 1.92	88.20 ± 5.98	90.33 ± 6.31[a]	**<0.001**
Insulin	SGA	4.06 ± 4.31	6.35 ± 5.63	6.96 ± 5.04	6.31 ± 5.54	6.20 ± 6.17	**0.007**
	Non-SGA	3.58 ± 3.81	7.40 ± 4.93	8.95 ± 6.44	3.79 ± 2.40	4.69 ± 4.06	**0.003**
HOMA-IR index	SGA	0.87 ± 1.19	1.31 ± 1.26	1.48 ± 1.04	1.37 ± 1.20	1.31 ± 1.30	**0.009**
	Non-SGA	0.71 ± 0.86	1.48 ± 0.95	1.91 ± 1.29	0.91 ± 0.56	1.10 ± 0.85	**0.011**
IGFBP-3	SGA	0.73 ± 0.23	1.76 ± 0.50	2.26 ± 0.65	2.36 ± 0.51	2.73 ± 0.59	**<0.001**
	Non-SGA	0.76 ± 0.12	2.01 ± 0.85	2.22 ± 0.24	2.51 ± 0.39	2.93 ± 0.30	**<0.001**
IGF-1	SGA	22.84 ± 9.54	68.59 ± 27.00	59.13 ± 27.05	48.39 ± 26.49	72.48 ± 40.87	**<0.001**
	Non-SGA	24.05 ± 11.09	72.84 ± 33.80	67.42 ± 34.59	50.54 ± 27.37	81.43 ± 44.70	**<0.001**
Leptin	SGA	0.52 ± 0.14	-	2.17 ± 1.25	1.94 ± 0.45	1.54 ± 0.85	**<0.001**
	Non-SGA	0.54 ± 0.01	-	1.45 ± 0.01	-	-	**0.001**
Weight	SGA	2336.95 ± 295.74[a]	3546.81 ± 530.96[a]	5306.61 ± 688.37	6890.32 ± 852.03	10,260.17 ± 1091.67	**<0.001**
	Non-SGA	2691.52 ± 391.60[a]	3892.50 ± 454.58[a]	5600.88 ± 782.01	7017.86 ± 796.31	9439.00 ± 1057.81	**<0.001**
Length	SGA	45.94 ± 2.06	51.18 ± 2.58	58.11 ± 2.44	64.68 ± 2.33	73.13 ± 2.34	**<0.001**
	Non-SGA	45.32 ± 2.11	51.15 ± 1.85	57.85 ± 1.89	64.22 ± 2.36	73.79 ± 2.94	**<0.001**
HC	SGA	32.27 ± 1.23	36.16 ± 1.37	39.56 ± 1.36	42.47 ± 1.38	45.72 ± 4.26	**<0.001**
	Non-SGA	33.15 ± 1.63	36.41 ± 1.05	39.84 ± 0.93	42.30 ± 1.48	45.61 ± 1.67	**<0.001**

Data are expressed as mean ± SD. *P* value shows differences among visits in the same group. Bold values represent statistically significant values.
Abbreviations: HC, head circumference; HOMA-IR, homeostasis model assessment - insulin resistance; IGFBP-3, IGF binding protein-3; SGA, small for gestational age.
[a]$P < 0.05$ between SGA and non-SGA groups.

Table 4. Biochemical and anthropometrical variables at each visit, dividing children into SGA (when length at birth was lower than -2 SDs for gestational age, n = 78) and non-SGA (when the length was higher than -2 SDs for gestational age, n = 55) groups

		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	*P*
Glycemia	SGA	71.68 ± 16.61	82.56 ± 9.37	87.20 ± 6.52	88.07 ± 6.90	84.10 ± 8.85	**<0.001**
	Non-SGA	72.83 ± 15.54	83.18 ± 11.16	88.90 ± 5.95	87.67 ± 8.10	83.84 ± 7.53	**<0.001**
Insulin	SGA	3.60 ± 3.03	6.58 ± 5.95	7.51 ± 5.02	5.62 ± 4.51	5.98 ± 6.09	**<0.001**
	Non-SGA	4.54 ± 5.54	6.48 ± 4.84	6.84 ± 5.67	6.33 ± 6.21	6.04 ± 5.81	0.336
HOMA-IR index	SGA	0.80 ± 1.09	1.37 ± 1.25	1.59 ± 1.03	1.29 ± 1.01	1.33 ± 1.32	**<0.001**
	Non-SGA	0.90 ± 1.21	1.29 ± 1.15	1.47 ± 1.17	1.33 ± 1.31	1.20 ± 1.16	0.261
IGFBP-3	SGA	0.71 ± 0.24	1.68 ± 0.44	2.12 ± 0.46[a]	2.26 ± 0.45	2.67 ± 0.52	**<0.001**
	Non-SGA	0.78 ± 0.18	1.94 ± 0.62	2.47 ± 0.76[a]	2.54 ± 0.51	2.87 ± 0.62	**<0.001**
IGF-1	SGA	22.63 ± 9.49	67.42 ± 27.45	61.45 ± 31.03	47.44 ± 26.94	76.65 ± 46.98	**<0.001**
	Non-SGA	23.66 ± 10.25	72.16 ± 29.37	58.63 ± 23.56	50.63 ± 26.06	68.30 ± 28.16	**<0.001**
Leptin	SGA	0.53 ± 0.14	-	1.99 ± 1.27	1.84 ± 0.43	1.65 ± 0.86	**0.09**
	Non-SGA	0.5 ± 0.15	-	2.46 ± 1.16	2.22 ± 0.30	2.87 ± 0.62	0.074
Weight	SGA	2374.17 ± 397.11	3592.50 ± 519.35	5323.58 ± 701.26	6947.41 ± 914.14	10,893.02 ± 1286.70	**<0.001**
	Non-SGA	2432.45 ± 237.48	3626.51 ± 556.56	5395.23 ± 724.02	6852.16 ± 724.55	8948.15 ± 1186.24	**<0.001**
Length	SGA	45.02 ± 1.72[a]	50.58 ± 2.12[a]	57.74 ± 2.11	64.47 ± 2.32	73.19 ± 2.76	**<0.001**
	Non-SGA	46.99 ± 1.99[a]	51.99 ± 2.67[a]	58.57 ± 2.63	64.83 ± 2.35	73.27 ± 1.80	**<0.001**
HC	SGA	32.16 ± 1.44[a]	36.19 ± 1.21	39.56 ± 1.28	42.52 ± 1.53	45.88 ± 1.95	**<0.001**
	Non-SGA	32.78 ± 1.11[a]	36.24 ± 1.46	39.66 ± 1.35	42.32 ± 1.16	45.42 ± 1.24	**<0.001**

P value shows differences among visits in the same group. Data are expressed as mean ± SD. Bold values represent statistically significant values.
HC, head circumference; HOMA-IR, homeostasis model assessment - insulin resistance; IGFBP-3, IGF binding protein-3; SGA, small for gestational age.
[a]$P < 0.05$ between SGA and non-SGA groups.

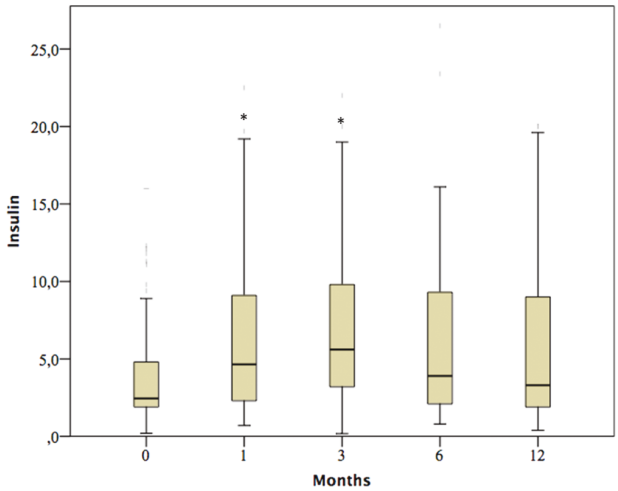

Figure 1. Insulin among visits, dividing children according to the length at birth. Each point represents the insulin mean value; the bar represents the 95% confidence interval. *Significant difference ($P < 0.001$) compared with baseline insulin levels.

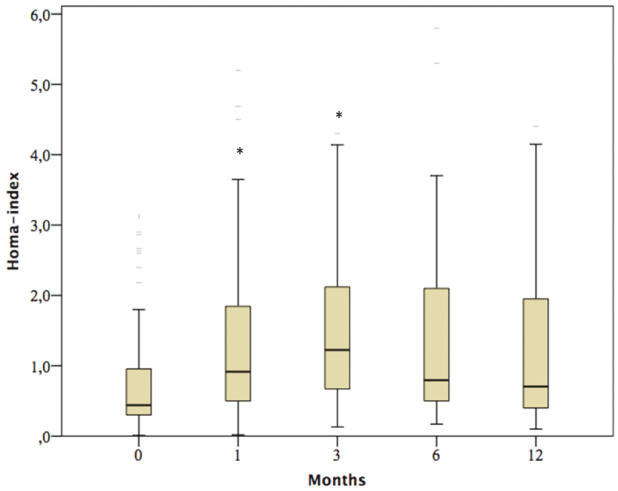

Figure 2. HOMA-IR index among visits, dividing children according to their length at birth. Each point represents the HOMA-IR index mean value; the bar represents the 95% CI. *Significant difference ($P < 0.001$) compared to baseline HOMA-index levels.

In our cohort of newborns, the catchup growth was accompanied by a significant increase in glucose and insulin serum levels. In particular, although glucose and insulin reached their highest levels 3 months after birth, glycemia remained stable during the first year of life, whereas insulin declined, reaching the baseline level. Thus, whether individuals with SGA have greater insulin resistance and higher prevalence of metabolic syndrome at birth than individuals born with AGA at birth [32], we demonstrate here that the glucose metabolism reached homeostasis within the first year of life. Longer prospective studies should be developed to evaluate when insulin resistance again characterizes these children, because, in preadolescence, it has been suggested that abnormal glucose metabolism begins earlier in SGA compared with AGA [22, 33]. Several studies have suggested that the continued adipose tissue accumulation in SGA children could increase insulin resistance, affecting blood glucose metabolism and contributing to metabolic syndrome [34, 35]. Moreover, we describe a significant increase of both IGF-1 and IGFBP-3 during the first year of life in SGA children. However, although this increasing pattern is related, IGFBP-3 increases after birth, month by month, reaching the highest values 1 year after birth. On the contrary, IGF-1 increases soon after birth, reaching the highest value 6 month after birth, and progressively declines. The GH axis fluctuation in SGA children is poorly described in the literature. Cance-Rouzard et al showed that SGA newborns for both weight and length (defined as symmetric) showed lower IGF-1 and higher GH levels than did neonates without short length (defined as asymmetric), whereas IGFBP-3 levels were comparable between these groups [36]. Different to our study, in this group, the majority of children were preterm, suggesting that low IGF-1 serum levels could be the result of important malnutrition. Indeed, in our study, we detect serum IGFBP-3 lower in symmetric SGA compared with not-symmetric SGA children, without differences in IGF-1. The different IGF-1 levels between asymmetric and symmetric SGA children have been proposed as a marker of fetal malnutrition. This latter condition leads to low birth weight, but not reduced length, which is normally achieved as long as IGF-1 bioavailability remains between normal limits [36]. However, this promising result is not confirmed by subsequent studies. Baker Meio et al demonstrated a positive correlation between length at birth and IGFBP-3 but not IGF-1 levels in SGA subjects at term [37]. Moreover, IGFBP-3 showed a strong positive correlation also with birth weight and HC, whereas IGF-1 showed a borderline correlation only with birth weight [37]. Levels of IGF-1 for gestational age reported in fetal samples throughout gestation have shown an increase toward the end of gestation, but the difference was not significant up to 33 weeks of gestation. This behavior was not confirmed for IGFBP-3 [37]. Leger et al performed a longitudinal study comparing auxological parameters and IGF-1, IGFBP-3, and GH levels during the first 2 years of life between symmetric and asymmetric SGA with a different ponderal index at birth and AGA [14]. Dizdarer et al demonstrated that growth factors and HOMA-IR index were higher in SGA children who have weight catchup growth compared with those who do not have catchup growth at 3 and 6 months of life [15]. In particular, insulin seems to have a regulator role on the GH-IGF-1 axis, increasing IGF-1 and IGFBP-3. Taken together, these results confirm the "catchup growth" hypothesis [38]. Our study fits within this hypothesis, showing the catchup growth in all SGA children evaluated and confirming the relevance of glucose metabolism on this phase. SGA children show low rates of insulin, IGF-1, IGF-2, and IGFBP-3 and high concentrations of GH, IGFBP-1, and IGFBP-2 at birth [38]. Tissues chronically depleted of insulin and IGF-1 during fetal life and exposed to high concentrations of these 2 hormones after birth could develop insulin resistance as a defense mechanism to protect the organism from hypoglycemia [38]. In addition, recent evidence of the ability of IGFBP-3 fragments to bind insulin, inhibiting its binding to its receptor, suggesting that the increased IGFBP-3 proteolysis occurring in early life can contribute to the development of insulin resistance [39].

Considering this pattern of growth, together with the correlation among variables, our data confirm the important role of IGF-1, IGFBP-3, glycemia, and insulin in the rapid weight and length growth in the first months of life in SGA children. We could speculate that the growth is first influenced by glucose metabolism, with metabolism-related parameters

Table 5. Biochemical and anthropometrical variables at each visit, dividing children in SGA (When both length and weight at birth were lower than -2 SDs for gestational age, n = 55) and non-SGA (when length or weight were higher than -2 SDs for gestational age, n = 78) groups

		Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	*P*
Glycemia	SGA	71.64 ± 16.52	82.45 ± 9.74	86.60 ± 5.97	88.03 ± 7.29	82.77 ± 8.83	**<0.001**
	Non-SGA	72.53 ± 15.93	83.06 ± 1.48	88.95 ± 6.45	87.81 ± 1.48	85.34 ± 7.67	**<0.001**
Insulin	SGA	3.61 ± 2.70	6.22 ± 6.36	7.07 ± 4.50	6.29 ± 4.94	6.32 ± 6.54	**0.012**
	Non-SGA	4.25 ± 5.07	6.76 ± 4.84	7.39 ± 5.88	5.61 ± 5.50	5.70 ± 5.39	**0.017**
HOMA-IR index	SGA	0.84 ± 1.17	1.33 ± 1.37	1.49 ± 0.93	1.41 ± 1.10	1.38 ± 1.41	0.092
	Non-SGA	0.84 ± 1.11	1.34 ± 1.09	1.58 ± 1.20	1.23 ± 1.18	1.18 ± 1.08	**0.011**
IGFBP-3	SGA	0.69 ± 0.27	1.61 ± 0.30[a]	2.09 ± 0.50	2.19 ± 0.45[a]	2.60 ± 0.55	**<0.001**
	Non-SGA	0.78 ± 0.17	1.95 ± 0.65[a]	2.41 ± 0.68	2.53 ± 0.48[a]	2.89 ± 0.56	**<0.001**
IGF-1	SGA	22.06 ± 8.82	65.02 ± 24.20	59.57 ± 30-07	46.30 ± 27.16	75.46 ± 48.25	**<0.001**
	Non-SGA	23.77 ± 10.43	72.37 ± 30.51	60.97 ± 26.80	50.61 ± 26.07	71.70 ± 32.79	**<0.001**
Leptin	SGA	0.52 ± 0.16	-	2.08 ± 1.37	1.84 ± 0.47	1.75 ± 0.89	**0.022**
	Non-SGA	0.52 ± 0.11	-	2.12 ± 1.01	2.09 ± 0.31	0.93 ± 0.07	**0.012**
Weight	SGA	2241.45 ± 318.67[a]	3465.58 ± 495.72[a]	5225.37 ± 650.99	6923.93 ± 957.95	11333.64 ± 1469.98	**<0.001**
	Non-SGA	2508.85 ± 312.25[a]	3704.53 ± 539.61[a]	5452.54 ± 739.86	6897.65 ± 740.56	9080.01 ± 1159.68	**<0.001**
Length	SGA	44.89 ± 1.54[a]	50.34 ± 2.21[a]	57.70 ± 2.20	64.55 ± 2.33	73.01 ± 2.72	**<0.001**
	Non-SGA	46.50 ± 2.16[a]	51.74 ± 2.48[a]	58.37 ± 2.45	64.66 ± 2.35	73.41 ± 2.14	**<0.001**
HC	SGA	31.74 ± 1-13[a]	36.08 ± 1.27	39.47 ± 1.37	42.60 ± 1.56	45.96 ± 5.62	**<0.001**
	Non-SGA	32.89 ± 1.29[a]	36.29 ± 1.35	39.71 ± 1.24	42.32 ± 1.24	45.47 ± 1.35	**<0.001**

P value shows differences among visits in the same group. Data are expressed as mean ± SD. Bold values represent statistically significant values.
Abbreviations: HC, head circumference; HOMA-IR, homeostasis model assessment - insulin resistance; IGFBP-3: IGF binding protein-3.
[a]$P < 0.05$ between SGA and non-SGA groups.

increasing alongside children's growth. The known interrelationship among biochemical variables is not evident 3 and 6 months after birth, suggesting that these parameters are not self-influencing at these stages of growth. In this context, the multivariate analyses identify as possible predictive markers of children growth, HOMA-IR index and IGFBP-3.

Using the term SGA, newborns lower than expected weight and length have been described [40]. However, the parameters and percentile of SGA definition is used differently in both clinical and research practice. In our cohort of SGA children, we recognize different groups of newborns considering the weight or length at birth lower than -2 SDs for gestational age. A total of 110 children were defined as SGA considering their weight, whereas considering only their length, 78 fulfilled this definition. Moreover, considering those newborns with both weight and length below -2 SDs for gestational age, the number of SGA diagnoses were reduced to 55 children. These subdivisions also recognize a different type of child, in which the growth in the first year of life seems to be different. Considering children with low weight, we recognize 2 groups of children showing the same increasing metabolic pattern, suggesting that the use of weight does not provide more information compared with other classifications. On the contrary, defining SGA according to length, 2 different population in terms of metabolic pattern are described. In particular, the insulin and HOMA-IR index increasing patterns are different when compared with the entire cohort of children. This suggests that SGA children for length show a different metabolic pattern. On the contrary, the limited number of children recognized considering weight and length separately lower than -2 SDs for gestational age to identify SGA children means we are not able to speculate about their metabolic patterns. Taken together, the metabolic and hormonal changes described in our study suggest that the classification of SGA children considering both weight and length at birth recognizes clearly different children, in particular regarding insulin levels and the GH/IGF-1 axis.

Finally, we confirm the recent literature data supporting that the definition of SGA children is complex and need a deeper revision. From our data, weight and length should be considered as independent parameters, each with a different role in early catchup growth and in later growth and metabolic status. They are not interchangeable parameters that define a single population of newborn, but they represent 2 auxological parameters related with different hormonal and metabolic patterns. Indeed, weight and length at birth define 2 different populations that should be studied separately both for the metabolic and auxological behavior. Consequently, different therapeutic approaches should probably also be considered.

Acknowledgments

The development of this publication was financially supported by Merck Serono S.p.A., Italy, an affiliate of Merck KGaA, Darmstadt, Germany, through an independent medical writing grant. The views and opinions described in this publication do not necessarily reflect those of the grantor.

Disclosures

The authors take full responsibility for the content of the paper. All authors have read and approved the final version of the manuscript. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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