ANTIOXIDANTS & REDOX SIGNALING
Volume 14, Number 6, 2011

DOI: 10.1089/ars.2010.3719

What Is the Significance of Soluble and Endogenous Secretory Receptor for Advanced Glycation End Products in Liver Steatosis in Obese Prepubertal Children?

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Abstract

The endogenous secretory receptor for advanced glycation end products (esRAGE) and soluble RAGE (sRAGE) have been shown in human plasma and have emerged as reliable biomarkers of several pathological conditions, including insulin resistance and liver injury. We examined esRAGE and sRAGE levels in obese prepubertal children with and without liver steatosis. esRAGE and sRAGE levels were significantly lower in obese prepubertal children affected by liver steatosis and were independently related to liver steatosis. These findings suggest that AGE-RAGE pathway plays an independent role in the development of liver injury already present in this age group. *Antioxid. Redox Signal.* 14, 1167–1172.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is becoming one of the most important emerging liver diseases in obese children and adolescents (15). Studies from autopsies in children (aged 2–19 years) reported prevalence of fatty liver of 9.6%, with an highest rate of the disease in obese children (38%) (19).

In obese youth, NAFLD is not only a marker of liver disease, but it is also associated with a high risk of developing type 2 diabetes (T2D) (5) and metabolic syndrome (5, 8, 16).

Although the pathogenesis of NAFLD is not completely understood, both insulin resistance (IR) and oxidative stress play an important role in the development of liver disease (1, 10).

Interestingly, among the several pathways able to activate the intracellular signaling involved in liver disease, the advanced glycation end products/receptor for advanced glycation end products (AGEs/RAGE) system has been recently proved to be involved in the pathogenesis and progression of NAFLD (11, 23, 24). In particular, the interaction between AGEs and RAGE elicits oxidative stress generation and subsequently alters gene expression in various types of cells including hepatocytes and hepatic stellate cells (9, 12).

RAGE is a multiligand cell-surface receptor expressed in human cells as three major splicing variants (21): the full-length RAGE and the N-truncated type are retained in the plasma membrane, whereas the third variant, the C-truncated variant, known as endogenous secretory RAGE (esRAGE), lacks the cytosolic and transmembrane domains and is therefore extracellularly secreted (14, 21). The enzymatic cleavage of the full-length cell-surface receptor produces an additional form of extracellularly secreted RAGE, known as soluble RAGE (sRAGE). Both esRAGE as well as sRAGE can be detected in blood serum and are able to bind the circulating ligands, neutralizing their actions. Therefore, in those conditions characterized by high concentrations of the circulating ligands, the decoy receptors are reduced drastically, revealing the system function (14).

In childhood obesity, especially in prepubertal age, it has not been yet clarified whether AGE-RAGE pathway plays a role in the natural course of liver injury.

Therefore, the aims of the present study were to evaluate esRAGE and sRAGE levels among a group of obese prepubertal children with and without liver steatosis and to assess the possible association between levels of esRAGE, sRAGE, or both with fatty liver disease in this age group.

Association Between AGE/RAGE Pathway and Liver Steatosis in Obese Prepubertal Children

Although NAFLD represents an important risk factor for the development of cardiovascular and metabolic complications in the obese pediatric population (5, 6, 16), the molecular mechanisms involved in its development and progression are not completely defined.

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To the best of our knowledge, in the present study, we have documented the first evidence of a possible role of RAGE pathway in the pathogenesis of NAFLD in obese prepubertal children. In fact, esRAGE and sRAGE were significantly lower in obese prepubertal children with liver steatosis than in those without. These results are supported by a previous study by Yilmaz *et al.* (24), in which, by evaluating only the sRAGE form, lower levels of sRAGE were documented in adult patients with NAFLD. However, in contrast to our study, impaired sRAGE levels were only documented in the most severe forms of NAFLD but not in subjects with simple steatosis.

In addition, in the present study, a significant association between RAGE pathway and the presence of NAFLD has been documented. In particular, both esRAGE and sRAGE values were significantly and independently associated with the presence of liver steatosis, representing novel and fascinating possible markers of obese-related liver disease in childhood.

These observations suggest that in young prepubertal children, RAGE system is impaired early in the course of liver disease, representing a useful marker of NAFLD already in the initial course of the disease. Further, the independent association between esRAGE, sRAGE, and NAFLD suggests a relevant role of the AGE/RAGE pathway in the development of NAFLD in early childhood obesity.

However, although RAGE system activation represents a key component related to NAFLD, further longitudinal studies are needed to completely define the cause–effect relationship in the course of obese-related liver disease.

Relationship Between sRAGE, esRAGE, and IR

As expected and according to previous studies (4, 6, 7), in this age group we confirmed an independent and significant association of IR in obese prepubertal children with liver steatosis. Thus, given the central role of IR in the development of NAFLD, we have explored the possible relationship between sRAGE, esRAGE, and IR.

During the last years, it has been demonstrated that the interaction of AGEs with their receptor (RAGE) is implicated in the pathogenesis of several disorders, including complications related to diabetes and cardiovascular diseases (13, 17, 20). In addition, growing evidences have supposed a relevant role of AGE/RAGE system in the development of impaired IR status in obese subjects (20). In fact, activation of the AGE/RAGE pathway has been shown to induce IR in different tissues through several intracellular mechanisms including the activation of nuclear factor-kB and reactive oxygene species, the modification of protein structure, and the phosphorylation of the intracellular domain of insulin receptor (14). According to these results, we documented a direct association between IR and AGE/RAGE pathway. In particular, a direct association between sRAGE and both homeostasis model assessment of IR (HOMA-IR) and whole-body insulin sensitivity index (WBISI) was documented, whereas esRAGE failed to show a significant correlation with both IR indexes. This important finding could be explained by taking into account the different origins of these two molecules (14, 21). In fact, being a splicing variant of the RAGE, esRAGE is intracellularly synthesized. In addition, as it lacks the cytosolic and transmembrane domains, this form is secreted in the extracellular space. In contrast, sRAGE is produced by the enzymatic cleavage of the full-length cell-surface receptor. It is well known that engagement of RAGE by circulating AGE, produced during hyperglycemia, induces the activation of several intracellular pathways and especially the nuclear factor-kB pathway (14). In particular, these activations result in the synthesis of several inflammatory molecules as well as of metalloproteinase molecules, which are well known to be associated and increased in patients with NAFLD. Therefore, in the patients with NAFLD and impaired AGE/RAGE pathway, RAGE engagements by circulating AGEs might primarily activate this intracellular pathway, indicating a relevant role of the sRAGE, the enzymatically cleavaged form, in revealing the system function.

Although these data showed a clear association between IR and AGE/RAGE pathway, longitudinal data are needed to verify whether IR and AGE/RAGE pathways are activated simultaneously or the activation of one of them is the first event in the natural course of NAFLD in childhood.

Limitations of the Study

It might be argued that a major limitation of the present study is related to the definition of liver steatosis by detectable ultrasound alterations instead of the gold-standard invasive liver biopsy. However, although radiological modalities are unable to distinguish between nonalcoholic steatohepatitis and other forms of NAFLD, liver ultrasonography has an acceptable sensitivity and specificity for the diagnosis of increased fat accumulation (steatosis) in the liver (18).

Conclusions and Future Directions

In conclusion, in this study, decreased sRAGE and esRAGE levels have been shown in obese prepubertal children affected by liver steatosis. Therefore, AGE-RAGE pathway seems to play a relevant and independent role in the development of liver injury already present in obese prepubertal children.

In view of the increasing prevalence of NAFLD in the pediatric population, future researches are needed to fully define its underlying pathophysiology. The complete characterization of the mechanisms involved in the development of fatty liver disease could help in the identification of therapeutic strategies for NAFLD, leading to the reduction of the associated cardiovascular and metabolic complications.

Notes

Study population

One hundred forty Caucasian prepubertal children (71 boys and 69 girls) aged between 6 and 10 years (mean age $\pm$ standard deviation [SD]: 8.6 ± 1.4 years), who had been referred to the Obesity Clinic of the Department of Pediatrics, University of Chieti, Italy, were included in the present study. All subjects were affected by obesity (body mass index [BMI] standard deviation score [SDS]: >2 SD for age and gender), were otherwise in good health, and were not affected by any chronic disease. Autoimmune hepatitis, Wilson disease, antitrypsin deficiency, hepatitis B and C, and iron overload were excluded with appropriate tests in subjects with significant elevation in alanine aminotransferase (ALT). None was taking any medication known to affect liver function and none had a history of consumption of alcohol.

A detailed medical and family history was obtained from all subjects and a complete physical examination was performed, including anthropometric parameters and staging of puberty, on the basis of breast development in girls and genital development in boys according to Tanner's criteria (all patients had prepubertal characteristics corresponding to stage 1).

The evaluation of steatosis was made by liver ultrasonography, performed by a single trained operator. In accordance with the presence or absence of liver steatosis, the study cohort was divided in two groups: the group with liver steatosis (72 subjects) and the group without liver steatosis (68 subjects).

The study was approved by the Ethical Committee of the University of Chieti. Written informed consent was obtained from all parents and oral consent was obtained from all children.

Anthropometric measurements

Body weight was determined to the nearest 0.1 kg and height was measured with Harpenden stadiometer to the nearest 0.1 cm. As fatness indexes we used the BMI-SDS for age and gender and waist circumference (WC). BMI-SDS was calculated using the following formula: SDS = (individual's measurement − population mean)/population SDS, and WC was measured at its smallest point between iliac crest and rib cage.

Oral glucose tolerance test

Subjects were seated for the test between 08:00 and 09:00 a.m., after an overnight fasting for at least 12 h. Baseline plasma glucose, insulin levels, ALT, aspartate aminotransferase (AST), and lipid profile (total cholesterol, triglycerides, high-density lipoprotein [HDL] cholesterol and low-density lipoprotein [LDL] cholesterol) were measured.

Multiple aliquots of blood samples were collected and stored at −70°C for later assessment of sRAGE and esRAGE.

Thereafter, a flavored glucose in a dose of 1.75 g/kg of body weight (up to a maximum of 75 g) was given orally, and blood samples were obtained every 30 min for the measurement of plasma glucose and insulin. The area under the curve for glucose during the oral glucose tolerance test was calculated using the trapezium rule (2).

Impaired glucose tolerance and T2D were defined according to American Diabetes Association guidelines (3).

IR indexes

We used the following indexes for the determination of IR: HOMA-IR (22) = (fasting insulin [mU/l]×fasting glucose [mmol/l]/22.5); and WBISI (22) calculated with the following formula: $10.000/\sqrt{}$[(fasting insulin×fasting glucose)×(mean insulin×mean glucose)].

Ultrasound examination

The diagnosis of hepatic steatosis was based on liver ultrasonography scanning performed in all participants by a single trained and experienced operator using a scanner LOGIQ 400 CL PRO with a 3.5 MHz transducer. The operator was unaware of the clinical course and laboratory details of the patients. Liver echotexture, liver–kidney differentiation in echo amplitude, hepatic echo penetration, and clarity of blood vessels were used to determine the presence of

Table 1. Clinical and Metabolic Characteristics of Patients with and Without Liver Steatosis

	Children with liver steatosis	*Children without liver steatosis*	p
Clinical characteristics			
Number	72	68	
Gender (M/F)[a]	38/34	33/35	0.6[a]
Age (years)	8.7 ± 1.49	8.52 ± 1.37	0.2
BMI-SDS	7.98 ± 2.43	7.39 ± 2.31	0.2
WC (cm)	84.4 ± 8.3	79.15 ± 7.4	<0.0001
Lipid profile			
Total cholesterol (mg/dl)	171.1 ± 36.0	166.1 ± 22.5	0.5
LDL-cholesterol (mg/dl)	102.8 ± 36.4	95.23 ± 22.8	0.4
TG (mg/dl)	108.8 ± 48.4	82.85 ± 38.4	<0.0001
HDL-cholesterol (mg/dl)	47.30 ± 14.1	51.7 ± 11.7	0.01
Metabolic parameters			
Fasting insulin (μU/ml)	18.4 ± 10.6	14.90 ± 19.9	<0.0001
Fasting glucose (mg/dl)	90.7 ± 9.57	89.6 ± 16.5	0.8
2-h glucose (mg/dl)	112.0 ± 18.6	102.7 ± 12.2	0.002
HOMA-IR	4.05 ± 2.60	2.27 ± 1.22	<0.0001
WBISI	3.64 ± 2.00	6.78 ± 3.58	<0.0001
AUC for glucose	12951.2 ± 2084.9	12887.9 ± 1879.9	0.8
AST (U/L)	32.6 ± 11.6	29.94 ± 5.5	0.6
ALT (U/L)	45.1 ± 26.2	33.6 ± 11.6	0.007

Data are expressed as mean ± SD.
[a]Chi-square test.
Significant differences: $p < 0.05$.
BMI, body mass index; SDS, standard deviation score; WC, waist circumference; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; TG, triglycerides; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; WBISI, whole-body insulin sensitivity index; AUC, area under the curve.

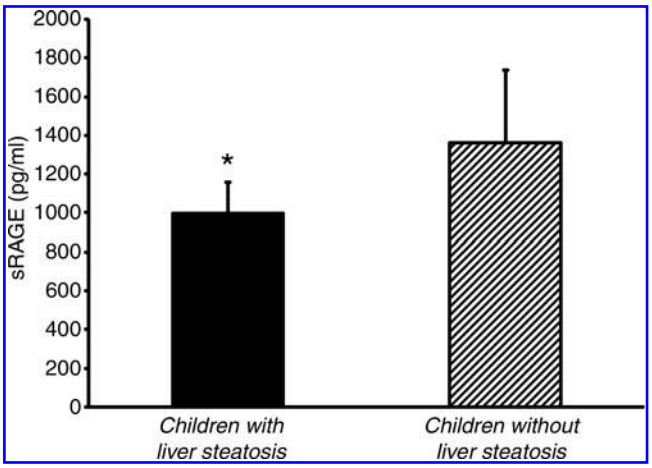

FIG. 1. Soluble receptor for advanced glycation end products (sRAGE) levels in obese children with and without liver steatosis. *$p < 0.0001$.

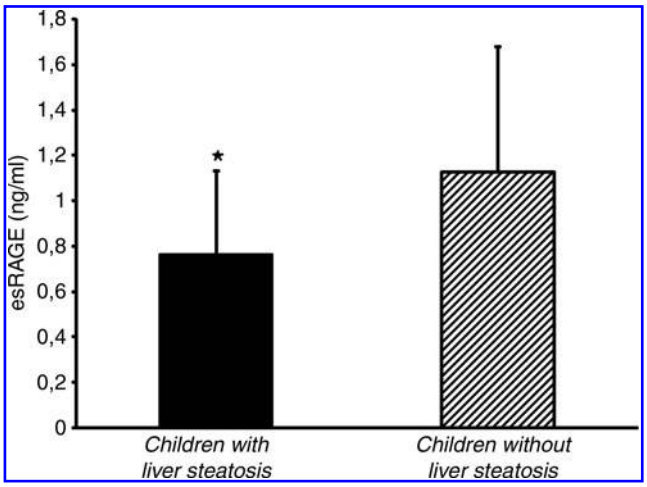

FIG. 2. Endogenous secretory receptor for advanced glycation end products (esRAGE) levels in obese children with and without liver steatosis. *$p < 0.0001$.

steatosis, as previously reported (7). For quality control assessment, 10% of the subjects were reexamined and these repeated measurements gave a coefficient of variation within 1%.

Biochemical analyses

Plasma glucose levels were determined using the glucose oxidase method and plasmatic insulin levels were measured by a two-site immunoenzymometric assay (AIA-PACK IRI; Tosoh, Tokyo, Japan). ALT and AST levels were measured using a standard automated kinetic enzymatic assay. Total cholesterol, HDL-cholesterol, and triglycerides were measured with an enzymatic calorimetric test. LDL-cholesterol was derived according to the Friedewald's equation.

esRAGE and sRAGE were measured all together by using the B-Bridge sRAGE and esRAGE ELISA Kit (distributed by B-Bridge International, Mountain View, CA). Measurements were performed following the manufacturer's instructions. The intra- and interassay coefficients of variations were <7.0% for both the parameters.

Statistical analysis

According to the presence or not of liver steatosis, as assessed by liver ultrasound, subjects were divided into two groups (the group with liver steatosis and the group without liver steatosis). Given the nonnormal distribution of the variables, differences in clinical and metabolic variables were assessed by the Mann–Whitney *U* test. Differences in gender prevalence between groups were assessed by χ^2 test.

Correlations were assessed by the Spearman rank correlation.

Logistic regression analysis was performed to assess the possible association between sRAGE, esRAGE, other main parameters, and the presence of liver steatosis by using four models: (a), (b), (c), and (d). In the models (a) and (b), the presence of liver steatosis was used as the dependent variable and sRAGE, IR indexes [using HOMA-IR in the model (a) and WBISI in the model (b)], age, gender, and BMI-SDS were used as the independent variables. In the models (c) and (d), the presence of liver steatosis was used as the dependent variable and esRAGE, IR indexes [using HOMA-IR in the model (c) and WBSI in the model (d)], age, gender, and BMI-SDS were used as the independent variables.

All data were expressed as mean ± SD. *p*-Values <0.05 were considered statistically significant.

Analysis was performed using the computer program SPSS, version 16.0 software for Windows.

Results

Clinical and metabolic characteristics

The study population included a total number of 140 prepubertal children (Table 1). Of the 140 children, liver steatosis was diagnosed in 72 children, whereas 68 prepubertal children had no signs of liver injury as assessed by liver ultrasound and were used as the control group.

The two groups were comparable for age, gender, and BMI-SDS (all *p*-values >0.05). The WC was significantly higher in the group with liver steatosis than in the group without ($p < 0.0001$).

As expected, children with liver steatosis showed significantly higher levels of ALT than children without ($p = 0.007$), whereas AST levels were comparable between the two groups ($p > 0.05$).

Triglyceride levels were significantly higher and HDL-cholesterol was significantly lower in the group with liver steatosis than in the group without ($p < 0.0001$ and $p = 0.01$, respectively), whereas the two groups had similar total cholesterol and LDL-cholesterol levels ($p > 0.05$).

Insulin resistance

Children with liver steatosis showed higher levels of fasting insulin ($p < 0.0001$) and HOMA-IR ($p < 0.0001$) and lower levels of WBISI ($p < 0.0001$) than children without. No patient had T2D or impaired glucose tolerance in both groups (Table 1).

The group with liver steatosis had higher levels of 2 h glucose than the group without ($p = 0.002$), whereas fasting

Table 2. Logistic Regression: Association Between Liver Steatosis, Soluble Receptor for Advanced Glycation End Products, Endogenous Secretory Receptor for Advanced Glycation End Products, and Other Main Parameters

Independent variables	*Dependent variable Hepatic steatosis*	
	Expected beta (95% CI)	p
(a) Model		
sRAGE	0.995 (0.993–0.997)	<0.0001
HOMA-IR	2.073 (1.404–3.062)	<0.0001
Age	0.973 (0.697–1.360)	NS
Gender	0.823 (0.296–2.289)	NS
BMI-SDS	1.065 (0.836–1.356)	NS
(b) Model		
sRAGE	0.994 (0.991–0.996)	<0.0001
WBISI	0.600 (0.456–0.789)	<0.0001
Age	0.864 (0.597–1.249)	NS
Gender	0.778 (0.251–2.413)	NS
BMI-SDS	1.006 (0.769–1.317)	NS
(c) Model		
esRAGE	0.151 (0.053–0.427)	<0.0001
HOMA-IR	2.104 (1.471–3.011)	<0.0001
Age	1.030 (0.756–1.402)	NS
Gender	1.252 (0.495–3.186)	NS
BMI-SDS	0.981 (0.791–1.215)	NS
(d) Model		
esRAGE	0.117 (0.039–0.353)	<0.0001
WBISI	0.593 (0.469–0.748)	<0.0001
Age	0.947 (0.682–1.314)	NS
Gender	1.416 (0.525–3.818)	NS
BMI-SDS	0.903 (0.718–1.134)	NS

sRAGE, soluble receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products.

glucose and area under the curve for glucose levels were similar between the two groups (both $p > 0.05$).

sRAGE and esRAGE values

Significant differences were documented in terms of sRAGE and esRAGE between the two groups. In details, the group with liver steatosis had significantly lower levels of sRAGE (Fig. 1) and esRAGE compared with the group without (both $p < 0.0001$) (Fig. 2).

Correlations and logistic regression analysis

To detect any association between sRAGE as well as esRAGE and the main metabolic parameters, a Spearman correlation was performed. In details, sRAGE correlated indirectly with HOMA-IR ($r = -0.244$, $p = 0.005$) and directly with WBISI ($r = 0.293$, $p = 0.001$), whereas no associations were found between esRAGE and other variables.

In addition, the association between sRAGE and esRAGE with the presence of liver steatosis was analyzed by a logistic regression analysis (Table 2). In the model (a), HOMA-IR and sRAGE were significantly and independently related to liver steatosis (both $p < 0.0001$); further, in the model (b), WBISI and sRAGE were significantly and independently related to liver steatosis (both $p < 0.0001$).

In the model (c), HOMA-IR and esRAGE were significantly and independently related to liver steatosis (both $p < 0.0001$), and in addition, in the model (d), WBISI and esRAGE were significantly and independently related to liver steatosis (both $p < 0.0001$).

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Date of first submission to ARS Central, October 22, 2010; date of acceptance, October 24, 2010.

Abbreviations Used

AGEs/RAGE = advanced glycation end products/receptor for advanced glycation end products
ALT = alanine aminotransferase
AST = aspartate aminotransferase
AUC = area under the curve
BMI = body mass index
esRAGE = endogenous secretory RAGE
HDL = high-density lipoprotein
HOMA-IR = homeostasis model assessment of IR
IR = insulin resistance
LDL = low-density lipoprotein
NAFLD = nonalcoholic fatty liver disease
SD = standard deviation
SDS = standard deviation score
sRAGE = soluble RAGE
T2D = type 2 diabetes
TG = triglycerides
WBISI = whole-body insulin sensitivity index
WC = waist circumference

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