Diabetologia (2005) 48: 2609–2614
DOI 10.1007/s00125-005-0036-z

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Longitudinal changes in insulin sensitivity and secretion from birth to age three years in small- and appropriate-for-gestational-age children

Received: 2 June 2005 / Accepted: 12 September 2005 / Published online: 8 November 2005

Abstract *Aims/hypothesis:* Insulin resistance and type 2 diabetes risk in human subjects who were small-for-gestational-age (SGA) at birth may be a consequence of rapid early postnatal weight gain. *Materials and methods:* We prospectively studied early changes in fasting insulin sensitivity and insulin secretion, assessed by a short intravenous glucose tolerance test that was conducted several times from birth to 3 years of age in 55 SGA (birthweight below fifth percentile) newborns and in 13 newborns with a birthweight appropriate for gestational age (AGA). *Results:* Most SGA infants showed postnatal upward weight centile crossing and by 3 years were similar in size to AGA infants. SGA infants had lower pre-feed insulin levels at postnatal age 48 h than AGA infants (median 34.4 vs 59.7 pmol/l, $p<0.05$), but by the age of 3 years they had higher fasting insulin levels (median 38.9 vs 23.8 pmol/l, $p<0.005$), which were related to rate of weight gain between 0 and 3 years ($r=0.47$, $p=0.0003$). First-phase insulin secretion did not differ between SGA and AGA infants, but SGA infants had a lower glucose disposition index (beta cell compensation) (median 235 vs 501 min $mmol^{-1}$ l^{-1}, $p=0.02$), which persisted after allowing for postnatal weight gain ($p=0.009$). *Conclusions/interpretation:* SGA infants showed a marked transition from lower pre-feed insulin and increased insulin sensitivity at birth to insulin resistance over the first 3 years of life. This transition was related to rapid postnatal weight gain, which could indicate a propensity to central fat deposition. The additional observation of reduced compensatory beta cell secretion underlines the need for long-term surveillance of glucose homeostasis in all SGA subjects, whether or not they show postnatal catch-up growth.

Keywords Birthweight · Catch-up growth · Disposition index · Human · Insulin secretion · Insulin sensitivity

Abbreviations AGA: appropriate for gestational age · AIR_g: incremental insulin area under for glucose 0–10 min · ALSPAC: Avon Longitudinal Study of Pregnancy and Childhood · HOMA-IR: homeostasis model assessment of insulin resistance · SGA: small for gestational age

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Introduction

Birth size that is small for gestational age (SGA) is associated with short adult stature [1] and increased risk of type 2 diabetes [2], cardiovascular disease [3] and insulin resistance [4]. Recent data indicate that most of these consequences are also related to rapid postnatal patterns of weight gain [5, 6]. Body fat mass and fat distribution are important determinants of insulin sensitivity, and associations between smaller size at birth and increased risks of insulin resistance are often evident only after allowing for current adiposity [7].

In young adults insulin sensitivity is decreased in SGA subjects compared with subjects whose birth size was appropriate for gestational age (AGA), in spite of a similar BMI [4]. Hence, it has been suggested that a combination of both pre- and postnatal factors may determine insulin sensitivity in SGA infants. Most SGA infants display postnatal upward weight centile crossing or catch-up growth [1]. In some populations this may lead to higher childhood weight and central fat distribution [8].

We recently reported that insulin sensitivity and secretion in 1-year-old SGA infants were closely related to patterns of postnatal weight gain. At age 1, increased fasting insulin levels, an indicator of insulin resistance, were associated with greater postnatal weight gain and larger current BMI, whereas insulin secretion was more closely related to early gains in length [9]. We have continued to follow this birth cohort up to the third year of life in order to further explore the early development of insulin resistance and insulin secretion, as markers of future risk of type 2 diabetes.

Subjects and methods

Study protocol

During the first year of life, 85 SGA and 23 AGA children attended the clinic for anthropometric evaluation and a short IVGTT; these numbers decreased to 66 SGA and 20 AGA during the second year and to 55 SGA and 13 AGA during the third year of the evaluation. Data on body size and insulin levels at birth and at age 1 year did not differ significantly between subjects who completed the 3-year follow-up and those who did not attend at 3 years.

Fifty-five SGA infants, defined as having a birthweight below the fifth percentile (corresponding to −1.65 SD) for gestational age using the Chilean birthweight reference [10], and 13 AGA infants (birthweight above the fifth percentile) completed participation in the study. Subjects were recruited at birth from the neonatal units of Hospital San Borja Arriarán and Hospital Sótero del Río, and subsequently completed follow-up to the third year of life at the Pediatric Endocrine Unit, Institute of Maternal and Child Research, University of Chile. All infants had a gestational age between 37 and 41 weeks and during the second day of life underwent a screening clinical evaluation to exclude those with significant medical, neurological or genetic conditions. All infants were exclusively breast-fed for a mean of 3.7 months; there were no differences between those born SGA or AGA. Thereafter, they received standard formula and solid meals as recommended by the American Academy of Pediatrics. No infants were taking any medication that could interfere with growth or appetite. A complete record of parental, pregnancy and perinatal data was completed at entry.

The study protocol was approved by the San Borja Arriarán Hospital Institutional Review Board. All parents or guardians of the participants gave written informed consent.

Measurements

All children had weight and length measured at birth, and at ages 1, 2 and 3 years by one nurse (A. Avila). Supine length was measured using a firm box with a fixed headboard and a movable footboard with the feet placed per-

Table 1 Anthropometric and hormonal data in small-for-gestational-age (SGA) and appropriate-for-gestational-age (AGA) infants at birth and 1 and 3 years

	SGA (n=55)	AGA (n=13)
Weight at birth (SDS)	−2.07±0.08[a]	0.76±0.30
Weight at 1 year (SDS)	−0.72±0.14[a]	0.20±0.31
Weight at 3 years (SDS)	−0.03±0.17	0.39±0.30
Change in weight from 1 to 3 years (SDS)	0.71±0.13[b]	0.20±0.14
Length at birth (SDS)	−1.64±0.12[a]	0.15±0.21
Length at 1 year (SDS)	−0.84±0.11[b]	0.33±0.30
Length at 3 years (SDS)	−0.60±0.13	−0.35±0.25
Change in length from 1 to 3 years (SDS)	0.26±0.09	−0.09±0.21
Ponderal index at birth	24.7±0.2[a]	27.8±0.5
BMI at 1 year (kg/m^2)	17.0±0.2[b]	18.1±0.4
BMI at 3 years (kg/m^2)	16.2±0.2	16.7±0.3
Fasting insulin at 48 h (pmol/l)	34.4 (21.9–51.4)[b]	59.7 (37.5–84.4)
Fasting insulin at 1 year (pmol/l)	19.8 (11.8–29.0)	19.1 (10.5–27.7)
Fasting insulin at 3 years (pmol/l)	38.9 (31.3–46.8)[a]	23.8 (14.2–41.2)
HOMA-IR at 48 h ([pmol/l] × [mmol/l])	5.2 (3.1–8.3)[b]	9.6 (5.6–11.3)
HOMA-IR at 1 year ([pmol/l] × [mmol/l])	4.2 (2.4–7.1)	3.8 (2.2–6.5)
HOMA-IR at 3 years ([pmol/l] × [mmol/l])	8.5 (6.5–11.0)[a]	4.9 (2.8–8.8)
Glucose at 48 h (mmol/l)	3.4 (2.8–4.0)[a]	3.8 (3.5–4.3)
Fasting glucose at 1 year (mmol/l)	4.8 (4.5–5.1)	4.7 (4.5–5.5)
Fasting glucose at 3 years (mmol/l)	4.8 (4.6–5.0)	4.4 (4.3–5.0)
Insulin secretion at 1 year ([pmol l^{-1}] × min)	1571 (682–2386)	883 (630–2769)
Insulin secretion at 3 years ([pmol l^{-1}] × min)	2062 (1494–2847)	1496 (850–3243)
Disposition index at 1 year ([min mmol^{-1}] × l)	377 (176–548)	238 (190–743)
Disposition index at 3 years ([min mmol^{-1}] × l)	235 (153–311)[a]	501 (256–683)

Data are mean±SE or median (interquartile range)
[a]p<0.01, [b]p<0.05, SGA vs AGA
SDS, SD score

pendicular to the plane determined by the supine length of the infant. Weight was measured using a manual scale with a 10-g graduation (Seca, Quickmedical, Snoqualme, WA, USA).

Forty-eight hours after birth, a pre-feeding 3-ml blood sample was obtained for determination of glucose, insulin and other markers of insulin sensitivity and secretion, as previously reported [11]. At 1 and 3 years of age, a short IVGTT was performed after an overnight fast (mean duration of fast, 9 h). Two venous access lines were established in contralateral antecubital veins. Glucose (25% dextrose solution) was administered at a dose of 0.5 g/kg (maximum 35 g) by continuous infusion over 3 min, according to a protocol recommended by National Diabetes Data Group for a short IVGTT. Blood samples were obtained at −5, 0, 1, 3, 5 and 10 min (where 0 is the start of glucose infusion) for determination of glucose and insulin levels. Glucose was measured immediately, whereas samples for insulin were kept on ice and centrifuged within 30 min, and sera were frozen at −20°C.

Assays

Blood glucose concentration was determined using a commercial glucometer (Accutrend Sensor Comfort; Roche Diagnostics. Basel, Switzerland), which yields values 8±5% (mean±SD) higher than standard enzymatic methods with a correlation coefficient of 0.987 for glycaemia between 2.2 and 8.0 mmol/l.

Serum insulin was measured using a commercial radioimmunoassay from Diagnostic System Laboratories (Webster, TX, USA). This assay has a cross-reactivity of 27.5% with proinsulin and 25% with insulin-32, 33. The sensitivity of this assay was 5.6 pmol/l. Intra-assay and interassay coefficients of variation were 3.8 and 4.7%, respectively.

Calculations and analysis

Weights and lengths at birth and at ages 1 and 3 years were converted to SD scores in order to adjust for chronological age and sex using the National Center for Health Statistics (NCHS) growth reference, which has been shown to be applicable to the Chilean population [12]. BMI was calculated at age 1 and 3 years (weight/length^2).

Insulin resistance was estimated using the homeostasis model (HOMA-IR) using the formula (insulin [pmol/l]×glucose [mmol/l]/22.5) [13]. HOMA-IR values showed extremely high correlation with fasting insulin levels (r=0.96, p<0.0001). Results of analyses using HOMA-IR were therefore nearly identical to those using fasting insulin levels. First-phase insulin secretion during the short IVGTT was expressed as the incremental insulin area under the curve for glucose 0–10 min (AIR_g), calculated using the trapezoidal rule ([pmol l^{-1}]×min). In order to account for the modulating effect of insulin sensitivity on the beta cell, the glucose disposition index was calculated as (insulin secretion [AIR_g]/HOMA-IR) ([min $mmol^{-1}$]×l) [14].

Results are expressed as mean±SEM. Differences between groups were assessed by ANOVA for normally distributed variables, and by non-parametric tests (Mann–Whitney *U*-test or Kruskall–Wallis test) for non-normally distributed variables (fasting insulin, and leptin). In order to examine the relationships between continuous variables, non-normally distributed variables were transformed to normal distributions by calculating logarithms. Univariate correlations were performed and Pearson's correlation coefficients (r) are

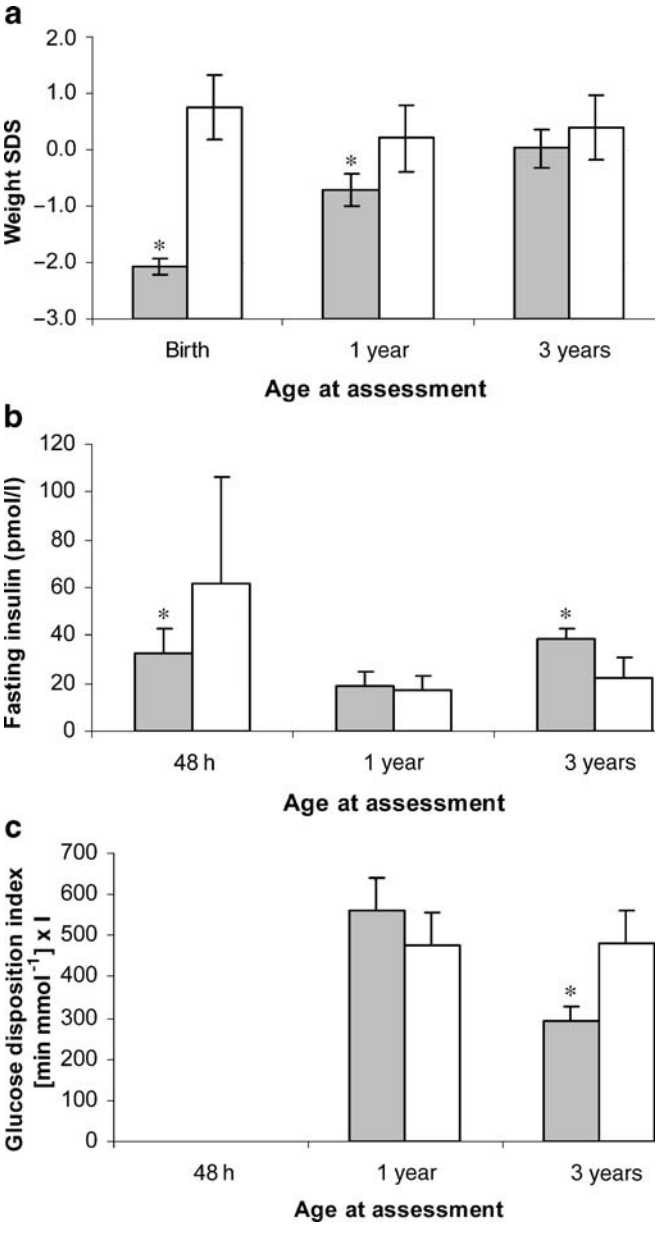

Fig. 1 Longitudinal measures of (**a**) weight SD score (SDS), (**b**) fasting insulin levels and (**c**) glucose disposition index from birth to 3 years in small-for-gestational age (SGA; n=55; *shaded bars*) and appropriate-for-gestational-age (AGA; n=13; *open bars*) infants. Means±95% CI are shown for weight SD scores, and geometric means +95% CI for fasting insulin and glucose disposition index. *p<0.05 for SGA vs AGA. At the age of 1 year, fasting insulin levels were only higher in SGA infants who showed weight catch-up compared with other infants (p<0.05 [9])

displayed. All statistics were run on SPSS 10.0 for Windows, and $p<0.05$ was considered to be significant.

Results

Compared with the AGA controls, SGA infants were significantly lighter and shorter at birth, and they continued to show significant gains in weight SD score throughout the 3 years of follow-up (Table 1, Fig. 1). In contrast to the time of birth and at 1 year of age, SGA infants were no longer significantly smaller than AGA infants by the age of 3 years (Table 1).

As previously reported for the complete cohort [11], at age 48 h the SGA infants had lower insulin levels (median 34.4 vs 59.7 pmol/l, $p=0.03$; Table 1) than the AGA infants. In contrast, at age 3 years, the SGA infants had higher fasting insulin levels (median 38.9 vs 23.8 pmol/l, $p=0.005$; Fig. 1b) compared with AGA infants. Similarly, SGA infants had higher HOMA-IR levels at 3 years (median 8.5 vs 4.9 pmol/l×mmol/l; $p=0.007$; Table 1), and this was independent of current body weight ($p=0.009$) or BMI ($p=0.01$). In a multiple regression analysis, the strongest determinant of fasting insulin at age 3 years was the rate of weight gain between birth and 3 years ($r=0.47$, $p=0.0003$; Fig. 2), with no further significant contribution of birthweight or current BMI.

First-phase insulin secretion (AIR_g) at age 3 years did not differ between SGA and AGA infants (Table 1), and was positively related to postnatal weight gain from birth to 3 years ($r=0.42$, $p=0.003$) and to fasting insulin level ($r=0.45$, $p=0.002$). The glucose disposition index, which accounts for the modulating effect of insulin sensitivity on the beta cell, was lower in SGA infants at age 3 years than in AGA infants (median 235 vs 501[min $mmol^{-1}$]×l, $p=0.02$; Table 1). In a multiple regression model, the glucose disposition index was positively related to birthweight ($p=0.009$) and rate of postnatal weight gain ($p=0.03$; Table 2).

Table 2 Multiple regression model showing the of determinants of the glucose disposition index (a marker of beta cell compensatory insulin secretion) at age 3 years in SGA and AGA children

Variable	Regression coefficient	*p*-value
Birthweight	0.36	$p=0.009$
Postnatal weight gain	0.31	$p=0.03$
Sex	−0.12	$p=0.34$

Discussion

This study presents unique longitudinal data on the development of insulin resistance and insulin secretion in term SGA and AGA infants from birth to age 3 years. We have previously reported that SGA infants have lower insulin levels at around the time of birth than AGA infants [11], but by the age of 1 year SGA infants, who showed catch-up weight gain (gain in weight SD score, >0.67), had higher fasting insulin levels and insulin resistance [9]. We now show that gains in weight SD score, or upward weight centile crossing, continued to the age of 3 years in SGA infants, and their insulin resistance also continued to progress during this period. By age 3 there were no differences in weight or BMI between the two groups and insulin resistance in SGA infants was related to rapid weight gain during infancy.

In many population studies, reduced fetal growth has been reported to be a risk factor for insulin resistance and type 2 diabetes [2, 4, 9, 15–17]. In particular, subjects who were small or thin at birth but subsequently developed obesity in childhood or in adulthood have the highest risk of developing insulin resistance [9, 15–17]. Smaller infants

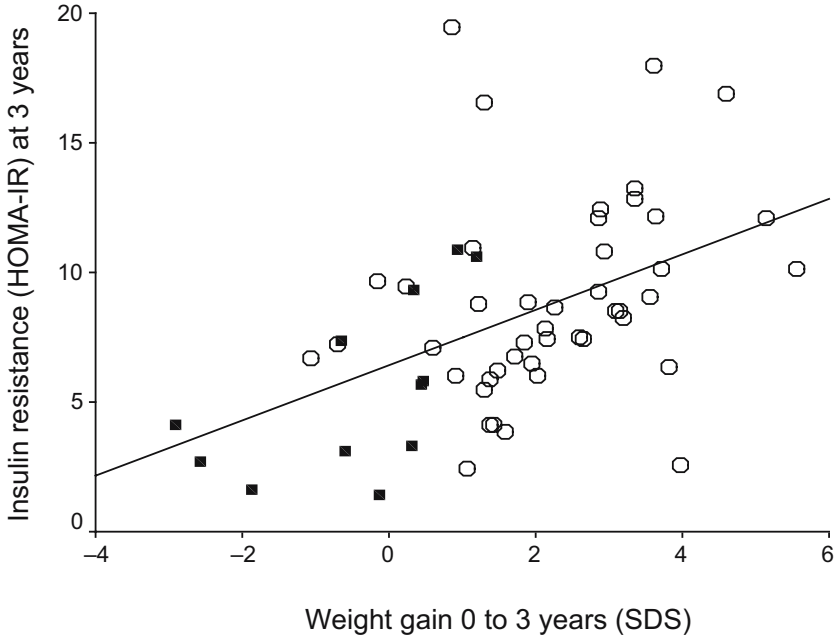

Fig. 2 Fasting insulin resistance (HOMA IR, [pmol/1] × [mmol/1]) at age 3 years related to rate of weight gain between 0 and 3 years in infants with normal birthweight (AGA, *filled-squares*) and low birthweight (SGA, *open symbols*). Regression for total population: $r=0.47$, $p=0.0003$ SDS, SD score

at birth are more likely to show faster postnatal weight gain. Such rapid catch-up growth may be initiated as a compensatory mechanism following in utero growth restraint; however, longer-term follow-up indicates that such early growth patterns are predictive of childhood and later obesity [8, 18].

In our study, the majority of SGA infants (48/55, 87%) showed postnatal catch-up weight gain between birth and age 3 years (as defined by gain in weight SD score >0.67), and rate of weight gain during this period was the most important predictor of insulin resistance at age 3 years. Rapid early weight gain could influence a more central or visceral distribution of body fat, rather than subcutaneous fat. Many studies have shown that fat distribution influences metabolism independently of the effects of total body fat stores [19, 20]. In the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) cohort, low birthweight followed by rapid infancy weight gain was associated with increased risk of obesity and larger waist circumference [8]. Similar findings have been observed in US cohorts [21] and recently in a Swedish longitudinal study [22].

Studies to assess the contribution of visceral fat to insulin resistance have shown that the omental adipose bed is a depot that drains directly into the portal vein, and is particularly associated with insulin resistance, probably as a result of the effects of increased non-esterified fatty acid flux to the liver [23]. Recent evidence suggests that not only non-esterified fatty acids but other adipokines are directly or indirectly involved in this process, and these may be dysregulated in SGA adipose tissue [24]. In this prospective cohort study, we recently showed that levels of the adipokine adiponectin declined from the first to the second year of life, and the rate of fall was related to age and greater weight gain in SGA infants [25]. In that analysis, adiponectin levels were unrelated to the degree of insulin resistance. However, in addition to adiponectin's effects on promoting insulin sensitivity, insulin may stimulate adiponectin secretion, and the resulting cross-sectional associations between insulin and adiponectin levels may also be influenced by body fat and fat distribution [26]. Greater understanding of adipokine regulation could inform future treatment strategies to control disease states associated with increased adiposity, an important outcome in view of the growing worldwide epidemic of obesity [20, 27].

The relationship between insulin sensitivity and compensatory insulin secretion is critical to the risk of the development of glucose intolerance [14]. In our study, SGA infants at age 3 years had a reduced disposition index, which may indicate an early deficiency in their compensatory first-phase insulin response. In a separate study of 850 children from the ALSPAC cohort aged 8 years, we showed that whereas the rate of early postnatal weight gain was an important determinant of obesity and insulin resistance, compensatory insulin secretion for the degree of insulin resistance was related to height gain and IGF-I levels [7]. In the present cohort, we reported earlier that insulin secretion at age 1 year was related to height gain [9], and it is possible that insulin secretion in response to growth-hormone-related insulin resistance could promote catch-up growth, particularly in length [28]. However, we could not confirm those associations with insulin secretion at age 3 years, perhaps because of the reduced sample size.

In conclusion, the development of insulin resistance in children born SGA occurs during early postnatal life, concurrently with their rapid early postnatal catch-up weight gain. It is speculated from recent studies that these associations may be linked to increased central fat deposition. By the age of 3 years the relationship between insulin sensitivity and insulin secretion may be perturbed in some of these SGA infants, as reflected in a reduced glucose disposition index. These findings have important implications for the reported association between size at birth, early weight gain and the risk of type 2 diabetes.

Acknowledgements This study was supported by Fondo Nacional de Desarrollo Cientifico y Techologico (National Fund for Scientific and Technological Research; Fondecyt; grant no.: N 1000939). D. B. Dunger is supported by the Wellcome Trust and the Juvenile Diabetes Research Foundation.

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