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)
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 z 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/meter²) 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 σ, 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 χ² 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.
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; R² for model = 0.3) and, as expected, positively by HOMA-IR (P < 0.001; R² for model = 0.1). The DI was positively and independently determined only by BW (P = 0.003; R² 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,
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 children when the confounding effect of physiological pubertal growth was 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 subcutaneous 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.

Acknowledgments

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