Longitudinal Changes in Insulin-Like Growth Factor-I, Insulin Sensitivity, and Secretion from Birth to Age Three Years in Small-for-Gestational-Age Children

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Introduction: Insulin resistance (IR) develops as early as age 1 to 3 yr in small for gestational age (SGA) infants who show rapid catch-up postnatal weight gain. In contrast, greater insulin secretion is related to infancy height gains. We hypothesized that IGF-I levels could be differentially related to gains in length and weight and also differentially related to IR and insulin secretion.

Methods: In a prospective study of 50 SGA (birth weight $<$ 5th percentile) and 14 normal birth weight [appropriate for gestational age (AGA)] newborns, we measured serum IGF-I levels at birth, 1 yr, and 3 yr. IR (by homeostasis model assessment) and insulin secretion (by short iv glucose tolerance test) were also measured at 1 yr and 3 yr.

Results: SGA infants had similar mean length and weight at 3 yr compared with AGA infants. SGA infants had lower IGF-I levels at birth ($P < 0.0001$), but conversely they had higher IGF-I levels at 3 yr ($P = 0.003$) than AGA infants. Within the SGA group, at 1 yr IGF-I was associated with length gain from birth and insulin secretion ($P < 0.0001$); in contrast at 3 yr IGF-I was positively related to weight, body mass index, and IR.

Conclusions: IGF-I levels increased rapidly from birth in SGA, but not AGA children. During the key first-year growth period, IGF-I levels were related to β-cell function and longitudinal growth. In contrast, by 3 yr, when catch-up growth was completed, IGF-I levels were related to body mass index and IR, and these higher IGF-I levels in SGA infants might indicate the presence of relative IGF-I resistance.

RAPID, OR "CATCH-UP", postnatal growth in small for gestational age (SGA) infants is associated with increased risks of developing obesity, insulin resistance, type 2 diabetes mellitus, and the metabolic syndrome (1). In a contemporary UK population-based birth cohort, those children who showed rapid weight gains between birth and ages 2 to 3 yr were fatter and had more central fat distribution and insulin resistance at 5 and 8 yr (2, 3). In SGA Chilean infants closely followed from birth, decreased insulin sensitivity was already evident by age 1 yr, although their body weight and body mass index (BMI) were still lower compared with appropriate for gestational age (AGA) controls (4). Insulin secretion, on the other hand, appears to be more closely related to height gains in both population studies (3) and in the case control studies of SGA children (5).

IGF-I is a key growth factor during both infancy and childhood. During infancy, growth and IGF-I levels are initially largely independent of GH and more closely related to nutrition and insulin secretion. Beyond infancy, childhood growth is determined by GH secretion, but the GH/IGF-I axis remains partly dependent on insulin and nutrition (6, 7). SGA newborns have low circulating IGF-I levels, consistent with an important role for IGF-I in fetal growth (8). In normal children, IGF-I levels are positively associated with rapid postnatal weight gain and increased lean body mass (6, 9, 10). Furthermore, in those population-based cohort studies, higher IGF-I levels predicted greater childhood height gains and higher levels of insulin secretion for the degree of insulin sensitivity (3). We therefore hypothesized that changes in IGF-I levels in SGA children might show different associations between weight gain and height gain, and between insulin resistance and insulin secretion. To explore this hypothesis, we measured serum IGF-I levels from birth to age 3 yr in a SGA case control study where growth, insulin resistance, and insulin secretion have been studied prospectively from birth to age 3 yr (4, 5).

Abbreviations: AGA, Appropriate for gestational age; BMI, body mass index; CV, coefficient of variation; SDS, SD score(s); SGA, small for gestational age.

Subjects and Methods

Study protocol

As previously described (4, 5), 136 SGA [defined as birth weight $<$ 5th percentile for gestational age using local birth weight standards (11)] and 35 AGA (birth weight $>$ 10th percentile) were recruited to a prospective study of insulin sensitivity and secretion. Serum samples at birth were only available for 55 SGA and 18 AGA newborns. This number decreased to 50 SGA and 14 AGA at age 3 yr (Table 1). There were no significant differences in birth weight or weight gain from birth to 1 yr between those infants with available IGF-I levels at various ages or followed up to 3 yr compared with other infants (our unpublished observations).

Subjects were recruited at birth from the neonatal units at Hospital San Borja Arriarán and Hospital Sótero del Río (Santiago, Chile) and

TABLE 1. IGF-I levels (ng/ml) in SGA *vs.* AGA infants

	SGA	AGA	*t* test
Birth	(n = 55)	(n = 18)	
Weight (SDS)	−2.10 ± 0.08	1.12 ± 0.34	$P < 0.0001$
Length (SDS)	−1.71 ± 0.12	0.69 ± 0.30	$P < 0.0001$
IGF-I (ng/ml)	41.9 ± 1.3	59.6 ± 2.4	$P < 0.0001$
1 yr	(n = 85)	(n = 23)	
Weight (SDS)	−0.81 ± 0.11	0.60 ± 0.29	$P < 0.0001$
Length (SDS)	−0.84 ± 0.11	−0.19 ± 0.21	$P = 0.004$
IGF-I (ng/ml)	67.0 ± 2.8	61.4 ± 5.6	$P = 0.4$
3 yr	(n = 50)	(n = 14)	
Weight (SDS)	0.12 ± 0.19	0.39 ± 0.30	$P = 0.5$
Length (SDS)	−0.62 ± 0.14	−0.35 ± 0.25	$P = 0.4$
IGF-I (ng/ml)	87.5 ± 3.3	64.8 ± 6.4	$P = 0.003$

Data represent means ± SE adjusted for sex.

subsequently completed follow-up to age 3 yr at the Pediatric Endocrine Unit, Institute of Maternal and Child Research, School of Medicine, University of Chile. All infants were delivered at full term (gestational age was between 37 and 41 wk) and underwent a clinical evaluation during their second day of life to exclude those with significant medical, neurological, or genetic conditions. Both SGA and AGA infants were exclusively breast-fed for a mean of 3.7 months (range, 0–8 months), and the duration of breast-feeding was not different between birth weight and weight gain groups. No infants were taking any medication that could interfere with growth, appetite, or insulin levels. A complete record of parental, pregnancy, and perinatal data was completed at entry.

The study protocol was approved by the Hospital San Borja Arriarán and Hospital Sótero del Río Institutional Review Boards. Parents or guardians gave written informed consent at recruitment.

Measurements

All children had weights and length or height measured at birth, 1 yr, and 3 yr of age by one nurse. Supine length at birth and 1 yr was measured with a wooden box consisting of a fixed board for the infant's head and a movable board allowing feet to be placed perpendicular to the longitudinal axis of the infant. Height at 3 yr was measured using a clinical stadiometer. Weight was measured using a manual scale with a 10-g gradation (Seca, Hamburg, Germany).

Forty-eight hours after birth, a prefeeding 3-ml blood sample was obtained for determination of glucose, insulin, and IGF-I. At postnatal ages 12 and 36 months, a short iv glucose tolerance test was carried out after an overnight fast (mean duration of fast, 9 h). Two venous accesses were established in contralateral antecubital veins. Glucose (25% dextrose solution) was administered at a 0.5 g/kg (maximum, 35 g) dose by continuous infusion over 3 min. Blood samples were obtained at −5, 0, 1, 3, 5, and 10 min (where t = 0 is the start of glucose infusion) for determination of glucose and insulin levels. Glucose was measured immediately, whereas samples for insulin were kept on ice, centrifuged within 30 min, and sera frozen at −20 C. In the −5-min sample, C-peptide and IGF-I levels were also measured. Insulin secretion during the short iv glucose tolerance test is expressed as the incremental insulin area the under the curve (calculated using the trapezoidal rule).

Assays

Blood glucose concentration was determined using a commercial glucometer (Accutrend Sensor Comfort, Roche Diagnostic Inc., Basel, Switzerland), which yields values 8 ± 5% (mean ± SD) higher than standard enzymatic methods with a correlation coefficient of 0.987 for glycemias between 2.2 and 8 mmol/liter.

Serum insulin was measured using a commercial RIA from Diagnostic System Laboratories (Webster, TX). This assay has a cross-reactivity of 27.5% with proinsulin and 25% with 32, 33 split proinsulin. The sensitivity of this assay is 5.6 pmol/liter. C-peptide was also determined by RIA, using kits supplied by Diagnostic Products Corp. (Los Angeles, CA). Intraassay coefficients of variation (CVs) are 3.8% for insulin and 4.1% for C-peptide. Interassay CVs are 4.7% for insulin and 5.6% for C-peptide.

Serum IGF-I levels were determined using a locally developed RIA (12) requiring sample extraction as a first step. The sensitivity of this assay is 5 ng/ml. Intra- and interassay CVs are 8.6 and 10.2%, respectively.

Calculations and analyses

Weight and length at birth were converted into SD scores (SDS) to adjust for gestational age using local normative data (11). Thereafter, SDS for weight and length were calculated based on the National Center for Health Statistics (NCHS) growth curves. These growth curves have been found to be applicable to Chilean children (13).

Insulin resistance was estimated using the homeostasis model assessment-insulin resistance using the formula (insulin [pmol/liter] × glucose [mmol/liter]/22.5) (14). Homeostasis model assessment-insulin resistance values showed extremely high correlation with fasting insulin levels. First-phase insulin secretion during the short iv glucose tolerance test was expressed as the incremental insulin area under the curve for glucose (AIRg), calculated using the trapezoidal rule ([pmol/liter] × min).

Results are shown as mean ± SEM. Differences between groups were assessed by ANOVA. Comparisons between males and females were tested by unpaired *t* tests. Multiple regression models were used to adjust for sex and also to identify independent associations with IGF-I levels at age 3 yr; from these models, standardized partial regression coefficients (β coefficients) are displayed. In these parametric models, covariates showing extremely skewed distributions (BMI, insulin secretion, and insulin resistance) were transformed by calculating logarithms. Comparison of longitudinal changes in IGF-I levels between SGA (n = 42) and AGA infants (n = 11) with complete data were performed by repeated measures analysis. Statistics were performed using SPSS v.13 (SPSS Inc., Chicago, IL).

Results

As expected, SGA infants were lighter and shorter at birth than AGA infants (Table 1), but they had similar parental target heights (SGA *vs.* AGA, −1.19 ± 0.13 *vs.* −1.36 ± 0.25; $P = 0.29$). By 1 yr, SGA infants had shown partial catch-up in weight and length, and by 3 yr there was no longer any significant difference in weight or height (Table 1).

Among the whole group (SGA + AGA children), IGF-I levels increased steadily with age in both boys and girls, although the rise was more rapid in girls than boys (Table 2). All subsequent analyses were adjusted for sex. IGF-I levels at birth were unrelated to IGF-I levels at age 1 yr (r = 0.00; $P = 0.9$) and 3 yr (r = −0.13; $P = 0.3$). In contrast, IGF-I levels at age 1 yr were positively related to IGF-I levels at 3 yr (r = 0.60; $P < 0.0001$).

TABLE 2. Sex differences in IGF-I levels (ng/ml) in SGA infants at birth, 1 yr, and 3 yr of age

	Males	Females	*t* test
Birth			
Mean	41.1 (5.4)	42.9 (8.8)	$P = 0.5$
N	15	40	
1 yr			
Mean	53.9 (19.3)	73.9 (28.8)	$P = 0.002$
N	24	61	
3 yr			
Mean	70.9 (9.7)	93.5 (26.4)	$P = 0.008$
N	11	39	

Data represent means (SD) or number.

SGA vs. AGA infants

At birth SGA infants had lower IGF-I levels than AGA infants ($P < 0.0001$, Table 1). However, IGF-I levels rose very rapidly in the SGA group, and in reversal of the situation at birth, by age 3 yr SGA infants had higher IGF-I levels than the AGA group ($P = 0.003$; Table 1).

In a multiple regression analysis, higher IGF-I at 3 yr was associated with female sex ($P = 0.004$), larger weight at 3 yr ($P = 0.005$), and SGA birth group ($P = 0.0001$). Longitudinal repeated measures analysis confirmed that there was a faster rise in IGF-I levels in SGA infants, with AGA infants showing little overall change in IGF-I levels between birth and age 3 yr ($P < 0.0001$; Fig. 1). Rates of rise in IGF-I between birth and 3 yr were similar in male and female infants (P interaction = 0.7).

Associations with IGF-I levels among SGA infants

This transition in IGF-I levels in the SGA group was accompanied by a change in the profile of factors associated with IGF-I from ages 1 to 3 yr. At 1 yr, IGF-I was associated with length gain from birth ($P = 0.049$), but not weight gain, and positively associated with insulin secretion ($P = 0.009$), but not insulin resistance (Table 3). In contrast, at age 3 yr, IGF-I was positively associated with body weight, weight gain (but not height gain), and insulin resistance; and IGF-I tended to be inversely associated with markers of β-cell capacity, such as insulin secretion and C-peptide levels (Table 3).

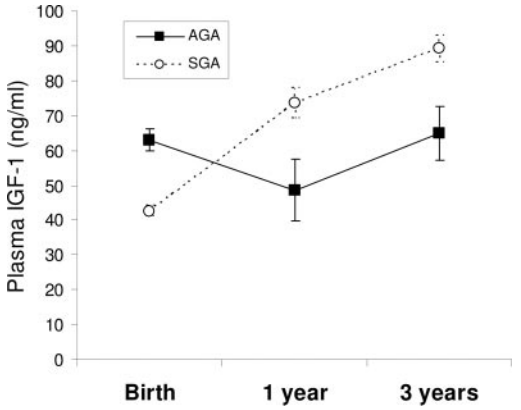

FIG. 1. Longitudinal changes in IGF-I levels from birth to age 3 yr in SGA (n = 42) and AGA (n = 11) subjects in the subgroup of infants with complete IGF-I data at all ages. Means ± SE, adjusted for sex. Repeated measures analysis for the difference in changes with age between SGA and AGA, $P < 0.0001$.

TABLE 3. Factors associated with IGF-I levels (ng/ml) at age 1 yr (n = 85) or 3 yr (n = 50) in SGA infants

	β	*P* value
Outcome variable: IGF-I at 1 yr		
Weight at 1 yr	0.07	0.5
Length at 1 yr	0.20	0.06
BMI at 1 yr	−0.06	0.5
Weight gain 0–1 yr	0.04	0.7
Length gain 0–1 yr	0.20	0.049
Insulin resistance at 1 yr	0.09	0.4
Insulin secretion at 1 yr[a]	0.28	0.009
C-peptide at 1 yr[a]	0.22	0.14
Outcome variable: IGF-I at 3 yr		
Weight at 3 yr	0.37	0.005
Length at 3 yr	0.25	0.07
BMI at 3 yr	0.28	0.04
Weight gain 1–3 yr	0.45	0.0008
Length gain 1–3 yr	0.05	0.7
Insulin resistance at 3 yr	0.42	0.003
Insulin secretion at 3 yr[a]	−0.28	0.14
C-peptide at 3 yr[a]	−0.42	0.002

Standardized partial regression coefficients (β) from separate regression models for each covariate, adjusted for sex.
[a] Further adjusted for current BMI and insulin resistance.

Longitudinal regression models of changes in IGF-I levels in SGA infants showed that change in IGF-I between birth and 1 yr showed a positive trend with length gain ($\beta = 0.19$; $P = 0.2$) but not weight gain ($\beta = -0.12$; $P = 0.5$). In contrast, change in IGF-I between birth and 3 yr was positively related to weight gain ($\beta = 0.44$; $P = 0.02$), but not length gain ($\beta = -0.18$; $P = 0.3$).

Discussion

The main finding from this prospective case control study was that IGF-I levels were lower in SGA *vs.* AGA infants at birth, but subsequently IGF-1 levels showed a faster rise in SGA infants. Therefore, by age 3 yr IGF-I levels were higher in SGA than in AGA children. As with other prospective studies of SGA infants, the vast majority showed spontaneous postnatal catch-up growth, and by age 3 yr they had heights and weights similar to the controls.

Previous studies in both SGA children and population-based cohorts showed that IGF-I levels at birth are positively related to birth weight, and these support a major role of IGF-I in promoting human fetal growth (15). However, IGF-I levels during childhood are completely unrelated to IGF-I levels at birth and appear to be related to childhood gains in both weight and length (9). In a large UK population-based study, IGF-I levels at age 5 yr were more closely related to fat-free mass than to fat mass (10) and predicted higher levels of insulin secretion at age 8 yr (3).

Similarly in this SGA cohort, at least at age 1 yr, the main determinants of IGF-I were insulin secretion, length, and length gain from birth. During infancy, IGF-I levels are largely nutritionally regulated (6). Insulin appears to promote IGF-I synthesis and secretion, as shown by studies in cultured hepatocytes (16) and by perfusion of insulin to the rat liver (17). In humans, a gradual transition toward GH regulation of IGF-I synthesis occurs during infancy, and this

is reflected by a rapid increase in numbers of hepatic GH receptors (7). We previously reported in this SGA cohort that insulin secretion was positively related to longitudinal growth between birth and age 1 yr (4). In 1976, Colle *et al.* (18) also reported a positive correlation between insulin release and growth velocity during the first 6 months in 15 term SGA newborns. Our current results support a possible role of higher insulin secretory capacity in inducing GH receptor numbers (19) and thus increased IGF-I levels. Longitudinal growth during the first year could be at least partly regulated by insulin secretion.

Surprisingly, in contrast to our findings in these SGA children at 1 yr and in normal children (3), IGF-I levels in these SGA children at 3 yr were more closely related to insulin resistance, weight, and weight gain than to measures of height gain or insulin secretion. We have previously described in this cohort that insulin resistance was already evident from age 1 yr and increased by age 3 yr in SGA children (5). Similar changes in insulin resistance in SGA children have recently been shown to be accompanied by rapid increases in adiposity and central fat (20). We found that IGF-I levels were higher in SGA than AGA children at age 3 yr, despite similar heights and weights. This could possibly be effected by the evolving peripheral insulin resistance, resulting in higher circulating insulin levels and increased hepatic generation of IGF-I. In a previous study of young short SGA children, higher baseline IGF-I levels appeared to be a marker for relative GH/IGF-I resistance, because they were associated with insulin resistance and poor growth responses to GH (21). Higher IGF-I levels in SGA children after spontaneous catch-up growth could therefore indicate relative IGF-I resistance, in addition to insulin resistance.

Previous studies of SGA children have reported IGF-I levels to be on average around one SD lower than the population reference; however, those studies were mostly in short SGA children without postnatal catch-up growth (22, 23). Recent data on IGF-I levels in an adult SGA cohort showed that they still had lower mean IGF-I levels compared with those born AGA (24). Those SGA adults were shorter and lighter than their normal birth weight controls; however, the differences in IGF-I levels persisted after adjustment for adult size.

Our data clearly show changes in the IGF system that coincide with the timing of intrauterine growth retardation and postnatal catch-up growth. Higher IGF-I levels could subsequently promote a faster tempo of growth and maturation in some SGA children who showed rapid catch-up growth (25, 26). It is possible that such SGA children with rapid maturation may end up with lower adult heights and lower adult IGF-I levels than average (27). IGF-I also has well-recognized effects on glucose metabolism. IGF-I may promote pancreatic β-cell growth and differentiation during fetal life (28, 29), and lower IGF-I levels in adults predict increased subsequent type 2 diabetes risk (24). IGF-I administration has been shown to restore β-cell function in experimental models of diabetes (30). Therefore, lower IGF-I levels in SGA children with reduced length growth in the first year of life could contribute to the observed links between decreased insulin secretion in childhood short stature (3) and also between type 2 diabetes and shorter adult height (31). Finally, rapid weight gain from birth to 3 yr could further contribute to future type 2 diabetes risks in SGA children by leading to insulin resistance and a greater demand on the β-cell.

In conclusion, IGF-I levels in SGA children during the first year of life are positively associated with length growth and may reflect their insulin secretory capacity. However, after spontaneous catch-up growth, the development of insulin resistance may be accompanied by higher IGF-I generation. Higher IGF-I levels in SGA children after completion of postnatal catch-up growth may be an indicator of relative insulin and IGF-I resistance and future type 2 diabetes risks.

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