Obese Children with Low Birth Weight Demonstrate Impaired β-Cell Function during Oral Glucose Tolerance Test

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Objective: Epidemiological studies have shown an association between birth weight and future risk of type 2 diabetes, with individuals born either small or large for gestational age at increased risk. We sought to investigate the influence of birth weight on the relation between insulin sensitivity and β-cell function in obese children.

Subjects and Methods: A total of 257 obese/overweight children (mean body mass index-SD score, 2.2 ± 0.3), aged 11.6 ± 2.3 yr were divided into three groups according to birth weight percentile: 44 were small for gestational age (SGA), 161 were appropriate for gestational age (AGA), and 52 were large for gestational age (LGA). Participants underwent a 3-h oral glucose tolerance test with glucose, insulin, and C-peptide measurements. Homeostasis model of assessment for insulin resistance, insulinogenic index, and disposition index were calculated to evaluate insulin sensitivity and β-cell function. Glucose and insulin area under the curve (AUC) were also considered. One-way ANOVA was used to compare the three groups.

Results: SGA and LGA subjects had higher homeostasis model of assessment for insulin resistance than AGA subjects, but they diverged when oral glucose tolerance test response was considered. Indeed, SGA subjects showed higher glucose AUC and lower insulinogenic and disposition indexes. Insulin AUC was not different between groups, but when singular time points were considered, SGA subjects had lower insulin levels at 30 min and higher insulin levels at 180 min.

Conclusions: SGA obese children fail to adequately compensate for their reduced insulin sensitivity, manifesting deficit in early insulin response and reduced disposition index that results in higher glucose AUC. Thus, SGA obese children show adverse metabolic outcomes compared to AGAs and LGAs. **(*J Clin Endocrinol Metab* 94: 4448–4452, 2009)**

Epidemiological studies have shown an independent, strong association between intrauterine growth retardation and increased risk of developing type 2 diabetes mellitus (T2DM) in adult life. In addition, a weak relationship between neonatal macrosomia and future glucose metabolism alterations has been reported, configuring a "U-shaped" association between birth weight (BW) and risk of T2DM (1).

Children born small for gestational age (SGA) are more insulin resistant compared with children born appropriate

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Abbreviations: AGA, Appropriate for gestational age; AUC, area under the curve; BMI, body mass index; BW, birth weight; DI, disposition index; HOMA-IR, homeostasis model of assessment for insulin resistance; LGA, large for gestational age; OGTT, oral glucose tolerance test; SDS, SD score; SGA, small for gestational age; T2DM, type 2 diabetes mellitus.

for gestational age (AGA) (2). It has also been suggested that fetal malnutrition resulting in low BW causes altered development of the endocrine pancreas, which in turn may lead to impaired insulin secretion in adult life (3). This model suggests that β-cell dysfunction as well as decreased insulin sensitivity may contribute to the pathophysiology of T2DM in adult life in individuals born SGA. Nevertheless, normal-weight children born SGA show, along with insulin resistance, normal β-cell function (4). In contrast, maternal diabetes, rather than increased fetal growth *per se*, may explain most of the positive association between high BW (>4 kg) and T2DM later in life, given the recognized association of both prepregnancy diabetes and gestational diabetes with macrosomia (1).

The aim of the present study was to investigate insulin sensitivity and β-cell function in obese children born SGA and large for gestational age (LGA) compared with children born AGA.

Subjects and Methods

Study population

Data obtained in obese children and adolescents referred to the Endocrinology and Diabetes Unit of Bambino Gesù Children's Hospital for obesity from January 2003 to October 2008 were used if they met the following criteria: 1) obesity established using body mass index (BMI) cutoff of the International Obesity Task Force (5); 2) absence of underlying diseases; 3) all four grandparents of Italian descent; 4) availability of data relative to gestation and birth; and 5) born at 36 wk gestation or later. Maternal diabetes (either preexisting or developed during or after the index pregnancy) was the only criterion of exclusion.

Gestational age was determined by ultrasound in the first trimester or otherwise calculated from the date of the last menses. Weight at birth was converted into percentiles for gestational age and sex, according to the Italian BW curves (6). Participants were divided into three groups on the basis of their BW percentile: SGA, BW below the 10th percentile; AGA, BW in at least the 25th percentile but below the 90th percentile; and LGA, BW in at least the 90th percentile. Written informed consent was obtained from parents before any testing procedure. The study was conducted in accordance with the Declaration of Helsinki.

Subjects were admitted to the clinic for a 1-d inpatient visit after an overnight fast. Height of patients and their parents was measured to the nearest 0.1 cm, and weight in underwear was measured to the nearest 0.1 kg. Target height was calculated as (mother's height + father's height)/2 − 6.5 for girls or + 6.5 for boys. Values of height (7) and BMI (5) were expressed as SD score (SDS). Corrected height for target height (target height SDS minus actual height SDS) was denoted as height SDS corrected. Regular catch-up growth for height at the time of the study was defined as an actual height SDS within 1.3 SD of the target height SDS (8). Physical maturation was assessed on the basis of breast development in girls and genitalia development in boys (9).

Oral glucose tolerance test (OGTT) was performed with the administration of 1.75 g of glucose solution per kilogram of body weight to a maximum of 75 g. Blood samples were drawn at −15, 0, 15, 30, 60, 90, 120, and 180 min for measurements of glucose, insulin, and C-peptide.

Calculations

Insulinogenic index, calculated as the ratio of the increment of plasma insulin to that of plasma glucose during the first 30 min of OGTT, was used to assess β-cell function. Disposition index (DI) (10), which reflects the capacity of pancreatic islets to compensate for lower insulin sensitivity, was defined as the product of insulin sensitivity index (11) and insulinogenic index. Homeostasis model of assessment for insulin resistance (HOMA-IR) was calculated as index of insulin resistance (12). The glucose and insulin area under the curve (AUC) during OGTT was calculated with the trapezoid rule.

Body composition

At least 10 d after the first inpatient visit, children's body composition was measured by dual-energy x-ray absorptiometry using Hologic QDR Delphi (Hologic Inc., Bedford, MA). Fat mass (kilograms) corrected for differences in height (fat BMI, kilograms/meter^2) and central obesity index (fat mass in truncal region divided by fat mass in lower extremity region, *i.e.* legs) were calculated.

Assays

Serum insulin and C-peptide were measured by chemiluminescence on ADVIA Centaur analyzer (both assays are two-site sandwich immunoassays using direct chemiluminescent technology) (intra- and interassay coefficients of variation, 3.3–4.6 and 2.6–5.9%; 3.7–4.1 and 1.0–3.3%, respectively); plasma glucose was measured by enzymatic method on Roche/Hitachi 904 analyzer (Roche Diagnostics, Mannheim, Germany) (intra- and interassay coefficients of variation, 0.9 and 1.8%).

Statistical analysis

A sample of 34 individuals for each group had been estimated sufficient to demonstrate a difference of 2 between the means of DI with 2.5 SD, with 90% power and a significance level of 95%.

Means and SD values were computed within BW groups, unless otherwise stated. The Kolmogorov-Smirnov goodness-of-fit test was used for determining whether sample data were likely to derive from a normal-distributed population. Insulin, C-peptide, HOMA-IR, insulinogenic index and DI were not normally distributed and were logarithmically transformed.

When looking for differences within BW categories, one-way ANOVA with three groups (SGA, AGA, LGA) and Bonferroni's *post hoc* test were carried out. Proportions were compared by χ^2 test. Stepwise multiple linear regression analysis was performed to evaluate the independent influence of BW percentile on insulinogenic index and DI. Age, gender, pubertal stage, HOMA-IR, BMI-SDS, and fat BMI were entered as covariates. Insulinogenic index and DI were the dependent variables. When DI was inserted as a dependent variable, HOMA-IR was omitted among covariates because DI is derived from an index of insulin sensitivity.

Significance level for all tests was set at $P < 0.05$. SPSS software version 13.0 (SPSS Inc., Chicago, IL) was used for all analyses.

TABLE 1. Characteristics of 257 obese children divided according to BW categories

	SGA	AGA	LGA	*P* (one-way ANOVA)
n	44	161	52	
BW (kg)	2.5 ± 0.3[a,b]	3.4 ± 0.3[b,c]	4.1 ± 0.3[a,c]	<0.001
Gestational week	39.4 ± 1.5	39.6 ± 1.3	39.5 ± 1.3	0.863
Gender (males/females)	21/23	83/78	23/29	0.636
Age (yr)	11.7 ± 2.6	11.6 ± 2.3	11.5 ± 1.9	0.881
Height (cm)	149.2 ± 13.9	152.7 ± 12.5	152.4 ± 1.8	0.275
Weight (kg)	68.5 ± 19.2	71.1 ± 19.7	72.2 ± 16.7	0.626
Height SDS corrected	−0.4 ± 1.1 (−3.6 to 1.7)	−0.8 ± 1.1 (−3.4 to 1.9)	−0.6 ± 1.0 (−2.9 to 1.6)	0.121
BMI (kg/m^2)	30.3 ± 4.9	30.0 ± 4.6	30.6 ± 3.5	0.617
BMI SDS	2.2 ± 0.4 (1.5 to 2.9)	2.2 ± 0.3 (1.3 to 3.0)	2.3 ± 0.3 (1.6 to 2.8)	0.438
Prepubertal (%)	38.6	41.6	36.5	0.791
Fat (% of total body)	40.7 ± 5.1	40.9 ± 4.5	41.0 ± 4.8	0.959
Central obesity index	1.24 ± 0.27[a,b]	1.15 ± 0.19[c]	1.14 ± 0.03[c]	0.034
Glucose AUC	14,763.2 ± 2,560.0[a]	13,634.7 ± 1,779.5	1,390.9 ± 1,834.1	0.008
Insulin AUC	9,686.7 ± 4,904.2	10,421.7 ± 7,053.1	10,908.9 ± 5,090.7	0.552
HOMA-IR	3.6 ± 1.6[a]	3.0 ± 1.8[b,c]	3.7 ± 2.2[a]	0.006
Insulinogenic index$_{0-30}$	1.3 ± 1.0[a,b]	1.9 ± 1.6[c]	2.1 ± 1.3[c]	0.007
DI$_{0-30}$	3.8 ± 2.8[a,b]	6.4 ± 4.3[c]	5.9 ± 2.5[c]	0.005

Data are expressed as percentage, mean ± SD, and (range) for variables expressed in SDS. Height SDS corrected is calculated as target height SDS minus recent height SDS. *Superscript letters* refer to comparison between individual BW groups (Bonferroni's *post hoc* test): [a] $P < 0.05$ *vs.* AGA; [b] $P < 0.05$ *vs.* LGA; [c] $P < 0.05$ *vs.* SGA.

Results

Subject characteristics

We studied 257 obese children divided into three groups according to their BW (SGA, n = 44; AGA, n = 161; LGA, n = 52). Children of the three groups were comparable for gestational weeks (range, 36–42), age, gender, height SDS corrected, pubertal stage, BMI-SDS, and fat mass. SGAs showed higher central obesity index than AGAs and LGAs ($P < 0.05$) (Table 1). Regular catch-up growth was achieved by most children; as a matter of fact, only two of 44, three of 161, and three of 52 of the SGA, AGA, and LGA groups, respectively, did not attain normal catch-up growth ($P = 0.321$).

Glucose, insulin, and C-peptide response to OGTT

SGA subjects showed higher glucose AUC during OGTT compared with AGAs ($P = 0.006$). In addition, glucose values were higher in SGA at 60 min ($P = 0.004$ *vs.* AGA), 90 min ($P = 0.011$ *vs.* AGA and 0.009 *vs.* LGA), and 180 min ($P = 0.041$ *vs.* AGA and 0.006 *vs.* LGA) (Fig. 1A).

Insulin AUC was not different between the three groups. However, SGAs showed reduced insulin level at 30 min ($P = 0.032$ and 0.002 *vs.* AGA and LGA, respectively), but higher values at 180 min ($P = 0.012$ *vs.* LGA) (Fig. 1B). Similar results were observed for C-peptide (Fig. 1C).

Insulin sensitivity and β-cell function

SGA and LGA subjects showed higher HOMA-IR (P *vs.* AGA = 0.039 and 0.034, respectively).

The insulinogenic index was lower in SGA ($P = 0.032$ *vs.* AGA and 0.007 *vs.* LGA), as was the DI compared with AGA ($P = 0.007$) and LGA ($P = 0.013$) (Table 1).

When these indexes were examined separately in prepubertal children and in subjects of Tanner stages II–V, a lower DI in SGA was still observed in both subgroups (Tanner I, $P = 0.031$; Tanner II–V, $P = 0.048$). Insulinogenic index also was lower in SGA of both subgroups, reaching a significant figure only in pubertal children ($P = 0.003$).

When subjects were divided according to gender, SGA again showed lower insulinogenic index and DI, but significance was only achieved in boys ($P < 0.05$).

Determinants of insulin secretion

In multivariate analysis, the insulinogenic index was positively influenced by BW percentile ($P = 0.003$; R^2 for model = 0.3) and, as expected, positively by HOMA-IR ($P < 0.001$; R^2 for model = 0.1). The DI was positively and independently determined only by BW ($P = 0.003$; R^2 for model = 0.1).

Discussion

Our data confirm that obese children born SGA and LGA have higher HOMA-IR than obese children born AGA, but also show that they have a different response to OGTT. Indeed, SGA individuals manifest impaired early insulin response (reduced insulinogenic index) and higher glucose values during OGTT (glucose AUC). Thus,

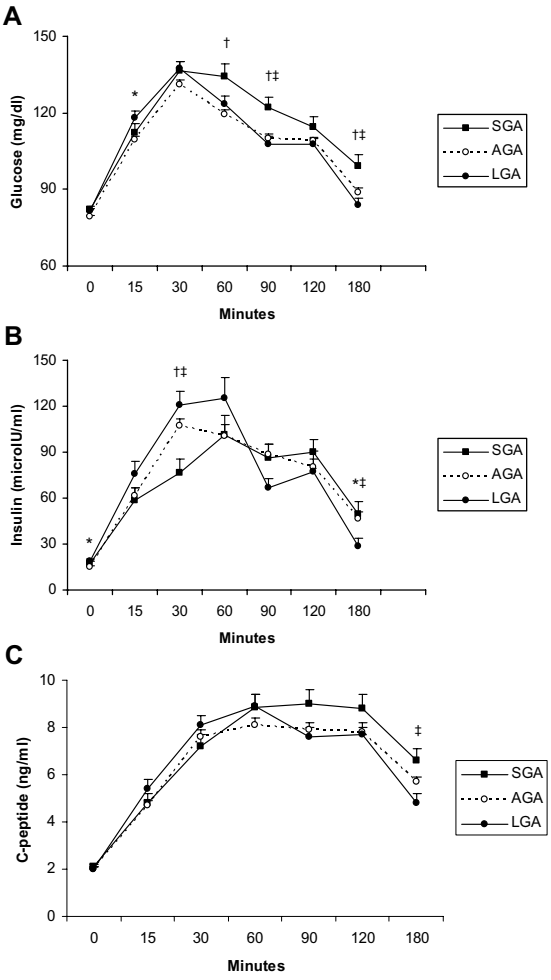

FIG. 1. Plasma glucose, insulin, and C-peptide response during OGTT. Data are expressed as mean + SE. *, $P < 0.05$ for AGA *vs.* LGA; †, $P < 0.05$ for SGA *vs.* AGA; ‡, $P < 0.05$ for SGA *vs.* LGA.

whereas LGA individuals can adequately compensate for insulin resistance by increasing insulin secretion, obese children born SGA seem to fail to do so (reduced DI). In multivariate analysis, low BW negatively influences both insulinogenic index and DI.

Because almost all subjects of this investigation have achieved regular catch-up growth for height with no difference among SGAs and AGAs/LGAs at the time of the study, the reduced insulin sensitivity observed in the obese SGA group may be due to a recent catch-up growth.

In general, reduced insulin sensitivity in subjects born SGA can be observed since childhood, whereas reduced insulin secretion has been reported in adulthood and not in all studies (2). To the best of our knowledge, there is one study describing impaired β-cell function in SGA individuals in their childhood that associated low postnatal weight gain with a reduced insulinogenic index (13).

In the present study, obese subjects born SGA show a reduction of early-phase insulin secretion with high insulin levels in the late phase, a pattern usually found in adult individuals at high risk of developing T2DM (14). Because early-phase insulin secretion is important in priming the liver and inhibiting endogenous glucose production during OGTT or a meal (15), this defect may reasonably account for the highest glucose levels we observed in OGTT late phases of obese SGA. In keeping with this view, the DI, considered the best predictor of future T2DM in adults (15), was reduced in SGA. Of note, alteration of DI was already visible in prepubertal children when the confounding effect of physiological pubertal decrease of insulin sensitivity is not at work.

Furthermore, in accordance with current literature data (2), when the distribution of body fat was considered, SGA showed a higher amount of central fat depot. One can hypothesize that, given the demonstrated role of enlarged sc abdominal adipocyte size in the pathogenesis of T2DM (16), abdominal fat composition could take part in determining higher glucose values in SGA.

Our findings on better metabolic profile in obese LGAs are in partial agreement with a study reporting higher insulin sensitivity index, lower plasma free fatty acids, and insulin levels during OGTT in high BW obese children (17).

Some limits of our study must be taken into account. First, we did not study insulin sensitivity with the gold standard of the euglycemic clamp. Second, cause-and-effect relationships cannot be drawn because of the cross-sectional study design. Moreover, Arslanian and colleagues (18) recently reported poor reproducibility of glucose tolerance status defined by OGTT in obese youth, although they also found that subjects with discordant OGTT results (two OGTT were performed within 1–25 d) show lower DI and higher insulin resistance.

Despite these limitations, our investigation provides some robust observational data on relationship between insulin secretion and insulin sensitivity in obese children according to their BW by showing that Caucasian obese children born SGA display the worst metabolic profile compared with AGAs and LGAs.

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References

1. **Whincup PH, Kaye SJ, Owen CG, Huxley R, Cook DG, Anazawa S, Barrett-Connor E, Bhargava SK, Birgisdottir BE, Carlsson S, de Rooij SR, Dyck RF, Eriksson JG, Falkner B, Fall C, Forsén T, Grill V, Gudnason V, Hulman S, Hyppönen E, Jeffreys M, Lawlor DA, Leon DA, Minami J, Mishra G, Osmond C, Power C, Rich-Edwards JW, Roseboom TJ, Sachdev HS, Syddall H, Thorsdottir I, Vanhala M, Wadsworth M, Yarbrough DE** 2008 Birth weight and risk of type 2 diabetes: a systematic review. JAMA 300:2886–2897
2. **Saenger P, Czernichow P, Hughes I, Reiter EO** 2007 Small for gestational age: short stature and beyond. Endocr Rev 28:219–251
3. **Phillips DI** 1998 Birth weight and the future development of diabetes: a review of the evidence. Diabetes Care 21(Suppl 2):B150–B155
4. **Veening MA, van Weissenbruch MM, Heine RJ, Delemarre-van de Waal HA** 2003 B-cell capacity and insulin sensitivity in prepubertal children born small for gestational age. Influence of body size during childhood. Diabetes 52:1756–1760
5. **Cole TJ, Bellizzi MC, Flegal KM, Dietz WH** 2000 Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 320:1240–1243
6. **Gagliardi L, Macagno F, Pedrotti D, Coraiola M, Furlan R, Agostinis L, Milani S** 1999 Standard antropometrici neonatali prodotti dalla task-force della Società Italiana di Neonatologia e basati su una popolazione italiana nord-orientale. Riv Ital Pediatr 25:159–169
7. **Cacciari E, Milani S, Balsamo A, Spada E, Bona G, Cavallo L, Cerutti F, Gargantini L, Greggio N, Tonini G, Cicognani A** 2006 Italian cross-sectional growth charts (2 to 20 yr). J Endocrinol Invest 29:581–593
8. **Boukes FS, Merkx JAM, Rikken B, Huisman J** 1988 Tracing, tracking, and diagnostics in general practice and criteria for referral. In: De Muinch Ueizer-Schrama SMPF, ed. Diagnostics short stature in childhood. Alphen aen den Rijn, The Netherlands: Van Zulden Communications
9. **Tanner JM** 1981 Growth and maturation during adolescence. Nutr Rev 39:43–55
10. **Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP** 1993 Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 42:1663–1672
11. **Matsuda M, DeFronzo RA** 1999 Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470
12. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
13. **Crowther NJ, Cameron N, Trusler J, Toman M, Norris SA, Gray IP** 2008 Influence of catch-up growth on glucose tolerance and β-cell function in 7-year-old children: results from the birth to twenty study. Pediatrics 121:e1715–e1722
14. **Abdul-Ghani MA, Tripathy D, DeFronzo RA** 2006 Contribution of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 29:1130–1139
15. **Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M** 2007 What is the best predictor of future type 2 diabetes? Diabetes Care 30: 1544–1548
16. **Weyer C, Foley JE, Bogardus C, Tataranni PA, Pratley RE** 2000 Enlarged subcutaneous abdominal adipocyte size, but not obesity itself, predicts type II diabetes independent of insulin resistance. Diabetologia 43:1498–1506
17. **Bouhours-Nouet N, Dufresne S, de Casson FB, Mathieu E, Douay O, Gatelais F, Rouleau S, Coutant R** 2008 High birth weight and early postnatal weight gain protect obese children and adolescents from truncal adiposity and insulin resistance: metabolically healthy but obese subjects? Diabetes Care 31:1031–1036
18. **Libman IM, Barinas-Mitchell E, Bartucci A, Robertson R, Arslanian S** 2008 Reproducibility of the oral glucose tolerance test in overweight children. J Clin Endocrinol Metab 93:4231–4237