

Stephanie Putzker*, Susanne Bechtold-Dalla Pozza, Karl Kugler, Hans P. Schwarz and Walter Bonfig

Insulin resistance in young adults born small for gestational age (SGA)

Abstract

Objective: This work aimed to assess glucose metabolism and insulin sensitivity in young adults born small for gestational age (SGA) as well as to measure the body composition and adipocytokines of these subjects.

Methods: A total of 108 out of 342 SGA-born participants were invited for reexamination from the former Bavarian Longitudinal Study (BLS), in which 7505 risk-newborns of the years 1985 to 1986 were prospectively followed. Of these, 76 (34 female/42 male) participants at the age of 19.7 ± 0.5 years were enrolled. Clinical examination and oral glucose tolerance testing (oGTT) was performed with assessment of insulin resistance indices, HbA1c, body mass index (BMI), adipocytokines, and body composition by bioimpedance analysis (BIA).

Results: A total of 25 out of 76 (32.9%) patients had abnormal fasting and/or glucose-stimulated insulin levels. Glucose values measured during oGTT showed no abnormalities, except one participant who had impaired glucose tolerance. Homeostasis model assessment insulin resistance index (HOMA-IR) was 1.92 ± 4.2 , and insulin sensitivity index by Matsuda ($ISI_{Matsuda}$) showed mean values of 7.85 ± 4.49 . HOMA-IR > 2.5 was found in 8 patients (10.5%), and 20 patients (26.3%) had an $ISI_{Matsuda} < 5$, both interpreted as insulin resistant. No alterations of adipocytokines were found. Fat mass (FM) measured by BIA was within the normal range for both genders and correlated significantly with BMI ($r = 0.465$, $p < 0.001$) and leptin ($r = 0.668$, $p < 0.001$), but not with adiponectin. Insulin resistance correlated with change in weight-for-height Z-score during the first 3 months of age, indicating that weight gain during that early phase might be a risk factor for the development of insulin resistance in children born SGA.

Conclusions: A high percentage of insulin-resistant subjects were reconfirmed in a large German cohort of young adults born SGA. Therefore, regular screening for disturbances in glucose metabolism is recommended in these subjects.

Keywords: body composition; insulin resistance; oral glucose tolerance test; small for gestational age (SGA).

***Corresponding author: Stephanie Putzker**, Division of Pediatric Endocrinology and Diabetology, University Children's Hospital, Lindwurmstrasse 4, D-80337 Munich, Germany, Phone: +49-89-5160-2811, Fax: +49-89-5610-3921, E-mail: sputzker@med.uni-muenchen.de

Susanne Bechtold-Dalla Pozza and Hans P. Schwarz: Division of Pediatric Endocrinology and Diabetology, University Children's Hospital, Munich, Germany

Karl Kugler: Division of Pediatric Neurology, University Children's Hospital, Munich, Germany

Walter Bonfig: Division of Pediatric Endocrinology, Department of Pediatrics, Technical University, Munich, Germany

Introduction

An association between low birth weight and impaired insulin sensitivity with the development of diseases such as type 2 diabetes, cardiovascular diseases or the metabolic syndrome later in life has been demonstrated in several studies (1–5). Hales et al. already hypothesized that undernutrition in utero could impair insulin secretion later in life and contribute to the risk of type 2 diabetes (6, 7). However, the underlying mechanisms and the relationship between low birth weight and impaired glucose tolerance or type 2 diabetes still remain unclear. One starting point to explore this further could be the known alteration of the development of adipose tissue, which could possibly explain the development of insulin resistance later in adulthood. Recent data show an influence of the insulin-like growth factor (IGF) system on insulin resistance (8). Until now, less is known about insulin sensitivity in young adults born small for gestational age (SGA). In a case-control study of young adults born with intrauterine growth retardation (IUGR) normal glucose tolerance, but higher plasma insulin and proinsulin concentrations during an oral glucose tolerance test (oGTT) were found in a French cohort (9). The objective of the current study was to assess glucose metabolism and insulin sensitivity in young adults born SGA, as well as to measure body composition and adipocytokines of these subjects.

Patients

A total of 108 out of 342 SGA-born participants of the former Bavarian Longitudinal Study (BLS) (10, 11) were selected for re-evaluation based on their postal code next to 100 km to the study center. BLS examined 7505 risk-newborns of the years 1985 to 1986 in a geographically defined region of south Bavaria who required admission to one of 19 children's hospitals of this region within the first 10 days of life. These children were followed over 8 years for follow-up examinations, in order to assess cognitive and developmental status until 1994 (10).

After inviting the now grown-up probands by letter for a re-evaluation, a personal contact by telephone call was performed in the years 2004 to 2006. Patients were included if their birth weight was below the 10th percentile, in reference to Largo's reference data (12). Exclusion criteria were manifest endocrine or metabolic disorders, chromosomal aberrations or syndromatic background, mental or physical handicap, or treatment with growth hormone. All patients were able to fill in questionnaires and to give written informed consent. Of the initial recruits, 76 [34 female/42 male] young adults with a mean age of 19.7 ± 0.5 years were enrolled. The baseline characteristics of the whole group are given in Table 1.

Materials and methods

After a clinical examination with assessment of adult height, weight, head circumference, waist-hip ratio and blood pressure, a 2 h oral glucose tolerance test (oGTT) with a 75 g glucose load (Dextro O.G.T.[®], Roche Diagnostics, Germany) was performed after an overnight fasting of at least 8 h. Participants also brought along their data of height and weight at the ages of 1, 2, 4, and 5 years using their "preventive

care" growth charts. During oGTT, venous blood samples were collected at four time points (0', 30', 60' and 120' after oral glucose load). Blood glucose was measured at all time points by a B-Glucose analyzer (Hemocue[®], Germany) based on the glucose dehydrogenase method (13, 14). Insulin concentrations were quantified using radio immuno assay (RIA; Adaltis[®], Italy). Fasting insulin level was considered to be abnormal if the value exceeded $28 \mu\text{U/mL}$ for the time points 60' and 120', after glucose load cut-off values were determined at 88 and $57 \mu\text{U/mL}$, respectively (15). Insulin sensitivity indices were calculated based on homeostasis model assessment insulin resistance index (HOMA-IR) (16) given by the following: (fasting insulin [mU/L] × fasting glucose [mmol/L])/22.5, and Matsuda's index (ISI_{Matsuda}) (17) was computed based on the formula expressed as: $(10000 / (\text{sqrt}[\text{fasting insulin [mU/L]} \times \text{fasting glucose [mg/dL]} \times \text{mean insulin value 60' and 120' [mg/dL]} \times \text{mean glucose value 60' and 120' [mg/dL]]))$.

HbA1c was measured using an immunological turbidimetric assay (Olympus[®], Germany, Olympus AU2700 Analyzer). Adiponectin was measured using enzyme-linked immunosorbent assay (ELISA; BioVendor GmbH[®], Germany). Leptin was analyzed by RIA (Linco[®], now Milipore[®], USA). Body composition was assessed using bio-electrical impedance analysis (BIA; DataInput[®], Germany) (18, 19). Body mass index (BMI) was calculated using the following formula: (weight [kg]/height [m]²), BMI-SDS was calculated based on German reference data (20). IGF-I and IGF-BP3 were measured by immuno assay (Siemens[®], Germany). Weight-for-height Z-scores were calculated using an anthropometric calculator (WHO Anthro, version 3.2.2, January 2011, Switzerland). Correlations were calculated using Spearman's correlation coefficient. Groups were tested on differences using the Mann-Whitney U-test. All data were stored in MS Access[®] 2007 and statistically analyzed in SPSS[®] (11–13). The study protocol was approved by the local Ethic Committee. The authors confirm that they have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects.

Results

A total of 76 (34 female/42 male) of 108 (70.4%) invited young adults born SGA at an age of 19.7 ± 0.5 years

Table 1 Main characteristics of the study population.

	Whole group (n=76)					Insulin-resistant group (n=25)				
	n	Mean	SD	Minimum	Maximum	n	Mean	SD	Minimum	Maximum
Chronological age, year	76	19.7	0.5	18.8	20.9	25	19.2	0.6	18.0	20.0
Height, cm	76	170.3	8.2	149.5	187.7	25	167.3 ^a	7.3	149.5	181.9
Height SDS	76	-0.25	0.92	-2.60	1.90	25	-0.3	0.9	-2.6	1.0
Weight, kg	76	61.3	10.6	40.5	88.3	25	61.9	10.7	41.6	77.7
BMI, kg/m ²	76	21.1	3.1	15.9	29.2	25	22.1	3.5	16.7	29.2
Waist-hip-ratio	76	0.83	0.06	0.7	1.06	25	0.84	0.06	0.70	0.95
Gestational age, weeks	72	35.4	4.15	26	42	18	34.8	3.5	28	40
ISI, Matsuda	76	7.9	4.5	0.2	26.5	25	4.2 ^b	1.8	0.2	7.2
HOMA-IR	76	1.9	4.2	0.5	37.9	25	3.4 ^b	7.2	0.6	37.9
HbA1c, %	76	5.3	0.3	4.7	5.8	25	5.3	0.2	4.7	5.7
HbA1c, mmol/mol	76	34.5	2.5	27.9	39.9	25	35.3	2.7	27.9	39.9

^ap<0.05, ^bp<0.001.

participated in our study. Birth weight was 1.97 ± 0.7 kg ($n=76$), birth length was 44.0 ± 5.2 cm ($n=66$). Weight-for-height Z-scores were -2.1 ± 1.2 at birth ($n=34$, due to lack of reference values with birth length <45 cm), -0.2 ± 1.6 at the age of 3 months ($n=61$), -0.9 ± 1.3 at the age of 6 months ($n=61$), and -0.4 ± 1.1 at the age of 12 months ($n=61$). BMI-SDS at birth ranged from -4.6 to 1.1 (mean value: -2.1 ± 1.3) and from -3.4 to 3.04 at the age of 12 months ($n=61$) (mean value: -0.3 ± 1.2). Adult height was -0.25 ± 0.92 SDS (170.3 ± 8.2 cm), two patients missed their parental target height range. All participants were Tanner stage 5. Actual BMI ranged from 15.9 to 29.2 kg/m², with a mean value of 21.1 ± 3.1 kg/m².

Adipocytokines and body composition

Adiponectin and leptin values showed normal results for the whole group. Adiponectin SDS ranged from -1.70 to 3.30 , with a mean value of -0.19 ± 1.03 SDS (absolute mean: 11.32 ± 5.07 µg/mL), leptin was 9.67 ± 10.60 ng/mL (absolute values). There were no significant differences between female and male patients. Correlations are given in Table 2. Fat mass (FM) values measured by BIA were within the normal range for both genders with values of $19.6 \pm 7.69\%$, which correlated significantly with BMI ($r=0.465$, $p<0.001$) and leptin ($r=0.668$, $p<0.001$), but not with birth weight or adiponectin.

Glucose metabolism

Glucose concentrations measured during oGTT showed no abnormalities, except one participant who had impaired glucose tolerance with a 2 h-value of 174 mg/dL. None had developed diabetes. Out of 76 patients, 25 (32.9%) had abnormal fasting and/or glucose-stimulated insulin levels. Insulin sensitivity measured by HOMA-IR and insulin sensitivity index by Matsuda ($ISI_{Matsuda}$) showed mean values of 1.92 ± 4.2 and 7.85 ± 4.49 , respectively. HOMA-IR >2.5 was found in 8 patients (10.5%), and 20 patients (26.3%) had an $ISI_{Matsuda} <5$, both interpreted as insulin resistant. BMI

correlated significantly with HOMA-IR ($r=0.258$, $p=0.024$) but not with $ISI_{Matsuda}$ ($r=-0.193$, $p=0.094$). Insulin concentrations for time points $0'$ and $120'$ correlated significantly with BMI ($r=0.316$, $p=0.003$; $r=0.243$, $p=0.017$). IGF-I levels correlated significantly with HOMA-IR ($r=0.283$, $p=0.013$) and with fasting insulin ($r=0.257$, $p=0.025$).

A positive correlation was also found between IGF-BP3 and insulin concentrations for the time points $0'$ ($r=0.254$, $p=0.027$), $30'$ ($r=0.326$, $p=0.005$), and $60'$ ($r=0.279$, $p=0.014$) after glucose load. A negative correlation was found for $ISI_{Matsuda}$ ($r=-0.234$, $p=0.041$). There were no statistically significant correlations between BMI, birth weight and glucose or insulin concentrations. However, there was a significant correlation between change in weight-for-height-Z score during the first 3 months of life and the insulin value at $60'$ after glucose load ($n=32$, $r=0.404$, $p=0.015$), as well as with $ISI_{Matsuda}$ ($n=32$, $r=-0.426$, $p=0.022$). Serum cortisol values correlated significantly inverse with $ISI_{Matsuda}$ ($n=76$, $r=-0.257$, $p=0.025$) and with waist-hip-ratio ($n=76$, $r=-0.249$, $p=0.030$). The values for glucose and insulin during oGTT are given in Table 4, while those for $ISI_{Matsuda}$, HOMA-IR, and HbA1c are given in Table 1. The values did not significantly differ between males and females.

Subgroup analysis (25 patients with insulin resistance)

The group of 25 participants with insulin resistance consisted of 15 female and 10 male patients. Actual BMI was not significantly higher than that of the insulin-sensitive probands as well as FM measured by BIA. Waist-hip-ratio was 0.84 ± 0.06 ($n=25$), and was not significantly lower than in the insulin-sensitive group ($n=51$; 0.83 ± 0.06). Furthermore, birth weights and birth lengths were not different from the rest of the cohort. Weight-for-height Z-scores were -2.7 ± 1.0 at birth ($n=9$, due to lack of reference values for length <45 cm), 0.1 ± 2.0 at the age of 3 months ($n=18$), -0.7 ± 0.7 at the age of 6 months ($n=17$), and -0.5 ± 0.9 at the age of 12 months ($n=18$). Auxological data during the first 12 months of life are given in Table 3.

Table 2 Correlations between adipocytokines and BMI and insulin concentration during oGTT.

	Adiponectin	Leptin	Birth weight	Birth length
Actual BMI	$r=-0.241$, $p=0.036$	$r=0.374$, $p=0.001$	n.s.	n.s.
Insulin $0'$	n.s.	$r=0.355$, $p=0.002$	n.s.	n.s.
Insulin $30'$	$r=-0.334$, $p=0.004$	$r=0.314$, $p=0.006$	n.s.	n.s.
Insulin $60'$	n.s.	n.s.	n.s.	n.s.
Insulin $120'$	$r=-0.249$, $p=0.030$	$r=0.251$, $p=0.029$	n.s.	n.s.

Table 3 Longitudinal auxologic data during the first 12 months of life.

Age, month	Whole group (n=76)			Insulin-resistant group (n=25)			Insulin-sensitive group (n=51)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
0									
Birth weight, kg	69	2.0	0.7	21	1.9	0.6	48	2.03	0.7
Birth length, cm	66	44.0	5.2	21	44.1	4.5	45	44.0	5.6
BMI, kg/m ²	66	9.8	1.8	21	9.9	1.6	45	9.8	1.7
Weight-for-height SDS	34	-2.1	1.2	9	-2.7	1.0	23	-1.9	1.3
3									
Weight, kg	61	5.0	1.0	18	5.1	1.0	43	5.0	1.1
Length, cm	61	56.6	5.3	18	55.8	7.8	43	57.2	3.7
BMI, kg/m ²	61	16.0	6.4	18	17.9	11.5	43	15.2	1.9
Weight-for-height SDS	61	-0.2	1.6	18	0.1	2.0	43	-0.4	1.3
6									
Weight, kg	61	6.8	0.9	17	6.8	0.6	44	6.8	1.0
Length, cm	61	65.4	3.5	17	65.3	2.2	44	65.4	4.0
BMI, kg/m ²	61	15.9	1.6	17	16.0	1.0	44	15.8	2.0
Weight-for-height SDS	61	-0.9	1.3	17	-0.7	0.7	44	-0.9	1.6
12									
Weight, kg	61	8.6	1.0	21	8.5	0.6	40	8.6	1.1
Length, cm	61	72.3	2.1	21	72.3	1.8	40	72.4	2.2
BMI, kg/m ²	61	16.3	1.6	21	16.2	1.2	40	16.4	1.7
Weight-for-height SDS	61	-0.4	1.1	21	-0.5	0.9	40	16.4	1.7
BMI-SDS	61	-0.3	1.2	21	-0.4	1.0	40	-0.3	1.3

All weight-for-height Z-scores did not differ significantly from those of the insulin-sensitive participants; however, change in weight-for-height Z-score during the first 3 months of life showed a significant positive correlation with insulin concentrations for time point 60' during oGTT (n=9, r=0.7, p=0.036), thereby indicating that weight gain during the first 3 months of age might be a predictor of later insulin resistance and therefore is a critical phase in early infancy.

No significant difference in BMI-SDS at birth and BMI-SDS at 12 months of age in comparison to the insulin-sensitive group was found. During the first year of life, no difference in catch-up weight gain was found between the insulin-resistant and the insulin-sensitive group.

Insulin concentrations during oGTT of each insulin-resistant patient are shown in Figure 1. As can be seen, insulin concentrations during oGTT were significantly lower in the insulin-sensitive group than in the

Table 4 Glucose metabolism: oGTT data.

	0'				60'				120'			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
Whole group (n=76)												
Glucose, mg/dL	78.2	11.8	48	112	99.9	29.9	28	203	84.1	23.2	41	174
Glucose, mmol/L	4.3	0.7	2.7	6.2	5.5	1.7	1.6	11.3	4.7	1.3	2.3	9.7
Insulin, μ U/mL	9.4	17.6	3.0	158.3	69.6	79.7	11.5	642.9	55.9	82.4	6.5	672.5
Insulin-resistant group (n=25)												
Glucose, mg/dL	77.7	13.1	55.0	107.0	109.4 ^a	30.8	50.0	203.0	92.9 ^a	25.7	53.0	174.0
Glucose, mmol/L	4.3	0.7	3.1	5.9	6.1 ^a	1.7	2.8	11.3	5.2 ^a	1.4	2.9	9.7
Insulin, μ U/mL	15.9 ^a	29.9	3.4	158.3	119.9 ^a	122.1	33.0	642.9	114.2 ^a	125.0	35.4	672.5
Insulin-sensitive group (n=51)												
Glucose, mg/dL	78.6	11.6	48.0	112	93.3	27.8	38	161	80.2	21.3	41	133
Glucose, mmol/L	4.4	0.6	2.7	6.2	5.2	1.5	1.6	8.9	4.4	1.2	2.3	7.4
Insulin, μ U/mL	6.2	2.3	3.0	11.4	41.6	17.5	11.5	77.0	27.1	12.4	6.5	52.0

^ap<0.001.

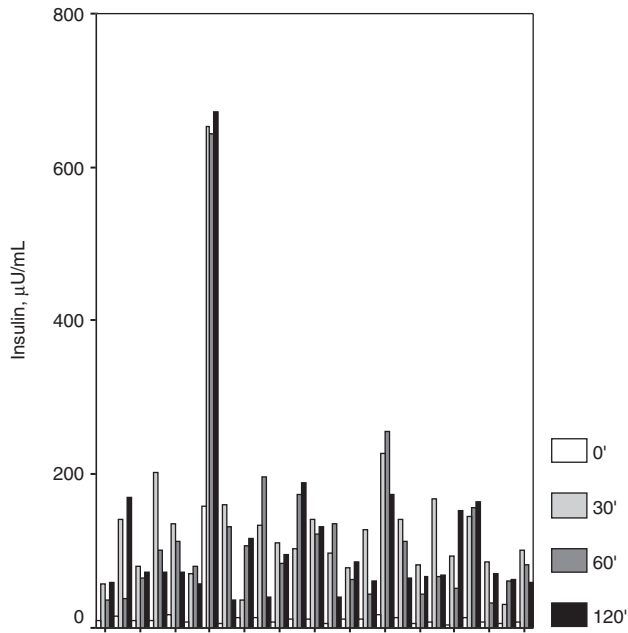


Figure 1 Insulin concentrations in the insulin-resistant subgroup.

insulin-resistant group ($p < 0.001$) (Figure 2). HOMA-IR and $ISI_{Matsuda}$ differed significantly between the two groups ($p < 0.001$ for both parameters; Table 1), but no difference was found in HbA1c. A significant difference between adiponectin concentrations of the insulin-resistant and the insulin-sensitive groups (adiponectin: $p = 0.013$, leptin: $p = 0.054$) was found.

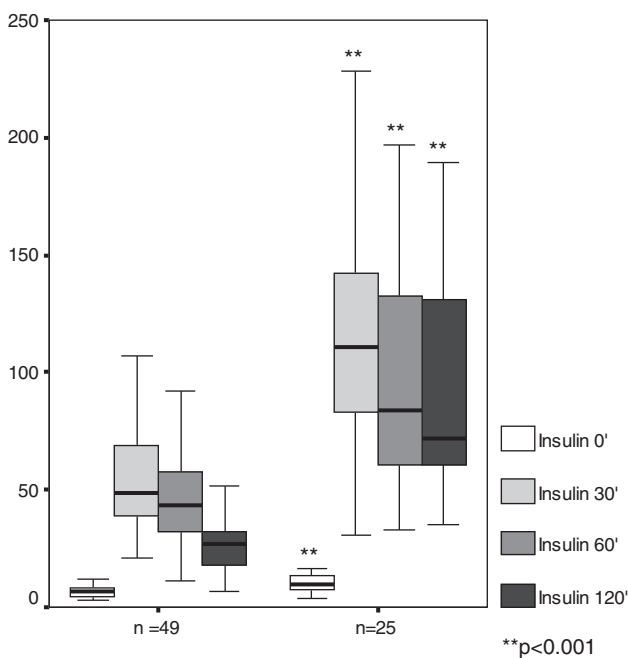


Figure 2 Comparison of insulin concentrations: insulin-sensitive vs. insulin-resistant subgroup.

IGF-BP3 values differed between the two groups, although this was not statistically significant ($p = 0.069$). The correlations of IGF-I concentrations with fasting glucose were only weak and statistically not significant. No correlation was found between IGF-I and HOMA-IR or $ISI_{Matsuda}$.

Discussion

Our results showed a high percentage of insulin-resistant subjects among healthy young adults born SGA, thus supporting the hypothesis of predisposition for later disturbed glucose metabolism in these patients. Nearly a third of the cohort had at least one abnormal insulin value during oGTT, confirming the data of Jaquet et al. (9). None had developed diabetes. No recommendations for the management of young adults born SGA have been established until now. However, the results showed that screening for disturbances in glucose metabolism seemed to be reasonable. While using the HOMA-IR with the established cut-off value of 2.5 for insulin resistance, only 8 patients of the subgroup would have been identified with abnormal insulin values. $ISI_{Matsuda}$ seems to be more sensitive when the aim is to prevent type 2 diabetes and cardiovascular disease as its consequence. A total of 20 of the 25 patients with abnormal insulin values would have been identified using $ISI_{Matsuda}$ with a cut-off value of ≤ 5 . Meanwhile, oGTT without measurement of insulin concentrations would also not have detected subjects, who are probably predisposed for type 2 diabetes.

It is well established that adipose tissue plays a key role in developing insulin resistance. However, in our cohort, BMI did not influence insulin or glucose values, possibly confirming the data of Arends et al. (21) and supporting the hypothesis of fetal programming. Genetic predisposition for insulin resistance in these subjects by possible interaction between the *INS* VNTR locus and insulin resistance in subjects born SGA has been proposed by Vu-Hong et al. (22). In addition, Leunissen et al. (23) showed that FM accumulation in early adulthood seemed to determine insulin sensitivity. In our cohort, FM was distributed normally in all subjects. Only change in weight-for-height Z-score within the first 3 months of life correlated significantly with insulin values for the time point 60' and even with $ISI_{Matsuda}$ for the whole group, and seemed to be a marker for insulin resistance in our cohort.

This effect could not be found after 1 year of life any more, but confirms the former data of Lévy-Marchal

et al. (24), Leunissen et al. (25), and Fabricius-Bjerre et al. (26). Neither actual BMI nor BMI in early childhood showed association with insulin sensitivity indices, thus supporting the theory of Meas et al. (27) that the progression in BMI and fetal programming may either be independent effects or due to the relatively small number of individuals. Birth weight also did not have an influence on insulin sensitivity in our cohort. This finding is in contrast to the findings of several authors, such as Newsome et al. (28), who found an inverse relationship of low birth weight with glucose and insulin concentrations. The influence of the IGF system on insulin resistance in SGA subjects brought up by Challa et al. (8) cannot be confirmed by our findings. Our data showed that the higher IGF-I and IGFBP-3 concentrations led to greater insulin resistance among the subjects.

The limitations of our study are the lack of an age- and gender-matched control group born appropriate for gestational age (AGA) and the lack of reference values for weight-for-height Z-scores for birth length <45 cm.

In conclusion, we found a high percentage of insulin-resistant young adults born SGA. Former factors associated with insulin resistance could only be confirmed in parts. The first 3 months of life seem to determine insulin resistance, especially when experiencing rapid weight gain. Thus, the early postnatal period should be a “nutritionally” controlled phase in children born SGA. Later in life, these children need to be followed up regularly to identify further metabolic disturbances.

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