Early Development of Visceral Fat Excess after Spontaneous Catch-Up Growth in Children with Low Birth Weight

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Context: The sequence of prenatal growth restraint and infantile catch-up of weight is by the age of 4 yr associated with hyperinsulinemic adiposity. We studied whether the adiposity of post-catch-up children born small for gestational age (SGA) is further amplified between age 4 and 6 yr and whether visceral fat excess has already emerged by the age of 6 yr.

Setting: The study took place at a university hospital.

Study Population and Design: A longitudinal cohort (age 2–6 yr) of 22 children born appropriate for gestational age (AGA) and 29 born SGA were studied. Auxological, endocrine, metabolic, and body composition (by absorptiometry) assessments were made at 2, 4, and 6 yr, and visceral fat was assessed (by magnetic resonance imaging) at 6 yr.

Main Outcomes: Outcome measures included fasting glucose, insulin, IGF-I, neutrophil to lymphocyte ratio, lean mass, and total, abdominal, and visceral fat mass.

Results: Between ages 4–6 yr, the relative adiposity of SGA children was further amplified. Between ages 2–6 yr, SGA children gained more total and abdominal fat and raised their insulin, IGF-I, and neutrophil to lymphocyte ratio more than did AGA children (all \( P \leq 0.0001 \)). At age 6 yr, the average amount of visceral fat was in SGA children more than 50% higher than in AGA children (\( P < 0.005 \)). The 0- to 2-yr increment in weight Z-score together with the 2- to 6-yr increment in fasting insulin accounted for 62% of visceral fat variability at age 6 yr.

Conclusion: The amount of visceral fat is in post-catch-up SGA children excessive by the age of 6 yr. In populations at risk for type 2 diabetes or metabolic syndrome after fetal growth restraint, the time window for early intervention may have to be advanced into prepubertal childhood. (J Clin Endocrinol Metab 93: 925–928, 2008)
(at age 2, 4, and 6 yr) and of body composition assessments by absorptiometry (at age 2, 4, and 6 yr) and by magnetic resonance imaging (at age 6 yr).

Inclusion criteria have been described (4), in brief: 1) birth at Hospital Sant Joan de Déu, Barcelona, after a term pregnancy (37–42 wk); 2) birth weight for gestational age either AGA (~1 to +1 SD) or SGA (~<−2 SD). Exclusion criteria were evidence for syndromatic, chromosomal, or infectious etiology of low birth weight, gestational diabetes, hypothyroidism, urogenital tract anomalies, systemic disease, or acute illness (4). All SGA children had developed spontaneous catch-up growth and were growing along a percentile appropriate for mid-parental height.

Consecutive study protocols were approved by the Institutional Review Board of Barcelona University Hospital. Informed consent was given by the parents.

**Auxology and assays**

Birth weight and gestational age were obtained from hospital records to derive birth weight Z-scores (4). Weight was in childhood measured in the fasting state (4). Insulin and IGF-I were measured by immunochemiluminescence (IMMULITE 2000; Diagnostic Products Corp., Los Angeles, CA). The detection limit for insulin was 2.0 μU/ml; below this limit, values were assigned as 1.9 μU/ml. The detection limit for IGF-I was 2.5 ng/ml; insulin and IGF-I intra- and interassay coefficients of variation (CV) were less than 10%.

**Body composition and abdominal fat partitioning**

Body composition was assessed by dual-energy x-ray absorptiometry with a Lunar Prodigy coupled to Lunar software (version 3.4.3/S; Lunar Corp., Madison, WI) (4). CV for scanning precision are 2.0 and 2.6% for fat and lean body mass, with an intra-individual CV for abdominal fat of 0.7%. Fat mass, lean mass, and abdominal fat were assessed; body composition was adjusted for height, according to Wells and Cole (5).

Subcutaneous and visceral adipose tissue areas in the abdominal region were assessed only at age 6 yr by magnetic resonance imaging (MRI) using a multiple-slice MRI 1.5 Tesla scan (Signa LX Echo Speed Plus Excite; General Electric, Milwaukee, WI). The children were positioned within a torso-array device placed overlaying the abdomen; sedation was not required. Axial T1-weighted images were then obtained through the abdomen and pelvis, using a 400-cm field of view, with the following imaging parameters: 6-mm slice thickness, repetition time of 360 msec, time to echo 21 msec, two excitations, 90-degree flip angle, matrix 256 × 224, bandwidth 8.33. Images were imported into the ADW 4.0 GE software package.

Subcutaneous and visceral adipose tissue areas were measured by fitting a spline curve to points on the border of the sc and visceral regions, selected by the same operator (blinded to the children’ birth weight). Nonfat regions within the visceral region were also outlined with a spline fit and subtracted from the total visceral region. The visceral fat region was subdivided into retroperitoneal and ip areas using the ascending and descending colon, the psoas muscles on each side of the spine, and the top of the vessels above the vertebral as guides for the spline fit. VAT area was calculated by subtracting the organ areas from the ip area (6). The same operator conducted all scans, and one radiologist processed all images. Images from a randomly selected subset of subjects (n = 10) were processed again by an independent radiologist, with α-reliability estimates of more than 0.90 (Cronbach’s α internal consistency analysis).

**Statistics**

Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL). Differences between AGA and SGA children for rates of change from age 2–6 yr were tested by analysis of covariance. Multiple stepwise regression models were used to identify independent contributions to visceral fat at age 6 yr. Before comparing the subgroups, skewed data were log-transformed into normal distributions.

**Results**

Table 1 summarizes the longitudinal changes identified in AGA and SGA children between ages 2 and 6 yr. Figure 1 highlights that SGA children increase their values for circulating insulin, IGF-I, and neutrophil to lymphocyte ratio (N/L) more than AGA children between ages 2 and 6 yr and that SGA children gain more total and abdominal fat.

Significant independent contributions to visceral fat at age 6 yr were the change in weight Z-score between birth and age

| TABLE 1. Longitudinal results in AGA (n = 22) and SGA (n = 29) children from ages 2–6 yr |
|-----------------------------------------|-----------------|-----------------|
|                                       | 2 ± 0.1 yr      | 4 ± 0.1 yr      | 6 ± 0.1 yr      | 2 ± 0.1 yr      | 4 ± 0.1 yr      | 6 ± 0.1 yr      |
| Height (cm)                            | 87 ± 1          | 102 ± 1         | 115 ± 1         | 85 ± 1          | 100 ± 1         | 113 ± 2         |
| Weight (kg)                            | 12.3 ± 0.3      | 16.2 ± 0.4      | 20.2 ± 0.5      | 11.4 ± 0.5      | 15.7 ± 0.6      | 21.2 ± 1.0      |
| BMI (kg/m²)                            | 16.3 ± 0.2      | 15.6 ± 0.2      | 15.4 ± 0.3      | 15.7 ± 0.3      | 15.7 ± 0.3      | 16.4 ± 0.5      |
| Glucose (mg/dl)                        | 82 ± 2          | 84 ± 2          | 86 ± 3          | 79 ± 1          | 89 ± 2          | 89 ± 1          |
| Insulin (μU/ml)                        | 3.2 ± 0.3       | 3.2 ± 0.3       | 3.4 ± 0.3       | 2.6 ± 0.2       | 5.6 ± 0.6       | 7.0 ± 0.6       |
| N/L                                    | 1.0 ± 0.1       | 1.1 ± 0.1       | 1.1 ± 0.1       | 0.6 ± 0.1       | 1.4 ± 0.1       | 1.5 ± 0.1       |
| IGF-I (mg/dl)                          | 83 ± 4          | 130 ± 6         | 124 ± 6         | 66 ± 5          | 121 ± 8         | 165 ± 9         |
| Body composition by DXA               |                |                |                |                |                |                |
| Lean mass (kg)                         | 9.8 ± 0.3       | 12.4 ± 0.3      | 15.2 ± 0.3      | 8.9 ± 0.3       | 11.2 ± 0.3      | 14.1 ± 0.5      |
| Fat mass (kg)                          | 2.2 ± 0.2       | 2.8 ± 0.2       | 3.7 ± 0.3       | 2.0 ± 0.2       | 3.6 ± 0.4       | 5.5 ± 0.6       |
| Fat mass (%)                           | 18.2 ± 1.0      | 18.1 ± 0.9      | 19.5 ± 1.1      | 17.3 ± 1.2      | 23.0 ± 1.4      | 26.6 ± 1.7      |
| Abdominal fat mass (kg)                | 0.6 ± 0.1       | 0.8 ± 0.1       | 1.1 ± 0.1       | 0.6 ± 0.1       | 1.2 ± 0.1       | 1.9 ± 0.2       |
| Abdominal fat by MRI                   | 51 ± 3          |                |                | 71 ± 9          |                |                |
| Total abdominal fat (cm²)              |                | 51 ± 3          |                | 71 ± 9          |                |                |
| Subcutaneous fat (cm²)                 | 32 ± 2          |                |                | 41 ± 7          |                |                |
| Visceral fat (cm²)                     | 19 ± 1          |                |                | 30 ± 3          |                |                |

Birth weights were 3.3 ± 0.1 kg for AGA children and 2.2 ± 0.1 kg for SGA children. All subjects completed all assessments at all time points, including an abdominal MRI study at age 6 yr. Values are mean ± SEM. DXA, Dual-energy x-ray absorptiometry.

*P ≤ 0.05; *P ≤ 0.005 for differences between groups by Student t test.

*P ≤ 0.01; **P ≤ 0.001 for difference in rate of changes between groups by two-way (time and group) repeated-measures ANOVA.
2 yr ($\beta = 0.53; P < 0.0001$) and the change in fasting insulin between age 2 and 6 yr ($\beta = 0.40; P < 0.0001$). Together, these two factors explained 62% of visceral fat variance at the age of 6 yr.

**Discussion**

There is a pathway that leads from growth restraint in prenatal life toward metabolic syndrome and type 2 diabetes in later life (2, 3). Early markers along this pathway appear to be rapid weight gain after birth and incipient insulin resistance by the age of 1 yr (7). Between ages 2 and 4 yr, insulin resistance increases in post-catch-up SGA children and starts to be accompanied by low-grade inflammation and central adiposity (4). Here, we disclosed that in post-catch-up SGA children, total and abdominal adiposity further increases between ages 4 and 6 yr and that visceral fat excess is already present at the age of 6 yr.

Our finding that visceral fat excess emerges early in post-catch-up SGA children aligns well with the experimental evidence that total and visceral adiposity appears early in lambs (by 6 weeks of age) after a controlled sequence of fetal growth restraint and neonatal catch-up (8). In that ovine model, enhanced insulin action on free fatty acid metabolism in neonatal life is thought to participate in the observed increase of visceral fat (9). Visceral adipocytes have a high lipolytic capacity that seems to be partly due to decreased sensitivity to the anti-lipolytic actions of insulin (10), resulting in an increased release of fatty acids into the portal circulation and subsequently into the liver. However, the cause-and-effect nature of the relationships between insulin secretion/action and fat distribution remains controversial (11). Associations between fasting insulin levels and visceral fat have been reported in adults, obese adolescents, and prepubertal children (12–15). In longitudinal studies, the increment of visceral fat during childhood is closely related to the increment in circulating insulin and is independent of parallel changes in sc fat (13).

In conclusion, visceral fat excess is in post-catch-up SGA children already present at the age of 6 yr. This finding implies that in populations at risk for type 2 diabetes or metabolic syndrome after fetal growth restraint, the time window for early intervention may have to be advanced into prepubertal childhood.

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