0021-972X/04/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 89(3):1346–1351

doi: 10.1210/jc.2003-031704

Adiponectin Levels Are Reduced in Children Born Small for Gestational Age and Are Inversely Related to Postnatal Catch-Up Growth

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Adiponectin is an adipocytokine with insulin-sensitizing and antiatherogenic properties. Reduced concentrations of adiponectin precede the onset of type 2 diabetes and the development of atherosclerosis. Our aim was to quantify adiponectin concentrations in small for gestational age (SGA) children. Fifty-one SGA children, 24 obese, and 17 short-normal children with birth weight appropriate for gestational age (short-AGA) were studied. The statures of the SGA children were corrected for their midparental height and subdivided into two groups according to their corrected height: catch-up growth group, children with corrected height of 0 z-score or greater (n = 17); and noncatch-up growth group, subjects with corrected height less than 0 z-score (n = 34). SGA children showed adiponectin levels significantly lower than short-normal children (35.2 ± 3.5 *vs.* 80.4 ± 26.6 μg/ml; $P < 0.0001$) and obese children (77.5 ± 39.4 μg/ml; $P < 0.0001$). Catch-up growth children showed adiponectin levels significantly lower than noncatch-up growth subjects (29.4 ± 10.3 *vs.* 38.1 ± 11.5 μg/ml; $P = 0.01$). Adiponectin concentrations were inversely related to height z-score, corrected stature, weight, and body mass index and were positively related to birth weight. Our results suggest that adiponectin levels are reduced in SGA children and are even lower in those with postnatal catch-up growth. Whether this finding implies a higher risk of developing type 2 diabetes and atherosclerosis remains to be established. (*J Clin Endocrinol Metab* 89: 1346–1351, 2004)

EPIDEMIOLOGICAL STUDIES HAVE revealed an association between low birth weight and the subsequent development of hyperlipidemia, insulin resistance, type 2 diabetes, and cardiovascular disease (1–3). Although several epidemiological surveys have confirmed the association between metabolic disturbances in adulthood and low birth size (4–6), few data exist in childhood. Reduced insulin sensitivity has been reported in small for gestational age (SGA) children (7–10). We have recently showed that SGA children do not have altered insulin sensitivity compared with auxologically identical AGA subjects, but show a significant reduction of glucose concentrations (11). According to previous studies in animal models, we speculated that an early phase of increased insulin sensitivity during childhood might precede the onset of insulin resistance in young adult SGA subjects (11).

Adiponectin is a 244-amino acid protein that is derived only from adipose tissue in humans (12). Paradoxically, the mRNA expression of adiponectin and its plasma level are significantly reduced in obese/diabetic mice and humans (13, 14). There is functional and genetic evidence that adiponectin plays a central role in the development of type 2 diabetes. A diabetes susceptibility locus has been mapped to human chromosome 3q27 (15), where the adiponectin gene is located. Spranger *et al.* (16) recently reported that high concentrations of adiponectin are associated with a reduced relative risk of type 2 diabetes. This finding is consistent with the observation that Pima Indians with lower adiponectin levels have increased risk of developing type 2 diabetes (17). Finally, administration of adiponectin causes glucose-lowering effects and ameliorates insulin resistance in mice (18, 19).

Most studies of the link between adiponectin and insulin resistance have been performed in rodents, nonhuman primates, and adult humans with obesity and type 2 diabetes. There is little information on circulating levels of adiponectin in children. In adolescent obese and Pima Indian children, adiponectin levels have been found to be reduced and related to obesity and insulin resistance (20, 21).

As intrauterine growth retardation is a risk factor for insulin resistance and type 2 diabetes, our aim was to quantify adiponectin concentrations in SGA children compared with those in short children born with a birth weight appropriate for gestational age (short-AGA) and with those in obese children. Furthermore, within the SGA group, we assessed the relationship between adiponectin levels and postnatal growth.

Subjects and Methods

Study population

We studied 51 children (mean age, 8.6 ± 3.5 yr; 27 females and 24 males) born small for gestational age (SGA), 17 short normal children (mean age, 10.5 ± 3.6 yr; seven females and 10 males) born appropriate for gestational age (short-AGA), and 24 obese AGA children with nor-

Abbreviations: AGA, Appropriate for gestational age; BMI, body mass index; CG, catch-up growth; CV, coefficient of variation; HOMA-IR, homeostasis assessment model for insulin resistance; IRMA, immunoradiometric assay; MPH, midparental height; NCG, noncatch-up growth; SGA, small for gestational age.

mal stature (mean age, 10.6 ± 2.8 yr; 10 females and 14 males) attending the Outpatient Growth Clinic of the Rina Balducci Center of Pediatric Endocrinology (Tor Vergata University, Rome, Italy).

SGA was defined as a birth weight less than the third percentile corrected for gestational age, AGA was defined as a birth weight above the 10th percentile according to Italian standards (22). Subjects with malformations or genetic disorders were excluded.

Short-AGA nonobese children (n = 17) were referred to our center for short stature and had normal GH peak responses (GH peak > 10 μg/liter for clonidine test and > 20 μg/liter for GHRH plus arginine test). Short-AGA children were chosen as suitable controls in that they matched SGA subjects not only for pubertal stage and body mass index (BMI), but also for height. In all children, endomysial and transglutaminase antibody testing was performed to exclude celiac disease. Free T_4 and TSH assessments were carried out to rule out hypothyroidism. Karyotype was normal in all girls. Insulin resistance variables were not tested in these children. However, all short-AGA children had normal BMI, and we have recently reported in a similar population that all insulin sensitivity-related variables were in the normal range (11).

All obese children (n = 24) had a BMI greater than 95th percentile specific for age and sex (23) and were referred to our center for ponderal excess. In all obese children, free T_4 and TSH assessments were carried out to rule out hypothyroidism. An oral glucose tolerance test was performed to rule out glucose intolerance and diabetes.

Pubertal stage was similar in the three groups (Table 1) as assessed by physical examination, ranging from stage I–III according to the criteria of Tanner stage for breast development in girls and genital development in boys (24).

The investigation was approved by the ethical committee of Tor Vergata University, and informed consent was obtained from all the parents.

Anthropometry

All children underwent anthropometric measurements using the growth standards of Tanner and Whitehouse (24). Height was expressed as the z-score for chronological age and sex according to the following formula: z-score = (x − average x)/SD, where x is the actual height, average x is the mean of the height at that age and for that sex, and SD is the SD from the mean. Midparental height (MPH), also called target height, was used as an indicator of genetic growth potential: MPH for boys (cm) = father height + (mother height + 13)/2; MPH for girls (cm) = mother height + (father height − 13)/2. Both parents of each child were measured in our clinic. Children's statures were corrected for their MPH according to the formula: corrected height (z-score) = actual height (z-score) − MPH (z-score). SGA children were subdivided into two groups according to their corrected height: catch-up growth (CG; n = 17) group, children with corrected height of 0 z-score or greater; and noncatch-up growth (NCG; n = 34) group, subjects with corrected height less than 0 z-score. In all subjects with actual or corrected height of −2 z-score or less, GH deficiency was ruled out by clonidine (100 $\mu g/m^2$, orally) or GHRH (1 μg/kg, iv) plus arginine (0.5 g/kg, iv) stimulation tests.

BMI was used as a measure of relative adiposity and was calculated according to the formula: BMI = kg/m^2 (23).

TABLE 1. Comparisons among SGA, short-AGA, and obese children

	SGA (n = 51)	Short-AGA (n = 17)	Obese (n = 24)	*P*
Age (yr)	8.6 ± 3.5	10.5 ± 3.6	10.6 ± 2.8	0.01[a] <0.005[b]
Birth weight (kg)	2.1 ± 0.4	3.0 ± 0.8	3.5 ± 0.7	<0.0001[a] <0.0001[b]
Pubertal stage	1.8 ± 1.3	1.4 ± 0.5	1.7 ± 0.7	NS[a]
Stage I	n = 42	n = 15	n = 19	
Stage II	n = 4	n = 1	n = 3	
Stage III	n = 5	n = 1	n = 2	
BMI (kg/m^2)	16.6 ± 4.1	16.1 ± 1.9	30.8 ± 5.8	NS[a] <0.0001[b]
Height (z-score)	−1.4 ± 1.3	−1.5 ± 1.4	1.0 ± 1.4	NS[a] <0.0001[b]

Values are the mean ± SD.
[a] SGA *vs.* short-AGA.
[b] SGA *vs.* obese.

Hormone and biochemical assays

Blood samples for baseline hormone assessments were collected between 0800–0900 h in fasting conditions.

Serum adiponectin was measured in the three groups of children by RIA kit (Linco Research, Inc., St. Charles, MO). The intraassay coefficient of variation (CV) was 1.8–6.2%, the interassay CV was 6.9–9.2%, and the sensitivity limit was 1.0 μg/ml.

In SGA and obese subjects, fasting insulin, fasting glucose/insulin ratio, and homeostasis assessment model for insulin resistance [HOMA-IR; fasting insulin (mU/liter) × fasting glucose (mmol/liter)/22.5] were chosen as measures of insulin sensitivity.

Serum insulin was measured by immunoradiometric assay (IRMA; RADIM, Rome, Italy). The intraassay CV was 2.2–3.9%, the interassay CV was 4.7–12.2%, and the sensitivity limit was 1.2 mU/liter. Serum GH was measured by IRMA (Diagnostic System Laboratories, Inc., Webster, TX). The intraassay CV was 3.1–5.4%, the interassay CV was 5.9–11.5%, and the sensitivity limit was 0.01 μg/liter. Serum TSH was measured by IRMA (Cambridge Life Sciences, Ely, UK). The intraassay CV was 2.0–7.7%, the interassay CV was 6.3–9.8%, and the sensitivity limit was 0.02 mU/liter. Free T_4 was measured by RIA (BYK-Sangtec Diagnostica, Dietzenbach, Germany). The intraassay CV was 2.0–4.6%, the interassay CV was 4.9–7.8%, and the sensitivity limit was 0.1 ng/dl.

Blood glucose was measured immediately by the glucose oxidase method using a glucose analyzer (YSI, Inc., Yellow Spring, OH). Plasma total and high density lipoprotein cholesterol were measured enzymatically by an automatic photometric method (Roche, Mannheim, Germany). In SGA children, plasma triglycerides were analyzed enzymatically (Roche). Low density lipoprotein cholesterol concentrations were calculated by the Friedewald-Fredrickson formula [LDL cholesterol = total cholesterol − (high density lipoprotein cholesterol + triglycerides/2.2)] (25).

Statistics

Results are reported as the mean ± SD. Differences between means were assessed using unpaired two-tailed *t* test and one-way ANOVA. After ascertaining that variables were normally distributed, the relationships among parameters were evaluated by Pearson correlation. Multiple regression and forward stepwise regression analyses were used in the selection of predictors of adiponectin concentrations. Significance was assigned for $P < 0.05$. A computer program was used for all statistical calculations (statistical software, SOLO 3.0, BMPD, Los Angeles, CA).

Results

Comparisons among SGA, short-AGA, and obese children

SGA children were significantly younger than short-AGA and obese subjects (Table 1). No significant difference in pubertal stage was found among the three groups. There was no difference in height between SGA and short-AGA children (−1.4 ± 1.3 *vs.* −1.5 ± 1.4 z-score), whereas obese children were significantly taller (1.0 ± 1.4 z-score; $P < 0.0001$).

Insulin sensitivity parameters were investigated in SGA and obese children. SGA subjects showed significantly lower values of fasting insulin (8 ± 5.4 *vs.* 19.3 ± 15 mU/liter; $P < 0.005$) and HOMA-IR (1.6 ± 1.2 *vs.* 4 ± 3.8; $P < 0.01$), and higher glucose/insulin ratio (17.9 ± 19.9 *vs.* 5.4 ± 3.3; $P = 0.02$; Table 2).

SGA children showed adiponectin levels significantly lower than short-AGA (35.2 ± 3.5 *vs.* 80.4 ± 26.6 μg/ml; $P <$

TABLE 2. Biochemical and endocrine variables in SGA and obese children

	SGA (n = 51)	Obese (n = 24)	*P*
Adiponectin (μg/ml)	35.2 ± 3.5	77.5 ± 39.4	<0.0001
Triglycerides [mg/dl (nmol/liter)]	57 ± 24.2 (0.87 ± 0.37)	97.7 ± 21.6 (1.5 ± 0.33)	<0.0001
Total cholesterol [mg/dl (mmol/liter)]	162 ± 28.4 (4.2 ± 0.7)	166.5 ± 25 (4.3 ± 0.6)	NS
HDL cholesterol [mg/dl (mmol/liter)]	53.3 ± 11.2 (1.4 ± 0.3)	46 ± 10.2 (1.2 ± 0.3)	NS
LDL cholesterol [mg/dl (mmol/liter)]	98.3 ± 23.5 (2.5 ± 0.6)	97.7 ± 21.6 (2.5 ± 0.5)	NS
Glucose [mg/dl (mmol/liter)]	79.3 ± 9.0 (4.4 ± 0.5)	73.9 ± 12.6 (4.1 ± 0.7)	NS
Insulin [mU/liter (pmol/liter)]	8.0 ± 5.4 (57.4 ± 38.7)	19.3 ± 15 (138.5 ± 107.6)	0.002
Glucose/insulin ratio	17.9 ± 19.9	5.4 ± 3.3	0.02
HOMA-IR	1.6 ± 1.2	4.0 ± 3.8	<0.01

Values are the mean ± SD. HDL, High-density lipoprotein; LDL, low-density lipoprotein.

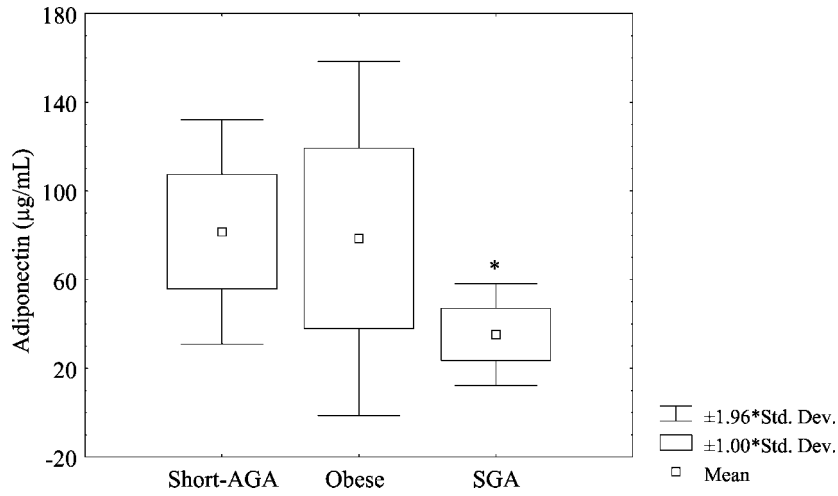


FIG. 1. Serum adiponectin levels were significantly lower in SGA than in short-AGA and obese children (*, $P < 0.0001$).

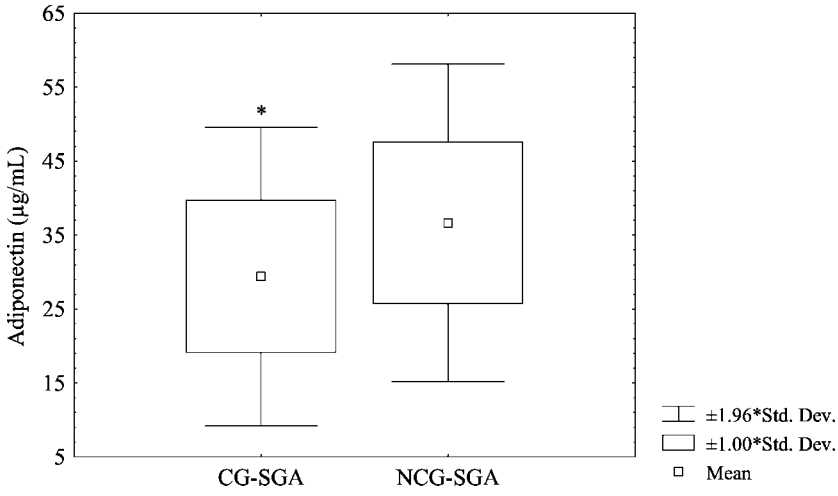


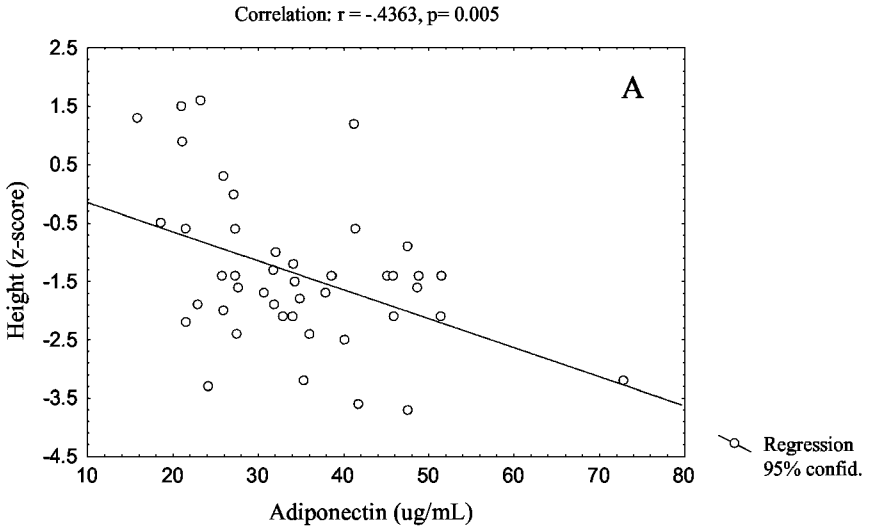
FIG. 2. Serum adiponectin levels were significantly lower in CG-SGA (SGA children with postnatal catch-up growth) than in NCG-SGA (SGA children without postnatal catch-up growth; *, $P < 0.01$).

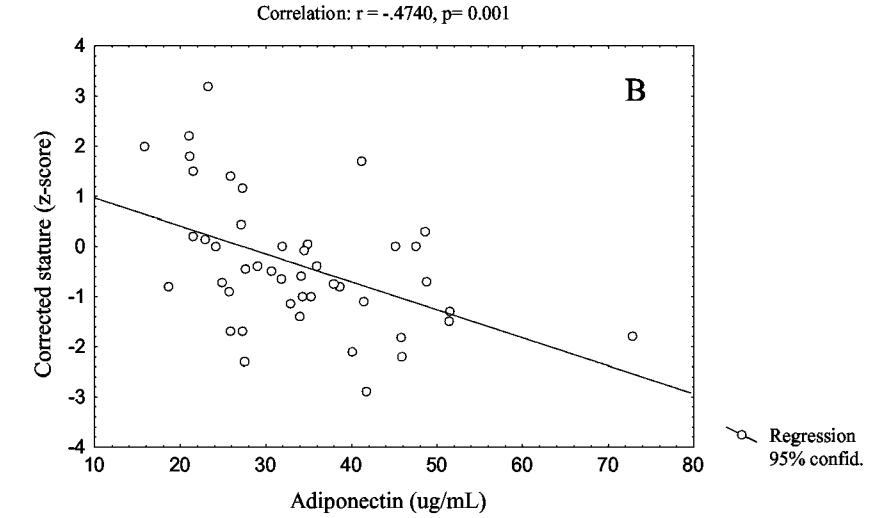
0.0001) and obese children (77.5 ± 39.4 μg/ml; $P < 0.0001$; Fig. 1). Even taking into account prepubertal children only, we found that SGA subjects (n = 42; mean adiponectin concentration, 37.2 ± 11.7 μg/ml) had adiponectin levels significantly lower than short-AGA children (n = 15; mean adiponectin concentration, 81.7 ± 23.4 μg/ml; $P < 0.001$) and obese children (n = 19; mean adiponectin concentration, 73.5 ± 37.7 μg/ml; $P < 0.001$), whereas no significant difference in adiponectin levels was observed between prepubertal short-AGA and obese children.

No significant difference in age and pubertal stage was observed between CG-SGA (mean age, 8.8 ± 3.0 yr; mean pubertal stage, 1.8 ± 1.1) and NCG-SGA (mean age, 7.8 ± 2.9 yr; mean pubertal stage, 1.4 ± 0.9).

Within the SGA group we found that CG-SGA children showed adiponectin concentrations significantly lower than NCG-SG children (29.4 ± 10.3 *vs.* 38.1 ± 11.5 μg/ml; $P = 0.01$; Fig. 2).

Finally, SGA children showed free T_4 levels significantly higher than obese children (9.4 ± 1.9 *vs.* 7.1 ± 4.1 pg/ml; $P = 0.02$), whereas no significant difference was found in TSH concentrations.





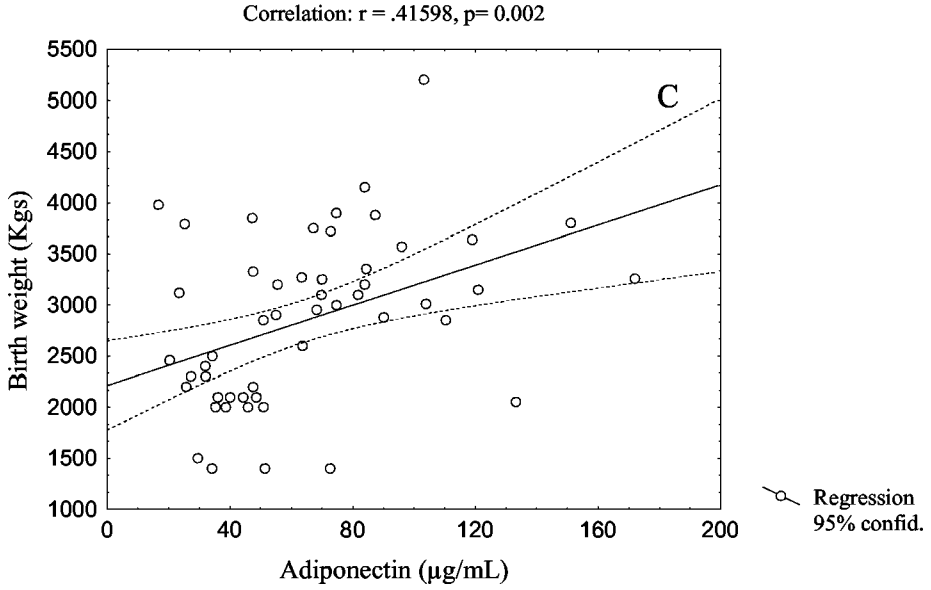


FIG. 3. Relationships between adiponectin levels (micrograms per milliliter) and height (z-score; A) and between adiponectin levels (micrograms per milliliter) and corrected stature (z-score; B) in SGA children. Relationship between adiponectin levels (micrograms per milliliter) and birth weight (kilograms) in the three groups (SGA, short-AGA, and obese children) pooled together (C).

Relationships between adiponectin levels and anthropometric and biochemical variables

In SGA children adiponectin concentrations were inversely related to birth length ($r = -0.33$; $P < 0.05$), age ($r = -0.36$; $P < 0.01$), height z-score ($r = -0.44$; $P = 0.005$; Fig. 3A), corrected stature ($r = -0.47$; $P = 0.001$; Fig. 3B), weight ($r = -0.47$; $P < 0.0005$), BMI ($r = -0.53$; $P = 0.001$), and puberty ($r = -0.42$; $P < 0.005$).

As expected, adiponectin correlated inversely with fasting insulin ($r = -0.37$; $P < 0.01$) and HOMA-IR ($r = -0.34$; $P = 0.02$) and positively with glucose/insulin ratio ($r = 0.35$; $P = 0.01$). In SGA children, stepwise regression analysis revealed that the major predictors of adiponectin levels were age ($t = -2.2$; $P = 0.03$), BMI ($t = -1.6$; $P = 0.1$), and corrected stature ($t = -1.6$; $P = 0.1$; adjusted $r^2 = 0.35$).

Likewise, in obese children, adiponectin was related to age ($r = -0.64$; $P = 0.001$), fasting insulin ($r = -0.58$; $P = 0.01$), HOMA-IR ($r = -0.64$; $P = 0.01$), and glucose/insulin ratio ($r = 0.69$; $P < 0.01$). Stepwise regression analysis revealed that the major predictors of adiponectin levels in obese subjects were age ($t = -4.9$; $P < 0.0005$) and fasting insulin ($t = -4.6$; $P < 0.0005$; adjusted $r^2 = 0.71$).

After pooling data for SGA, short-AGA, and obese children, we found a close relationship between birth weight and adiponectin levels ($r = 0.41$; $P = 0.002$; Fig. 3C).

Discussion

Several independent observations have shown a relationship between low birth weight and insulin resistance, type 2 diabetes, and cardiovascular disease in adulthood (26–31). To explain this association, the concept of programming has been introduced. Fetal adaptation to an adverse intrauterine environment (*i.e.* a reduced nutrient supply) induces an altered programming of metabolic pathways, leading to permanent metabolic changes, including reduced insulin sensitivity (32). Studies in animal models support this hypothesis, showing that nutrition in infancy or fetal life can induce lifetime effects on metabolism (33, 34).

Increasing evidence indicates that adiponectin exerts important effects on carbohydrate metabolism, improving glucose metabolism by increasing insulin sensitivity (18, 19). Furthermore, adiponectin has been reported to modulate endothelial inflammatory response (35), inhibit macrophage to foam cell transformation (36), and suppress the development of atherosclerosis *in vivo* (37). The unique properties of adiponectin prompted us to assess the concentrations of this adipocytokine in SGA children. The results of this study show, for the first time, that SGA children have a significant reduction of adiponectin levels even compared with obese subjects. This finding supports the concept that children born SGA have a predisposition to develop insulin resistance and atherosclerosis. In addition, our results suggest that the assessment of adiponectin concentrations in childhood might be helpful in identifying SGA children at higher risk of developing metabolic consequences, as recently observed in a prospective case-control study of adult subjects (16). Another potential clinical implication of our results is the theoretical therapeutic use of adiponectin in high risk SGA children. Data from lipoatrophic mice indicate that the replenishment of adiponectin might provide a novel treatment strategy for insulin resistance and type 2 diabetes (18).

As SGA children showed adiponectin levels lower than those in obese children, thus indicating a minimal effect of adiposity on adiponectin secretion at this age, it is tempting to speculate that intrauterine programming might permanently affect adiponectin secretion. Consistent with this, we found a close positive relationship between birth weight and adiponectin concentrations.

However, genetic influence cannot be entirely excluded. Hattersley *et al.* (38) suggested that genetically determined insulin resistance could result in low insulin-mediated fetal growth *in utero* as well as insulin resistance in childhood and adulthood. Dunger *et al.* (39) showed an association between common allelic variation (class I or class III) at the variable number of tandem repeat locus in the promoter region of the insulin gene and birth weight. The finding of reduced levels of adiponectin in SGA children might thus reflect an inherited predisposition to develop insulin resistance and type 2 diabetes.

The finding of a nonsignificant difference in adiponectin values between short-AGA and obese children was unexpected. It has, in fact, been reported that obese adults (40), adolescents (20), and Pima Indian children (21) have reduced adiponectin concentrations. A possible explanation for this discrepancy is that we studied, for the first time, obese children younger than those previously investigated. In support of this, the relationship between adiponectin values and nutritional status was observed in older Pima Indian children only (21).

Finally, a difference in adiponectin levels was found between CG-SGA and NCG-SGA children, the former having significantly lower concentrations. In addition, adiponectin resulted closely inversely related to both height and corrected stature. These findings are consistent with previous reports showing that postnatal catch-up growth in height and/or weight increases the risk of developing type 2 diabetes in later life (10, 41–44) and with our catch-up growth hypothesis (45).

In conclusion, our results show the presence of reduced adiponectin levels in SGA children, confirming the predisposition to develop insulin resistance and atherosclerosis. In addition, postnatal catch-up growth is associated with lower concentrations of adiponectin. Further longitudinal studies are needed to establish whether the reduced adiponectin secretion signifies a higher risk of type 2 diabetes and cardiovascular disease in adulthood.

Acknowledgments

We are particularly grateful to the nurse Luigia Merli for the excellent care given to our children during the study.

Received September 30, 2003. Accepted December 8, 2003.

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This work was supported in part by Ministero dell'Istruzione dell'Università e della Ricerca Grant COFIN 40%–2003064547.

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