The Somatotrophic Axis in Short Children Born Small for Gestational Age: Relation to Insulin Resistance

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ABSTRACT

To determine whether hyperinsulinemia and reduced insulin sensitivity in individuals born small for gestational age (SGA) could be related to persisting abnormalities of the GH/IGF-I axis, we assessed overnight GH secretory profiles and measured fasting glucose, insulin, intact and 32,33 split proinsulin, and IGF-I levels in 16 short SGA children (age range 2.3–8.0 y) and in controls. Insulin sensitivity was calculated using the homeostasis model. Compared with short normal-birthweight controls ($n = 7$, age range 2.3–5.0 y), short SGA children had higher fasting insulin levels (means: 26.8 vs 20.6 pmol/L, $p = 0.02$), lower insulin sensitivity [means: 204 vs 284 %homeostasis model assessment (HOMA), $p = 0.01$], and higher beta cell function (112 vs 89 %HOMA, $p = 0.04$). SGA children also had lower levels of IGFBP-1 (87.0 vs 133.8, $p = 0.04$), but similar IGF-I levels (IGF-I SDS: -1.1 vs -1.7, $p = 0.4$). Compared with normal-height controls ($n = 15$, age range 5.6–12.1 y), SGA children had higher overnight GH secretion (GH maximum: 55.9 vs 39.6 mU/L, $p = 0.01$; mean: 13.1 vs 8.9, $p = 0.004$; minimum:

1.2 vs 0.6, $p = 0.02$). Interestingly, among SGA children, fasting insulin levels and insulin sensitivity were significantly related to overnight GH secretion (insulin sensitivity vs maximum GH: $r = -0.68$, $p = 0.01$; vs GH pulse amplitude $r = -0.71$, $p = 0.007$). The only hormone level significantly related to current height velocity was C-peptide ($r = 0.75$, $p = 0.008$). In conclusion, elevated fasting insulin levels and reduced insulin sensitivity in short SGA children was related to elevated levels of overnight GH secretion. We hypothesize that resistance to the somatotrophic actions of GH and IGF-I in short SGA children may contribute directly to reduced insulin sensitivity. (*Pediatr Res* 51: 76–80, 2002)

Abbreviations

SDS, SD score
SGA, small for gestational age
HOMA, homeostasis model assessment
IGFBP-1, IGF binding protein-1

Endocrine studies *in utero* show that growth retarded fetuses have reduced insulin (1, 2) and IGF-I levels (3–5), and in the neonatal period, babies born SGA have low IGF-I levels despite elevated GH secretion (6–10), a pattern characteristic of GH insensitivity (11, 12). Approximately 10% to 15% of these SGA infants remain small in childhood, as defined by height < -2 SDS (13–15). Failure of catch-up growth is associated with severity of intra-uterine growth retardation and persisting low IGF-I levels (9, 16–18), suggesting ongoing dysfunction of the GH/IGF-I axis (19). In contrast to their high

neonatal GH levels, older SGA children may have reduced GH secretion, although most do not develop “classic” GH deficiency (17, 19–21).

In addition to impaired postnatal growth, reduced size at birth has been associated with increased risk of adult diseases, including type 2 diabetes, syndrome X, and cardiovascular disease (22, 23). Insulin resistance is a common feature of these conditions and has been independently associated with low birthweight both in adults (24) and children (25, 26), suggesting that this metabolic abnormality may be central to the link between reduced prenatal growth and adult disease.

The GH/IGF-I axis and insulin sensitivity/secretion are closely related. Sustained elevation of GH levels results in decreased insulin sensitivity at the liver and in peripheral tissues (27, 28). In contrast, IGF-I has insulin-like metabolic effects, particularly in muscle where IGF-I receptor density is high (29) and low IGF-I levels might reduce peripheral glucose

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uptake. In subjects with insulin deficiency and insulin resistance, such as those with malnutrition or type 1 diabetes, a GH resistant pattern of elevated GH and reduced IGF-I is often observed (30, 31). We postulated that insulin resistance in short SGA children might be related to persisting abnormalities of the GH/IGF-I axis. To explore this hypothesis, we examined GH secretion, IGF-I levels, and insulin secretion/sensitivity in young SGA children with postnatal growth failure.

METHODS

Subjects

Short SGA children. Subjects were selected from two centers (John Radcliffe Hospital, Oxford, UK, and Gasthuisberg University Hospital, Leuven, Belgium) according to the following criteria: birthweight and/or length < -2 SD for gestational age; current height SDS < -3.0 ; height velocity SDS < 0.0 ; and chronological age 2–8 y. Subjects with an identified syndrome other than Silver-Russell syndrome were excluded, and no child was receiving medication for chronic disease. Sixteen children were recruited and their clinical characteristics are summarized in Table 1. Birthweight, length, current height, weight, and body mass index (BMI kg/m²) were converted to age and sex-adjusted SD scores using the current UK reference (32). Height velocity was calculated as height gained over the previous 12 mo (cm/y) as measured in the hospital-based Growth Clinics.

Controls. Two control groups were studied: short normal-birthweight children (height SDS < -2 and birthweight SDS > -2 ; $n = 7$; Table 1) were identified from community screening records and had fasting blood samples collected; and overnight GH profiles were performed on 15 (8 male) normal-stature (mean height SDS = -0.1 , range -1.3 to 1.1) prepubertal children (mean age = 9.3 y, range 5.6 to 12.1). Protocols for GH profiles and GH assays were similar to those used in the SGA group (33, 34).

Study Protocol

The local ethics committees in Oxford and Leuven approved the study and informed consent was obtained from parents and children. SGA children were first admitted to hospital for the overnight GH profile. Blood for serum GH estimation was withdrawn from an indwelling venous canula at 20-minute intervals between 19.00 and 07.00 h. Children followed their normal eating pattern during this period.

On a separate occasion, after 3 d of unrestricted diet and an overnight fast, at 8.30h a venous blood sample was collected for measurement of glucose, insulin, C-peptide, intact proinsulin, 32,33 split proinsulin, IGF-I, IGFBP-I, IGFBP-3, and leptin.

Short normal-birthweight controls. These children were fasted from midnight and had a single blood sample at 08.30 h assayed for glucose, insulin, C-peptide, intact proinsulin, 32,33 split proinsulin, IGF-I, IGFBP-I, IGFBP-3, and leptin.

Normal-stature controls. These children underwent an overnight GH profile using the same protocol and assays as used in the SGA children.

Assays

Blood glucose was measured using a Y.S.I. model 2300 stat plus analyser (Yellow Springs Instruments, Ltd, Hants, UK). The intra and inter-assay coefficients of variation (CV) were 2.6% and 8.8% at 4.4 mmol/L. Insulin was measured using a double antibody RIA from Diagnostic Systems Laboratories (DSL, Webster, TX, U.S.A.). Intra-assay CV was 8.3% at 33.6 pmol/L and inter-assay CV was 12.2% at 34.3 pmol/L. Cross-reactivity with proinsulin in this assay is approximately 40%. Intact proinsulin and 32,33 split proinsulin were measured using a time resolved fluorometric assay (35); inter-assay CVs were $< 10\%$. The intact proinsulin assay shows typically $< 1\%$ cross-reaction with insulin and 32,33 split proinsulin. Cross-reaction of the 32,33 split proinsulin assay with insulin was $< 1\%$ at 2500 pmol/L, and there was 100% cross-reaction with intact proinsulin; therefore, to obtain a specific measure of 32,33 split proinsulin, the intact proinsulin concentration of the specimen was subtracted. C-peptide was measured using a double antibody RIA from Diagnostic Products Corporation (Glyn Rhonwy, Llanberis, UK); intra and inter-assay CVs were 3.4% and 10.0%. IGF-I was measured by RIA using an established in-house method (36) following acid-acetone extraction; intra and inter-assay CV's were 6.2% and 3.5%. IGFBP-1 was measured by RIA using a solid phase second antibody separation phase; intra and inter-assay CVs were 4.0% and 5.7%. IGFBP-3 was measured using a Coated-Tube immunoradiometric assay (IRMA) from distal sensory latency; intra-assay CV was 3.9% at 7.3 ng/mL and inter-assay CV was 0.6% at 8.0 ng/mL. Leptin was measured by RIA from Linco (St. Charles, MO, U.S.A.); intra and inter-assay CVs were 4.0% and 5.7% at 4.9 ng/mL. GH was measured by IRMA (North East Thames Regional Immunoassay Unit, Bartholomew Close, London,

Table 1. Clinical characteristics of the short SGA and short normal birthweight children

	Short SGA ($n = 16$) 9 M, 7 F		Controls ($n = 7$) 5 M, 2 F	
	Mean	Range	Mean	Range
Age	*5.82 (M 5.4, F 6.3)	2.3 to 8.0	3.64	2.3 to 5.0
Birth weight SDS	** -3.0 (M -3.1 , F -2.8)	-4.7 to -0.8	-0.5	-1.5 to -0.1
Birth length SDS	-3.6 (M -4.9 , F -2.9)	-0.3 to -6.1	NA	NA
Height SDS	** -3.4 (M -3.6 , F -3.2)	-5.5 to -2.8	-2.3	-2.7 to -2.0
Weight SDS	** -4.4 (M -4.5 , F -4.3)	-7.2 to -2.6	-2.1	-2.7 to -0.9
BMI SDS	** -2.3 (M -2.0 , F -2.5)	-5.0 to 0.0	-0.4	-1.3 to 1.0

M, male; F, female; NA, not available.

* $p < 0.05$. ** $p < 0.005$.

UK) using the international reference standard 80/505; intra-assay CVs were 8.0, 2.0, and 3.4% at 2.9, 14.3 and 69.4 mU/L and inter-assay CVs were 9.4, 7.7, and 10.5% at 3.5, 15.2 and 77.4 mU/L.

Calculations

Overnight GH profiles were analyzed using the Pulsar program. Peak selection criteria appropriate for our own assay conditions and data set were established. The minimum, mean and maximum GH levels, area under the curve above baseline (AUCb), total number of peaks, and mean peak amplitude were derived.

Insulin sensitivity and beta cell function were calculated from fasting glucose and insulin values using HOMA, version 2, a structural computer model of the glucose/insulin feedback system (37). Insulin sensitivity and beta cell function are expressed in relation to "standard adults," accorded the value 100%.

Sex- and age-standardized SD scores for IGF-I levels were calculated by comparison with normal reference data (38).

Statistical analysis

Analyses were carried out using the computer statistical package SPSS (Version 7.5) for windows. Mean values were compared using *t* test or one-way ANOVA. The relationships between continuously distributed parameters were explored using linear regression.

RESULTS

Fasting Hormone Levels. Short SGA children had higher fasting insulin levels ($p = 0.02$) compared with short normal-birthweight children, with no differences in glucose and C-peptide levels (Table 2). HOMA modeling of fasting insulin and glucose levels indicated that short SGA children had lower insulin sensitivity ($p = 0.01$), but higher beta-cell function ($p = 0.04$) reflecting compensatory hyperinsulinemia.

IGF-I levels in short SGA children were on average one SD lower than published population means (37), but these levels were not lower compared with short normal-birthweight con-

trols ($p = 0.2$). Short SGA children also had lower IGFBP-1 levels ($p = 0.04$), and lower leptin levels ($p = 0.004$) than controls, reflecting their lower BMI.

Overnight GH levels. Of the 16 short SGA children, 13 had overnight GH profile completed, and all these had a maximum overnight GH level of at least 30 mU/L, ruling out GH insufficiency. Indeed, when compared with normal-stature controls, short SGA children had higher maximum ($p = 0.01$), mean ($p = 0.004$), minimum ($p = 0.004$), and AUCb ($p = 0.02$) overnight GH levels and also an increased GH pulse frequency ($p = 0.02$; Table 3).

GH/IGF-I axis and insulin sensitivity. Among short SGA children, fasting insulin levels and insulin sensitivity were significantly related to maximum overnight GH levels (fasting insulin level: $r = 0.65$, $p = 0.02$; HOMA insulin sensitivity: $r = -0.68$, $p = 0.01$; Fig. 1). HOMA insulin sensitivity was even more closely related to the maximum GH pulse amplitude ($r = -0.71$, $p = 0.007$), but was unrelated to minimum GH levels ($r = 0.0$, $p = 1.0$) or GH pulse frequency ($r = -0.15$, $p = 0.6$).

Maximum overnight GH levels were also inversely related to leptin ($r = -0.56$, $p = 0.05$), but not to BMI, IGF-I, IGFBP-1, or IGFBP-3 levels. Among SGA children, the only hormone or growth factor which correlated significantly with current height velocity was C-peptide ($r = 0.75$, $p = 0.008$, Table 4).

DISCUSSION

The aim of this study was to examine the relationship between the GH/IGF-I axis and insulin sensitivity/secretion in young short SGA children. Our short SGA children were younger (mean age = 5.8 y) and shorter (mean height SDS = -3.4) than those in whom insulin sensitivity has previously been reported (26). Despite being thinner and shorter than the short normal-birthweight controls, these short SGA children had higher fasting insulin levels. HOMA assessment of insulin sensitivity takes into account the effect of variation in fasting blood glucose levels on the insulin levels; although this model has only been validated in adult populations, our findings that short SGA children have reduced insulin sensitivity and increased beta cell function are entirely consistent with results from a similar population using the modified minimal model assessment (26). Furthermore, the elevated fasting insulin levels and reduced insulin sensitivity in these short SGA children

Table 2. Fasting hormone levels in short SGA and short normal-birthweight children

	SGA group (<i>n</i> = 16)	Controls (<i>n</i> = 7)	<i>p</i> value (<i>t</i> test)
Glucose (mmol/l)	3.8 (0.5)	3.9 (0.6)	NS
Insulin (pmol/l)	26.8 (6.3)	20.6 (8.1)	0.02
Insulin sensitivity (HOMA %)	204 (61)	284 (67)	0.01
Beta cell function (HOMA %)	112 (33)	89 (15)	0.04
Proinsulin (pmol/l)	2.0 (1.3)	1.8 (0.7)	NS
32, 33 split proinsulin (pmol/l)	5.9 (6.1)	3.5 (1.0)	NS
Insulin/proinsulin ratio	5.0 (4.0)	10.0 (4.3)	0.02
C-peptide (nmol/l)	0.19 (0.13)	0.23 (0.07)	NS
Leptin (ng/ml)	2.6 (0.7)	3.9 (1.1)	0.004
IGF-I SDS	-1.1 (1.1)	-1.7 (0.6)	NS
IGFBP-1 (ng/ml)	87.0 (87.2)	133.8 (127.0)	0.04
IGFBP-3 (ng/ml)	3.1 (1.2)	2.3 (0.3)	NS (0.07)

Values are mean (SD).

NS, no significant difference ($p > 0.05$).

Table 3. Parameters of overnight GH secretion in SGA children and normal-stature controls

	SGA group (<i>n</i> = 13)	Control group (<i>n</i> = 15)	<i>p</i> value (<i>t</i> test)
GH (mU/l)			
Maximum	55.9 (30.4–80.5)	39.6 (15.6–75.9)	0.01
Mean	13.1 (7.2–19.1)	8.9 (3.7–18.5)	0.004
Minimum	1.2 (<0.4–2.1)	0.6 (0.5–1.3)	0.004
No. of pulses	5.4 (3–7)	4.3 (3–8)	0.02
Area under curve	115.8 (62.0–171.1)	84.1 (28.7–165.8)	0.02
Pulse amplitude	25.2 (17.4–36.7)	20.6 (9.1–40.8)	NS (0.12)

Values are mean (range).

NS, not significant.

Figure 1. Scattergraph of insulin sensitivity (HOMA) against maximum overnight GH level in short SGA children ($r = -0.68$, $p = 0.01$, $n = 13$).

Table 4. Correlation coefficients between current height velocity and hormone levels in short SGA children

	<i>r</i>	<i>p</i> value
Glucose	0.12	NS (0.7)
Insulin	-0.11	NS (0.7)
C-peptide	0.75	0.008
Proinsulin	0.21	NS (0.5)
IGF-I	0.13	NS (0.6)
IGFBP-1	-0.54	NS (0.08)
IGFBP-3	0.37	NS (0.3)
GH maximum	0.06	NS (0.9)
GH mean	0.06	NS (0.9)
Insulin sensitivity	0.20	NS (0.5)
Beta-cell function	-0.15	NS (0.6)

NS, not significant.

was significantly related to their levels of overnight GH secretion.

Despite their severe short stature, all parameters of overnight GH secretion (maximum, mean, minimum, AUCb, and pulse frequency) were higher in short SGA children compared with normal-stature prepubertal controls, and also higher compared with published normative data in prepubertal populations (17, 19, 39). Previous studies in short SGA children have reported reduced spontaneous GH secretion compared with controls, although most are not GH deficient (17–19). The different findings in our short SGA children may relate to their younger age; young SGA children have been noted to have a distinct pattern of GH secretion with high baseline levels and increased pulse frequency (19).

IGF-I levels in our short SGA children were on average one SD lower than the population reference (38), which is consistent with other studies (9, 16–18). However, despite being shorter and thinner, the IGF-I levels in our short SGA children were not lower compared with short normal-birthweight controls. It has been suggested that short SGA children may have a degree of IGF-I resistance as higher basal and GH-induced IGF-I levels are required to achieve a growth velocity similar to that of other children (40). Relative IGF-I resistance at the

pituitary could contribute to the elevated GH secretion seen in our short SGA children, and would also be compatible with the observation that supra-physiologic GH doses are required to significantly improve final height prognosis in short SGA children (41–43). Thus, short SGA children may appear to have a shift in the set point of their GH/IGF-I axis.

In addition to its effects on IGF-I production, GH has important metabolic effects that are in part independent of IGF-I action. These “direct” GH effects include enhancement of protein synthesis, lipolysis, and reduction in body fat mass (44). Thus, children with GH deficiency or GH receptor deficiency tend to be obese (45, 46). However, as in our study, short SGA children are often thin (17, 19, 41), suggesting that they remain sensitive to the metabolic effects of GH. The elevated pattern of GH secretion seen in our short SGA children is similar to that observed during fasting or malnutrition (47) and could lead to increased lipolysis and the development of insulin resistance.

GH also has well-documented insulin antagonistic effects (27, 28). GH reduces glucose uptake in peripheral tissues such as muscle through an effect on postreceptor insulin signaling (28, 48). GH may also reduce insulin sensitivity by increasing lipolysis and circulating free-fatty acid levels (49). Thus, defects in the GH/IGF-I axis in short SGA children resulting in elevated GH secretion may directly contribute to their increased fasting insulin levels and reduced insulin sensitivity.

In the presence of reduced insulin sensitivity, the ability of the beta-cell to produce compensatory hyperinsulinemia are important in maintaining glucose homeostasis, as clearly shown by recent animal knockout studies of the genes encoding insulin receptor substrate 1 and 2 (50, 51). In our study, C-peptide, a marker of integrated insulin secretion, was the only hormone level related to current height velocity. Thus, the ability to increase insulin secretion in compensation for insulin resistance may be an important determinant of both glucose homeostasis and continuing growth in short SGA children.

In contrast, the role of the GH/IGF-I axis in regulating growth in short SGA children is less obvious from our data. The lack of significant association between GH and IGF-I levels may be expected in this small sample; however, neither hormone was related to growth velocity. Our short SGA children had lower IGFBP-1 levels than controls, and it could be postulated that the compensatory hyperinsulinemia in response to peripheral insulin resistance might lower IGFBP-1 levels and thereby improve IGF-I bioavailability. This could be a mechanism whereby growth is maintained in the presence of relative GH and IGF-I resistance. The improvement in IGF-I bioavailability, if sustained, could eventually lead to suppression of GH secretion as seen in older SGA children (17–19).

In conclusion, these data suggest that the GH/IGF-I axis may be impaired in young short SGA children and this may contribute to their reduced insulin sensitivity. These observations indicate the need to carefully monitor the use of high dose GH therapy in SGA children, which could influence any association between reduced prenatal growth, small size at birth, and the subsequent risk of adulthood disease.

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