Serum Levels of Receptors for Advanced Glycation End Products in Normal-Weight and Obese Children Born Small and Large for Gestational Age

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OBJECTIVE—To assess potential alterations in soluble and endogenous secretory receptors for advanced glycation end products (sRAGE and esRAGE) in normal-weight (NW) and obese (Ob) children born small (SGA) and large (LGA) compared with appropriate for gestational age (AGA) subjects and to explore if birth weight (BW), insulin resistance (IR), and obesity represent independent risk factors.

RESEARCH DESIGN AND METHODS—We categorized 130 prepubertal children into six groups according to BW and obesity and evaluated sRAGE, esRAGE, and homeostasis model assessment of IR.

RESULTS—sRAGE and esRAGE were lower in Ob SGA and LGA children than Ob AGA subjects (all $P < 0.05$), and in NW SGA and LGA children than NW AGA subjects (all $P < 0.05$). Interestingly, BW and IR were significantly and independently related to RAGE.

CONCLUSIONS—sRAGE and esRAGE are decreased in SGA and LGA children, and BW and IR seem to play an important role in the reduction of RAGE.

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Children born small and large for gestational age (SGA and LGA) are at increased risk of cardiometabolic complications later in life (1–4).

Interestingly, in recent years, the soluble and endogenous secretory receptors for advanced glycation end products (sRAGE and esRAGE) have been proven to be involved in the pathogenesis of cardiovascular diseases (5–8).

Our aims were to evaluate sRAGE and esRAGE in normal-weight (NW) and obese (Ob) prepubertal SGA and LGA children compared with subjects born appropriate for gestational age (AGA), and to explore the potential association of these markers with birth weight (BW), insulin resistance (IR), and obesity.

RESEARCH DESIGN AND METHODS—We enrolled 130 Caucasian children. All subjects were born full term and singleton from NW mothers without carbohydrate metabolism alterations during pregnancy. According to BW, the study cohort was divided into the following: AGA (BW 10th–90th percentile for gestational age), SGA (BW less than or equal to −2 SDs), and LGA (BW ≥95th percentile). Moreover, based on BMI at the time of recruitment, children in each BW category were further divided into NW (BMI between −2 and 2 SDs for age and sex) and Ob (BMI >2 SD). All children were prepubertal (pubertal stage 1, according to Tanner criteria). Obesity indexes (BMI and BMI–SD score [SDS]), fasting glucose, IR indexes (fasting insulin [FI] and homeostasis model assessment of

IR [HOMA-IR]), sRAGE, and esRAGE were evaluated.

The study was approved by the local ethical committee. Written informed parental consent and oral assent from children were obtained.

sRAGE, esRAGE, glucose, and insulin levels were determined as previously described (5). Differences between the six groups (NW AGA, NW SGA, NW LGA and Ob AGA, Ob SGA, and Ob LGA) were analyzed by one-way ANOVA test, with Tukey test for post hoc comparisons between pair groups. The independent contribution of BW, obesity, and IR on sRAGE and esRAGE was evaluated by a multiple linear regression analysis. In order to include the BW categories as predictors, dummy coding was used. All data were expressed as mean ± SD. P values <0.05 were considered statistically significant. SPSS program version 16.0 for Windows was used.

RESULTS—Clinical and metabolic characteristics of the study cohort are reported in Table 1. A significant difference between the six groups was found in terms of FI and HOMA-IR ($P < 0.001$ for both). In the post hoc analysis, FI and HOMA-IR were higher in Ob SGA, AGA, and LGA children than NW AGA, SGA, and LGA subjects (all $P < 0.001$). Within the Ob groups, SGA and LGA children showed higher FI and HOMA-IR than AGA subjects (all $P < 0.001$). Within the NW groups, no difference was detected in terms of FI between the three BW groups, whereas HOMA-IR was higher in SGA and LGA children than AGA subjects (both $P < 0.05$).

sRAGE and esRAGE

sRAGE and esRAGE were significantly different between the six groups ($P < 0.001$ for both) (Table 1). In the post hoc analysis, sRAGE and esRAGE were lower in Ob SGA and LGA children than NW AGA, SGA, and LGA subjects (all $P < 0.05$). Within the Ob groups, SGA and LGA children showed lower sRAGE and

Table 1—Clinical and metabolic characteristics of the study population

	Ob AGA	Ob SGA	Ob LGA	NW AGA	NW SGA	NW LGA	P*
Clinical characteristics							
Number	21	20	22	20	27	20	
Age (years)	7.3 ± 1.2	7.4 ± 0.6	7.3 ± 1.7	6.4 ± 1.5	6.4 ± 1.7	6.5 ± 2	NS
Sex	10 M/11 F	11 M/9 F	11 M/11 F	13 M/7 F	12 M/15 F	10 M/10 F	
BW (g)	3,449 ± 201	2,518 ± 204	4,263 ± 234	3,293 ± 232	2,513 ± 137	4,111 ± 248	<0.001
Height-SDS	2.24 ± 0.83	1.67 ± 1.12	1.55 ± 1.33	−0.57 ± 2.11	−0.13 ± 1.11	0.38 ± 1	<0.001
BMI (kg/m^2)	27 ± 3	26 ± 2.5	27 ± 4.1	16.1 ± 0.4	15.6 ± 1	16 ± 0.8	<0.001
BMI-SDS	8.63 ± 2.24	8 ± 2.17	8.1 ± 3	0.28 ± 0.53	−0.0 ± 0.86	0.23 ± 0.71	<0.001
Metabolic parameters							
Fasting glucose (mg/dL)	84 ± 4	89 ± 5	86 ± 6	74 ± 4	79 ± 10	84 ± 5	<0.001
Fasting insulin (μU/mL)	10.6 ± 2.4	16 ± 2.8	16.2 ± 3.5	4.4 ± 0.9	6.5 ± 3.4	6.7 ± 2.1	<0.001
HOMA-IR	2.24 ± 0.57	3.51 ± 0.66	3.47 ± 0.80	0.81 ± 0.17	1.29 ± 0.71	1.40 ± 0.47	<0.001
RAGE							
sRAGE (pg/mL)	982 ± 72	834 ± 100	738 ± 191	1,221 ± 228	1,071 ± 191	1,002 ± 100	<0.001
esRAGE (ng/mL)	0.58 ± 0.05	0.44 ± 0.04	0.43 ± 0.23	0.76 ± 0.22	0.60 ± 0.16	0.60 ± 0.07	<0.001

Data are expressed as mean ± SD. M, male; F, female. *One-way ANOVA.

esRAGE than AGA subjects (all $P < 0.05$). Within the NW groups, SGA and LGA children showed lower sRAGE and esRAGE than AGA subjects (all $P < 0.05$).

Multiple linear regression analysis
In a multiple linear regression analysis with sRAGE as the dependent variable, SGA ($\beta = -0.237$, $P = 0.008$) and LGA ($\beta = -0.414$, $P = 0.0001$) BW categories as well as HOMA-IR ($\beta = -0.275$, $P = 0.01$) were significantly related to sRAGE, independently of BMI-SDS, age, and sex.

In a second model, using esRAGE as the dependent variable, SGA ($\beta = -0.307$, $P = 0.001$) and LGA ($\beta = -0.400$, $P = 0.0006$) BW categories as well as HOMA-IR ($\beta = -0.246$, $P = 0.04$) were significantly related to esRAGE, independently of BMI-SDS, age, and sex.

CONCLUSIONS—To the best of our knowledge, this report represents the first evidence of decreased sRAGE and esRAGE levels in NW and Ob prepubertal children born SGA and LGA compared with AGA subjects. Interestingly, BW and IR emerged as two independent determinants of reduced RAGE levels.

The AGE/RAGE system is a new discovered pathway implicated in the pathogenesis of several cardio-metabolic diseases (5–8). RAGE is a multiligand, cell-surface receptor expressed as three variants. The full-length RAGE and the NH_2-truncated type are retained in the plasma membrane, and the COOH-truncated variant, called esRAGE, is extracellularly secreted (9). The enzymatic cleavage of the full-length, cell-surface receptor produces an additional form of full-length RAGE, called sRAGE (5,9). Under pathological conditions there is a gradual accumulation of AGE, inducing oxidative stress generation and vascular inflammation. Thus, low levels of sRAGE and esRAGE (10,11) are explained by their ability to bind toxic AGE, neutralizing their action (5).

In this study, sRAGE and esRAGE were lower in NW SGA and LGA than NW AGA children, likely reflecting the metabolic derangements of SGA and LGA populations even in the NW condition. In addition, when Ob SGA and LGA were compared with Ob AGA children, adiposity appeared to exacerbate the reduction of RAGE, suggesting that a greater fat mass provokes deterioration in the metabolic status of these children. Our results are supported by a previous study (12), in which decreased sRAGE was found in very low BW infants after funisitis. However, in that study, esRAGE was not assessed, and SGA and LGA children were not enrolled.

Notably, in our report, both BW and IR were associated with sRAGE and esRAGE, independently of BMI-SDS. This finding could be explained by the altered metabolic status characterizing the SGA and LGA populations, due to the adaptive responses and the pathophysiological alterations that occur during intrauterine life (13,14). Furthermore, we hypothesize that IR might play a role in the reduction of RAGE, probably by activating common intracellular signaling pathways (15), although the cause-effect relationship between IR and RAGE remains speculative.

It needs to be acknowledged that a potential limitation of our study is its cross-sectional design, which does not allow the demonstration of any pathogenetic mechanism. Furthermore, we did not perform a direct assessment of glomerular filtration rate, which may influence circulating RAGE levels. However, the young age of our study population and the detection of decreased RAGE concentrations even in the NW condition suggest that these receptors could be involved in the natural history of metabolic complications in SGA and LGA children.

In conclusion, sRAGE and esRAGE are decreased in prepubertal SGA and LGA subjects, particularly in those showing excess body weight during childhood. Furthermore, IR emerged as an independent determinant of reduced RAGE levels. Further longitudinal studies are needed to verify the cause-effect relationship between IR and RAGE in these children.

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