Growth Factors and Adipocytokines in Prepubertal Children Born Small for Gestational Age

Relation to insulin resistance

ANNA S. CHALLA, PHD[1]
ELENI N. EVAGELIDOU, MD[2]
VASILIOS I. CHOLEVAS, PHD[1]
DIMITRIOS N. KIORTSIS, MD[3]
VASILEIOS I. GIAPROS, MD[2]
AIKATERINI A. DROUGIA, MD[2]
STYLIANI K. ANDRONIKOU, MD[2]

OBJECTIVE — The aim of this study was to test whether being born small for gestational age (SGA) has an impact on adiponectin and leptin levels and the IGF system in relation to insulin sensitivity, taking into consideration the severity of growth restriction.

RESEARCH DESIGN AND METHODS — Serum levels of adiponectin, leptin, fasting glucose, fasting insulin (I_F), the homeostasis model assessment insulin resistance index (HOMA-IR), IGF-1, free IGF-1, IGF-binding protein (IGFBP)-1 and -3, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides were evaluated in 57 children at age 4–10 years. Of these, 32 had been born appropriate size for gestational age (AGA) and 25 SGA (14 in the <3rd percentile and 11 in the 3rd–10th percentile).

RESULTS — The SGA 3rd–10th percentile children were already insulin resistant at prepubertal age (I_F 39.6 ± 16.8 vs. 27 ± 12 pmol/l, $P < 0.01$, and HOMA-IR 1.4 ± 0.6 vs. 0.95 ± 0.42 in SGA vs. AGA children, $P < 0.05$). Their IGF-1 and IGFBP-3 concentrations were significantly lower than those in AGA children (160.4 ± 66.2 vs. 207 ± 66.8 μg/l, $P < 0.05$ and 2.3 ± 0.4 vs. 3.51 ± 1.21 mg/l in SGA vs. AGA children, $P < 0.01$). The SGA <3rd percentile children had higher adiponectin (15.6 ± 5.7 mg/l, $P < 0.05$) and IGFBP-1 levels (113.5 ± 33.9 μg/l, $P < 0.05$) than AGA children (11.3 ± 6.6 mg/l and 90.8 ± 24.2 μg/l, respectively) and lower IGF-1 and IGFBP-3 concentrations (162.6 ± 68.4 μg/l, $P < 0.05$ and 2.4 ± 0.7 mg/l, $P < 0.01$). They also had significantly lower waist circumference ($P < 0.05$). Leptin levels did not differ among groups, but an inverse correlation with IGFBP-1 ($r = -0.55$, $P < 0.01$) was found in the pooled SGA group.

CONCLUSIONS — Intrauterine growth restriction appears to affect the IGF axis at prepubertal age, and its severity plays a role in insulin sensitivity.

Diabetes Care 32:714–719, 2009

Changes in the secretion of and sensitivity to the hormones insulin, IGF-1, and IGF-binding proteins (IGFBPs) during gestation or after may be associated with metabolic syndrome in adulthood (1). The IGF-1 in circulation is bound to the IGFBP-3, which in turn modulates IGF-1 availability. The data generated from studies in IGFBP-3 transgenic mice clearly demonstrate that IGFBP-3 plays a role in glucose homeostasis, possibly by regulating free IGF-1 levels in tissues (2). Low circulating levels of serum IGF-1 and IGFBP-1 (3) are considered to be implicated in impaired glucose tolerance, elevated blood pressure, and obesity. Low birth weight has been associated with an increased risk of obesity, insulin resistance, and diabetes in adulthood (4).

Adiponectin, the most abundant of the "adipocytokines," appears to exert antidiabetic, antiatherogenic, and anti-inflammatory activities. Low adiponectin levels are observed in the metabolic syndrome and are considered to be an independent risk factor for development of type 2 diabetes later in life (5). Leptin, which reflects body fat mass, has been thought to play a role in the genesis of metabolic syndrome and cardiovascular disease (CVD). It is thought to be associated with insulin resistance, through inhibition of insulin secretion, and is inversely related to adiponectin levels (6).

To our knowledge there have been no reports of studies dealing with the relationship between the IGF axis, adipocytokines, and insulin resistance in prepubertal children born small for gestational age (SGA). In this study, we attempted to evaluate serum adiponectin and leptin levels in relation to components of the IGF system and indexes of insulin resistance in healthy prepubertal children born SGA, taking into consideration the severity of growth restriction at birth.

RESEARCH DESIGN AND METHODS

— The study included 57 prepubertal children aged 4−10 years born either SGA ($n = 25$) or appropriate size for gestational age (AGA) ($n = 32$) between April 1997 and December 1998 at the University Hospital of Ioannina, which hosts the majority (>85%) of births in a well-defined geographical area of northwestern Greece. The anthropometric measures at birth were obtained retrospectively by a chart review. All of the study children were born between the 36th and 40th weeks of gestation, with no evidence of congenital malformations or genetic disorders. The AGA children were matched with the SGA children according to age and sex. All of the subjects selected for the study were to be nonobese, with BMI <85th percentile, based on growth charts specific for age and sex for Greek

From the [1]Pediatric Research Laboratory, Child Health Department, University of Ioannina, Ioannina, Greece; the [2]Neonatal Intensive Care Unit, University Hospital of Ioannina, Ioannina, Greece; and the [3]Laboratory of Physiology, Medical School, University of Ioannina, Ioannina, Greece.
Corresponding author: Styliani K. Andronikou, sandroni@cc.uoi.gr.
Received 26 August 2008 and accepted 27 December 2008.
Published ahead of print at http://care.diabetesjournals.org on 8 January 2009. DOI: 10.2337/dc08-1570.

children, to exclude children with an elevated risk factor profile in the higher range of BMI (7). The Ethics Committee of Ioannina University Hospital approved the study protocol, and informed written consent was obtained from the parents of each child.

SGA was defined as birth weight <10th percentile for gestational age. The SGA children were divided into two subgroups based on the severity of growth restriction: children with birth weight between the 3rd and 10th percentiles (n = 11) and children with birth weight <3rd percentile (n = 14). AGA was defined as birth weight between the 10th and 90th percentiles for gestational age.

At the time of the study, BMI was estimated and BMI z scores specific for age and sex were calculated. Body weight, body height, head circumference, and waist circumference as an indicator of central obesity were measured using techniques described previously (8). Pubertal stage was assessed by physical examination according to the criteria of Tanner staging.

The parent of each child completed a weekly food record for that child, from which total energy intake, proteins, lipids, and carbohydrates were calculated. To estimate the effect of catch-up growth, the SGA children were reclassified into two additional subgroups according to their corrected height standard deviation scores (SDSs): actual height SDS − midparental height SDS, where midparental height for boys equals father's height + (mother's height + 13)/2 and for girls equals mother's height + (father's height − 13)/2 (9,10). This gave one subgroup with no catch-up growth (n = 10), comprising children with a corrected height of <0 SDS, and one subgroup with catch-up growth (n = 15), with a corrected height of ≥0 SDS. SGA infants were also classified into two groups, symmetrical (n = 7) and asymmetrical (n = 18), according to their ponderal index (birth weight [grams] × 100/length at birth in cubic centimeters).

Hormone and biochemical assays

Venous blood samples for laboratory analysis were collected between 7:00 and 8:00 A.M., after 12-h overnight fasting. Serum adiponectin levels were measured by an enzyme-linked immunosorbent assay (ELISA) using a kit from Phoenix Pharmaceuticals Inc. (EK-ADI-01; Belmont, CA). The sensitivity of the adiponectin assay was 0.40 mg/l. The intra- and interassay coefficients of variation (CVs) were <10 and <15%, respectively. Fasting insulin (I_F) levels were determined with an immunoenzymatic method (AxSYM analyzer; Abbott), and fasting glucose (G_F) concentrations were measured by the glucose oxidase method. I_F and the homeostasis model assessment for insulin resistance (HOMA-IR, equal to I_F [milliunits per liter] × G_F [millimoles per liter]/22.5) were chosen as measures of insulin sensitivity (11). The IGFs and their binding proteins were determined by ELISA using kits from Diagnostic Systems Laboratories. The sensitivities for IGF-1, free IGF-1, IGFBP-1, and IGFBP-3 were, respectively, 0.01, 0.02, 0.025, and 0.04 μg/l. The intra- and interassay CVs were 4.5 and 6.0% for IGF-1, 3.6 and 10.1% for free IGF-1, 2.5 and 6.8% for IGFBP-1, and 9.5 and 10.4% for IGFBP-3. Serum leptin levels were measured by the ELISA method using a kit from BioVandor Laboratory Medicine (Modrice, Czech Republic). The sensitivity of the leptin assay was 0.50 μg/l. The intra- and interassay CVs were 5 and 10%, respectively. Lipids were analyzed in the Olympus AU 640 automatic analyzer (Olympus Diagnostica, Hamburg, Germany). LDL cholesterol was calculated using the Friedewald formula.

Statistical analysis

Results are reported as means ± SD and range (minimum and maximum values). The Mann-Whitney U test or Student's t test was used for variables displaying nonnormal or normal distribution, respectively. Simple linear regression analysis was used to identify possible correlations between variables. Statistical analyses were performed using the StatView software package of SAS Institute (Cary, NC). Differences were considered statistically significant at $P < 0.05$.

RESULTS — The retrospective analysis of the hospital neonatal records identified 70 children born SGA during the 20-month period, of which 47 were eligible to participate in the study and had adequate perinatal information about gestational age, birth weight, and possible risk factor for growth restriction. A further 22 children were eliminated: for 6 contact details were inadequate; for 5 the parents did not give consent; for 6 the serum specimens were inappropriate; and for 5 BMI was >85th percentile. The remaining 25 SGA children were enrolled in the study. Risk factors for growth restriction had been detected in 17 of the 25 SGA children, with hypertensive disease of pregnancy being the most common (9 of 17), followed by placental insufficiency (3 of 17), low maternal weight gain during pregnancy (3 of 17), and multiple gestation (2 of 17). SGA with risk factors for growth restriction were distributed equally in the <3rd percentile subgroup (n = 10) and the 3rd–10th percentile subgroup (n = 7) (NS). The 32 matched control subjects were selected from a sample of 165 AGA children born at the hospital during the same period who were initially contacted. All of the study children were at Tanner stage I. No differences were found in mean intake of calories, protein, lipids, and carbohydrates between the SGA and AGA groups, which were well within the European recommended dietary allowances for sex and age (http://www.euro.who.int/Document/WS_115_2000FE_A.pdf). The mean daily calorie intakes were 1,430, 1,450, and 1,470 kcal/day in the AGA, SGA <3rd percentile, and SGA 3rd–10th percentile groups, respectively (NS).

Mean ± SD values for the anthropometric indexes of the subjects at birth and in the study period are depicted in Table 1. Children born SGA <3rd percentile had lower body height ($P < 0.05$) and waist circumference ($P < 0.01$) than the AGA children (Table 1).

The G_F levels were similar in all groups and subgroups (Table 2), but in the pooled SGA children the I_F concentrations and the HOMA-IR values were significantly higher than those in the AGA children ($P < 0.05$). These differences were due mainly to the differences observed between the 3rd–10th percentile SGA subgroup and the AGA group. Serum IGF-1 concentrations were lower in the pooled SGA group ($P < 0.05$) and in both SGA subgroups than in the AGA group, whereas free IGF-1 showed no difference between groups (Table 2). The IGFBP-3 levels were also lower in the pooled SGA group ($P < 0.001$) and the two subgroups compared with the AGA group (Table 2). IGFBP-1 circulating levels were significantly higher only in the SGA <3rd percentile subgroup ($P < 0.05$) compared with the AGA group (Table 2).

In the SGA <3rd percentile subgroup, adiponectin concentrations were significantly higher than those in the AGA group and the SGA 3rd–10th percentile subgroup ($P < 0.05$) (Table 2). Leptin concentrations did not differ significantly

Table 1—*Anthropometric indexes at birth and at the time of study in two groups of prepubertal children, born AGA or SGA (<10th percentile) plus SGA subgroups (3rd–10th and <3rd percentile)*

	AGA	Pooled SGA	SGA 3rd–10th percentile	SGA <3rd percentile
n	32	25	11	14
At birth				
Sex (male)	18	13	6	7
Gestational age (weeks)	37.3 ± 1.1	37 ± 1.2	36.9 ± 1.3	37.1 ± 1.6
Birth weight (g)	3,375 ± 407	1,880 ± 490*	1,995 ± 430*	1,750 ± 422*
Crown-to-heel length (cm)	51.4 ± 2	44.8 ± 4.6*	45.5 ± 4.2*	43.7 ± 5.1*
Head circumference (cm)	34.6 ± 1.3	31 ± 2.8*	31 ± 2.6*	30.5 ± 2.9*
Ponderal index (g/cm^3)	2.48 ± 0.22	2.15 ± 0.2*	2.1 ± 0.2*	2.2 ± 0.2*
At the time of study				
Age (years)	6.59 ± 1.6	6.2 ± 2.9	6.36 ± 1.6	6.04 ± 2.3
Body weight (kg)	26 ± 6.2	25.4 ± 6	25.6 ± 6.3	25 ± 6.7
Body height (cm)	121.9 ± 13.3	118 ± 9.2	121.4 ± 11.2	114.5 ± 15.5†
Waist circumference (cm)	60.6 ± 7.4	58.4 ± 9.6	59.6 ± 10.1	53.8 ± 8.8***
BMI (kg/m^2)	18.4 ± 2	17.4 ± 3.6	17.7 ± 3.4	17.6 ± 3.9
BMI SDS	0.18 ± 0.43	0.17 ± 0.62	0.17 ± 0.6	0.16 ± 0.64

Values are means ± SD. *$P < 0.0001$, ***$P < 0.01$, and †$P < 0.05$ for comparison with the AGA group.

between groups, but there was a tendency for these to be higher in the SGA 3rd–10th percentile subgroup than in the AGA group (Table 2). No significant difference was observed in the serum total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride levels among the pooled SGA group or their two subgroups and the AGA control group (Table 2).

In the pooled SGA group adiponectin was found to be negatively associated with BMI, waist circumference, body weight and body height, IGF-1, and free IGF-1 (Table 3). In the AGA group, only waist circumference was negatively associated with adiponectin. No correlation with the other parameters was observed. A positive association of leptin with the insulin resistance indexes I_F and HOMA-IR, BMI, and waist circumference was found in both the pooled SGA and the AGA children. A negative association between leptin and adiponectin was seen only in the pooled SGA group (Table 3). In addition, circulating IGFBP-1 levels and free IGF-1 concentrations were found to be inversely correlated in the pooled SGA group only ($R = -0.72$, $P < 0.0001$).

SGA children were further analyzed according to catch-up growth. The two subgroups, with and without catch-up growth, did not differ for age or sex. Eight

Table 2—*Fasting blood glucose, insulin, HOMA-IR, leptin, adiponectin, IGF-1, free IGF-1, IGFBP-1 and -3, and lipids at the time of study in children of prepubertal age born AGA or SGA (<10th percentile) and SGA subgroups (3rd–10th and <3rd percentile)*

	AGA	Pooled SGA	SGA 3rd–10th percentile	SGA <3rd percentile
n	32	25	11	14
G_F (mmol/l)	4.65 ± 0.4 (3.9–5.5)	4.58 ± 0.5 (3.2–5.4)	4.67 ± 0.3 (4.1–5.1)	4.52 ± 0.6 (3.2–5.4)
I_F (pmol/l)	27.0 ± 12 (6–60)	36.6 ± 20.4 (12–95.4)*	39.6 ± 16.8 (12–63.6)**	34.8 ± 23.4 (12–95.2)
HOMA-IR	0.95 ± 0.42 (0.18–1.85)	1.3 ± 0.8 (0.3–4.1)*	1.4 ± 0.6 (0.4–2.2)*	1.2 ± 1 (0.3–4.1)
IGF-1 (μg/l)	207 ± 66.8 (65–332)	161.6 ± 66 (52–302)*	160.4 ± 66.2 (52–277)*	162.6 ± 68.4 (63–302)*
Free IGF-1 (μg/l)	0.87 ± 0.78 (0.01–2.4)	0.61 ± 0.34 (0.2–1.2)	0.64 ± 0.37 (0.2–1.2)	0.58 ± 0.33 (0.2–1.17)
IGFBP-3 (mg/l)	3.51 ± 1.21 (0.85–5.7)	2.36 ± 0.58 (1.3–3.6)***	2.3 ± 0.4 (1.4–3.1)**	2.4 ± 0.7 (1.3–3.6)**
IGFBP-1 (μg/l)	90.8 ± 24.2 (46.2–137.9)	107.8 ± 40.1 (45.2–194)	100.5 ± 47.5 (45.2–194)	113.5 ± 33.9 (67–189)*
Adiponectin (mg/l)	11.3 ± 6.6 (3.9–18.3)	13.3 ± 6.7 (2.6–25.2)	12.5 ± 7 (2.6–22.5)†	15.6 ± 5.7 (5.5–25.2)*
Leptin (μg/l)	8.47 ± 7.36 (1.8–31.4)	11.4 ± 12.9 (2.2–50)	13.9 ± 16.2 (2.2–50)	9.4 ± 9.8 (2.2–30.5)
Total cholesterol (mmol/l)	4.4 ± 0.59 (3.15–5.5)	4.3 ± 0.62 (3.23–5.18)	4.37 ± 0.64 (3.23–5.15)	4.25 ± 0.62 (3.36–5.18)
HDL cholesterol (mmol/l)	1.28 ± 0.15 (0.9–1.8)	1.29 ± 0.12 (0.82–1.68)	1.29 ± 0.1 (0.82–1.65)	1.29 ± 0.28 (0.93–1.68)
Triglycerides (mmol/l)	0.75 ± 0.31 (0.56–1.63)	0.76 ± 0.3 (0.55–1.5)	0.82 ± 0.35 (0.55–1.5)	0.68 ± 0.13 (0.62–1.46)
LDL cholesterol (mmol/l)	2.77 ± 0.56 (1.34–3.88)	2.6 ± 0.54 (1.2–3.7)	2.66 ± 0.5 (1.26–3.4)	2.59 ± 0.59 (1.2–3.7)

Data are means ± SD (ranges). *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ for comparison with the AGA group. †$P < 0.05$ for comparison between the SGA 3rd–10th percentile and the SGA <3rd percentile subgroups.

Table 3—*Correlations between adiponectin or leptin and growth factors, anthropometric parameters, or insulin sensitivity index in AGA and SGA (<10th percentile) children*

	Adiponectin versus:					
	IGF-1	Free IGF-1	BMI	Waist circumference	Body weight	Body height
AGA	NS	NS	NS	$R = -0.40$	NS	NS
	NS	NS	NS	$P = 0.03$	NS	NS
Pooled SGA	$R = -0.44$	$R = -0.48$	$R = -0.40$	$R = -0.47$	$R = -0.50$	$R = -0.55$
	$P < 0.05$	$P < 0.02$	$P < 0.05$	$P < 0.05$	$P = 0.012$	$P = 0.005$

	Leptin versus:					
	I_F	HOMA-IR	BMI	Waist circumference	Adiponectin	IGFBP-1
AGA	$R = 0.67$	$R = 0.66$	$R = 0.75$	$R = 0.67$	NS	NS
	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	$P < 0.0001$	NS	NS
Pooled SGA	$R = 0.50$	$R = 0.48$	$R = 0.70$	$R = 0.73$	$R = -0.41$	$R = -0.55$
	$P < 0.01$	$P < 0.05$	$P < 0.0001$	$P < 0.0001$	$P < 0.05$	$P < 0.01$

children with catch-up growth in height had birth weight <3rd percentile and seven had birth weight between the 3rd and 10th percentiles (NS). SGA children who did not exhibit catch-up growth had higher adiponectin and IGFBP-1 levels than AGA children (16.2 ± 6.5 vs. 11.3 ± 6 mg/l, $P < 0.05$ and 128 ± 44.7 vs. 90.8 ± 24.2 μg/l, $P < 0.01$, respectively). Children who exhibited catch-up growth had a tendency to have higher leptin levels only (13.8 ± 1.4 vs. 8.47 ± 7.36 μg/l, $P = 0.07$). Both SGA catch-up subgroups had lower IGFBP-3 levels than the AGA group (2.2 ± 0.6, 2.46 ± 0.5, vs. 3.5 ± 1.2 mg/l, respectively, $P < 0.01$). No differences were observed in the rest of the parameters examined.

After taking into consideration proportionality in the SGA children, the only difference found was the lower IGF-1 and IGFBP-3 levels in both subgroups, symmetrical or asymmetrical SGA, compared with the AGA group. No distinct differences in any other of the parameters examined were found, either between the two SGA proportionality subgroups or between the subgroups and the AGA group. Four asymmetrical SGA children had birth weight <3rd percentile and three had birth weight between the 3rd and 10th percentile.

CONCLUSIONS — Reduced plasma IGF-1 and IGFBP-3 levels are reported in insulin-dependent diabetes and may represent a state of partial growth hormone resistance in patients with poorly controlled diabetes (12). Low serum IGF-1 levels are also associated with the development of CVD and are considered to reflect a higher risk for insulin resistance and later appearance of diabetes (1). In the present study, IGF-1 and IGFBP-3 were found to be lower and I_f and the HOMA-IR index were higher in the pooled SGA group than in the AGA children in the prepubertal phase. These differences were more pronounced in the SGA children born between the 3rd and 10th percentiles. IGF-1 is believed to have insulin-like actions in fine-tuning insulin sensitivity (2). The effects of IGF-1 on increasing insulin sensitivity have been demonstrated in normal subjects during euglycemic clamps (13). Hence, the lower total IGF-1 levels seen in the SGA 3rd–10th percentile study group could be responsible for the higher I_F levels found with normal fasting glucose levels. The lower IGF-1 levels could be a factor for an increased risk of development of diabetes in later life.

Higher insulin concentrations at baseline were also observed in a study of 25-year-old subjects born with intrauterine growth retardation (14). An oral glucose tolerance test for those subjects showed that there was decreased insulin-stimulated glucose uptake, leading to the suggestion that intrauterine growth retardation exerts an independent effect on insulin sensitivity (14). Although glucose tolerance tests were not done in the present study, the higher I_f levels and HOMA-IR with G_F similar to those for AGA children may suggest an early start of insulin resistance in the SGA study children, especially in the 3rd–10th percentile subgroup.

IGFBP-1 concentrations showed no differences between the AGA group and the SGA 3rd–10th percentile subgroup but were higher in the SGA <3rd percentile subgroup. There is experimental evidence that IGFBP-1 can finely regulate bioactivity of IGF-1 and is involved in glucose homeostasis (2,13). An inverse relationship between IGFBP-1 and free IGF-1 has been reported in normal human subjects and was found in the pooled SGA group of the present study, although free IGF-1 levels were not higher in the SGA <3rd percentile subgroup, whereas their glucose and insulin levels were comparable with those of the AGA group. The higher IGFBP-1 levels in the SGA <3rd percentile subgroup might be a protective factor for diabetes, whereas this may not be so for the SGA 3rd–10th percentile subgroup, which also had higher I_F levels. The SGA <3rd percentile children had lower waist circumference, which may mean that they had a leaner stature than the AGA children, thus having an additional protecting factor, because waist circumference is regarded as an index of abdominal fat and the degree of central obesity (7) and has been associated with insulin sensitivity. Those children were also shorter. Lower height has been associated with higher IGFBP-1 in studies with adults (15).

Adiponectin has been reported to be closely related to insulin sensitivity (5,16,17). Yamamoto et al. (17) observed in adults that when adiponectin levels

were high, insulin resistance was low. In addition, strong inverse correlations between adiponectin levels and BMI or waist circumference have been reported in adults (16,17). In the present study, an inverse correlation of adiponectin with waist circumference was found both in the pooled SGA group and in the AGA group, indicating a strong relationship between this protein and abdominal fat or central obesity, independent of birth weight. However, the inverse relationship of adiponectin levels with BMI, body weight, and body height that were observed only in the pooled SGA group may be explained by differences in the growth process in SGA children. The lower adiponectin concentrations in the SGA 3rd–10th percentile subgroup in relation to the SGA <3rd percentile subgroup may be due to their differences in height and waist circumference. The fact that the subgroup of SGA <3rd percentile children, which had higher IGFBP-1 levels, was also found to have higher adiponectin levels than the AGA control children may reflect their capability to maintain higher insulin sensitivity than the SGA 3rd–10th percentile subgroup. These findings could be interpreted as additional protective factors for this subgroup with respect to insulin resistance.

With regard to leptin, there was a tendency for higher levels in the pooled SGA group and even more so in the SGA 3rd–10th percentile subgroup, but the differences from the AGA group were not statistically significant. It appears that this hormone is related mainly to current weight rather than the SGA status at birth, and a very strong relationship was found in both the AGA and the SGA study groups between leptin levels and current BMI.

Catch-up growth has been postulated to be associated with insulin resistance and increased risk for type 2 diabetes (18,19). To clarify the effects of catch-up growth in the SGA children of the present study, an analysis was made after classifying SGA children into two subgroups according to catch-up growth in height. Children without catch-up growth had higher levels of adiponectin and IGFBP-1 compared with the AGA children, implying that this subgroup of SGA children may have higher insulin sensitivity than the SGA subgroup who exhibited catch-up growth and who had adiponectin levels comparable to those of the control subjects. These results are in agreement with those reported for prepubertal SGA children, in whom a hyperinsulinemic-euglycemic clamp study was performed to determine insulin sensitivity (18). Cianfarani et al. (10) estimated catch-up growth by calculating the corrected height and Lopez-Bermejo et al. (20) by considering the BMI SDS. Both reported higher adiponectin levels in SGA groups not experiencing catch-up growth in height or BMI, respectively (10,20), which is in agreement with the findings of the present study. The trend for higher leptin levels in the SGA subgroup who exhibited catch-up growth is in agreement with the findings of other studies, which showed that catch-up growth after intrauterine growth retardation was associated with increased leptin levels (21).

Fasting insulin and leptin levels have been reported to correlate inversely with IGFBP-1 (22). One of the suggested mechanisms is that higher body fat could lead to elevation of leptin and insulin resistance and to a secondary hyperinsulinemia, which in turn suppresses the IGFBP-1 levels (22). This appears to apply in the SGA 3rd–10th percentile subgroup. Inverse correlation between leptin and IGFBP-1 or adiponectin was also found in the pooled SGA group. In addition, an inverse relationship was observed between leptin and adiponectin in the pooled SGA group. The lower adiponectin and higher leptin levels found in the SGA 3rd–10th percentile subgroup in comparison with the SGA <3rd percentile subgroup suggest additional factors for insulin resistance in this subgroup. Thenola et al. (23) reported that SGA children at the age of 12 years had levels of total cholesterol in the high normal range, whereas other researchers found no difference in the lipid profile in 10-year-old SGA children, in accordance with our results (24).

The classification of the SGA children into subgroups according to the severity of growth restriction, as was done in the present study, appears to unveil distinctive differences, both between the subgroups and in comparison with the AGA control subjects, with regard to most of the parameters examined. A further classification according to the catch-up growth pattern revealed distinctive differences only in adiponectin and IGFBP-1 levels between the two groups of SGA and the AGA children. Some investigators support the hypothesis that hyperinsulinemia precedes the development of insulin resistance and perhaps even the development of obesity (25). If this hypothesis proves correct, the hyperinsulinemia observed in the SGA 3rd–10th percentile subgroup is an early predictor for development of insulin resistance and for the subsequent development of diabetes. Thus, SGA children with birth weight between the 3rd and 10th percentiles with catch-up growth in height appear to be at a greater risk for insulin resistance, with adverse consequences for their later life. However, the possibility that this subgroup of SGA children may exhibit later adaptation against insulin resistance, i.e., a rise in adiponectin, that the more severely growth-restricted children exhibited earlier in life cannot be excluded. Until more data are available, continued long-term monitoring is necessary for both subgroups of SGA children.

In summary, the mechanism for developing an abnormal metabolic profile and the appearance of insulin resistance are complex processes and may be of various etiologies in the different subgroups of children born SGA. Intrauterine programming of the adipose tissue and the IGF axis could influence insulin sensitivity and consequently the risk of metabolic syndrome and CVD. Catch-up growth in height also appears to play a role in modulating the metabolic profile even at prepubertal age.

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

References

1. Holt RI: Fetal programming of the growth hormone-insulin-like growth factor axis. *Trends Endocrinol Metab* 13:392–397, 2002
2. Murphy L: The role of the insulin-like growth factors and their binding protein in glucose homeostasis. *Exp Diabetes Res* 4:213–224, 2003
3. Sandhu MS, Heal AH, Gibson MJ, Cruickshank JK, Dunger DB, Wareman NJ: Circulating concentrations of insulin like growth factor I and development of glucose intolerance: a prospective observational study. *Lancet* 359:1740–1745, 2002
4. Levy-Marchal C, Jaquet D: Long-term metabolic consequences of being born small for gestational age. *Pediatr Diabetes* 4:147–153, 2004
5. Weyer C, Funahashi T, Tanaka S, Hotta K, Matzuzawa Y, Pratley RE, Tatarani PA: Hypoadiponectemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinaemia. *J Clin Endocrinol Metab* 86:1930–1935, 2001
6. Havel PJ, Sechon IV: Lipid modulators of

islet function of energy balance and carbohydrate/lipid metabolism. *Diabetes* 53: 5143–5151, 2004
7. Katzmarzyk PT, Srinivasan SR, Chen W, Malina R, Bouchard C, Berenson GS: Body mass index, waist circumference and clustering of cardiovascular disease risk factors in a biracial sample of children and adolescents. *Pediatrics* 114: 198–205, 2004
8. Evagelidou EN, Kiortsis DN, Bairaktari ET, Giapros VI, Cholevas VK, Tzallas CS, Andronikou SK: Lipid profile, glucose homeostasis, blood pressure and obesity-anthropometric markers in macrosomic offspring of nondiabetic mother. *Diabetes Care* 29:1197–1201, 2006
9. Tanner JM, Goldstein H, Whitehouse RH: Standards for children's height at ages 2–9 years allowing for height of parents. *Arch Dis Child* 45:755–762, 1970
10. Cianfarani S, Martinez CH, Maiorana A, Scirè G, Spadoni GL, Boemi S: Adiponectin levels are reduced in children born small for gestational age and are inversely related to postnatal catch-up growth. *J Clin Endocrinol Metab* 89:1346–1351, 2004
11. Gungor N, Saad R, Janosky J, Arslanian S: Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. *J Pediatr* 144: 47–55, 2004
12. Cohen RM, Abplanalp WA: Resistance of growth hormone secretion to somatostatin in men with type I diabetes mellitus. *Diabetes* 40:1251–1258, 1991
13. Hussain MA, Schmitz O, Mengel A, Keller A, Christiansen JS, Zapf J, Froesch ER: Insulin-like growth factor I stimulates lipid oxidation, reduces protein oxidation, and enhances insulin sensitivity in humans. *J Clin Invest* 92:2249–2256, 1993
14. Jaquet D, Gaboriau A, Czernichow P, Levy-Marchal C: Insulin resistance early in adulthood in subjects born with intrauterine growth retardation. *J Clin Endocrinol Metab* 85:1401–1406, 2000
15. Hong Y, Brismar K, Hall K, Pederson ML, de Faire U: Associations between insulin-like growth factor-I (IGF-I), IGF-binding protein-1, insulin and other metabolic measures after controlling for genetic influences: results from middle-aged and elderly monozygotic twins *J Endocrinol* 153: 251–257, 1997
16. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, Retzlaff BM, Knopp RH, Brunzell JD, Kahn SE: Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins. *Diabetologia* 46:459–469, 2003
17. Yamamoto Y, Hiroshi H, Saito I, Tomita M, Taniyama M, Matsubara K, Okazaki Y, Ishii T, Nishikai K, Saruta T: Correlation of the adipocyte-derived protein adiponectin with insulin resistance index and serum high-density lipoprotein-cholesterol, independent of body mass index, in the Japanese population. *Clin Sci* 103: 137–142, 2002
18. Veening MA, Van Weissenbrugh MM, Van de Waal HAD: Glucose tolerance, insulin sensitivity and insulin secretion in children born small for gestational age. *J Clin Endocrinol Metab* 87:4657–4661, 2002
19. Ong KK, Petry CJ, Emmett PM, Sandhu MS, Kiess W, Hales CN, Ness AR, Dunger DB: Insulin sensitivity and secretion in normal children related to size at birth, postnatal growth, and plasma insulin-like growth factor-I levels. *Diabetologia* 47:1064–1070, 2004
20. Lopez-Bermejo A, Casano-Sancho P, Fernadez-Real JM, Kihara S, Funahashi T, Rodriguez-Hierro F, Ricart W, Ibanez L: Both intrauterine growth restriction and postnatal growth influence childhood serum concentrations of adiponectin. *Clin Endocrinol (Oxf)* 61:544–552, 2004
21. Jaquet D, Leger J, Tabone MD, Czernichow P, Levy-Marchal C: High serum leptin concentrations during catch-up growth of children born with intrauterine growth retardation. *J Clin Endocrinol Metab* 84:1949–1953, 1999
22. Liew CF, Wise SD, Yeo KP, Lee KO: Insulin-like growth factor binding protein-1 is independently affected by ethnicity, insulin sensitivity, and leptin in healthy glucose-tolerant young men. *J Clin Endocrinol Metab* 90:1483–1488, 2005
23. Thenola S, Martikainen A, Rahiala E, Herrgard E, Halonen P, Voutilainen R: Serum lipid concentrations and growth characteristics in 12-year-old children born small for gestational age. *Pediatr Res* 48: 623–628, 2000
24. Decsi T, Erhardt E, Marcus A, Burus I, Molnar D: Plasma lipids, phospholipid fatty acids and indices of glycaemia in 10-year old children born as small-for-gestational-age or preterm infants. *Acta Paediatr* 88:500–504, 1999
25. Odeleye OE, de Courten M, Pettit DJ, Ravussin E: Fasting hyperinsulinemia is a predictor of increased body weight gain and obesity in Pima Indian children. *Diabetes* 46:1341–1345, 1997