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REGULAR ARTICLE

Advanced glycation end products and their receptors did not show any association with body mass parameters in metabolically healthy adolescents

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Keywords
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ABSTRACT

Aim: We determined the relationship between circulating advanced glycation end products (AGEs), AGE receptors and homeostatic model assessment for insulin resistance (HOMA-IR) in metabolically healthy obese and normal weight adolescents.

Methods: In 2015, we recruited 80 normal weight adolescents and 80 with obesity from schools Leon city, Mexico, and put them into metabolically healthy (HOMA-IR <3.0) and unhealthy (HOMA-IR >3.0) groups. We measured their body mass index (BMI) and carried out detailed blood analyses.

Results: We found a higher triglycerides, triglycerides/high-density lipoproteins cholesterol (TG/HDL-C) index, HOMA-IR, tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) in the metabolically healthy group and found correlations between HOMA-IR with BMI, the TG/HDL-C index and IL-6 and the TG/HDL-C index and BMI and (TNF-α). There was no correlation between markers of obesity and circulating N-carboxymethyl-lysine (CML) or soluble receptor for advanced glycation end products (sRAGE). Some unhealthy adolescents had higher CML (15.5 ± 2.7 U/mL, $p < 0.028$) and sRAGE (3123 ± 1364 pg/mL, $p < 0.001$) than the healthy group.

Conclusion: HOMA-IR and the TG/HDL-C index were associated with BMI and inflammation markers. CML and sRAGE were not associated with obesity or inflammation. These parameters were higher in unhealthy obese adolescents.

INTRODUCTION

Obesity is an increasingly important public health problem in the Western world and its prevalence is increasing in adolescents (1). It is associated with low-grade inflammation, attributed to the increased production of proinflammatory cytokines by abdominal fat and is a potential risk factor for type 2 diabetes mellitus (2). Advanced glycation end products (AGEs) are one of the many factors known to contribute to elevated inflammation (3), and we would expect them to be increased in obese subjects. AGEs have been shown to have both endogenous and exogenous sources. Whatever their origins, they may bind to receptors, such as the receptor for advanced glycation end products (RAGE), and initiate a cascade of intracellular signals that eventually conclude with the release of inflammatory cytokines and reactive oxygen species (4,5). The pathogenesis of many of the comorbidities associated with obesity

Abbreviations

AGER1, Advanced glycation end product receptor 1; AGEs, Advanced glycation end products; BMI, Body mass index; CML, ε-N-carboxymethyl-lysine; HOMA-IR, Homeostatic model assessment index; IL-6, Interleukin-6; MHO, Metabolically healthy obese; MUHA, Metabolically unhealthy obese; PCR, Polymerase chain reaction; RAGE, Receptor for advanced glycation end products; RNA, Ribonucleic acid; sRAGE, Soluble receptor for advanced glycation end products; TG/HDL-C, Triglycerides/high-density lipoproteins – cholesterol; TNF-α, Tumour necrosis factor alpha.

Key notes

- This study examined the relationship between circulating advanced glycation end products (AGEs), AGE receptors and homeostatic model assessment for insulin resistance in 80 metabolically healthy obese and 80 normal weight adolescents.
- Metabolically healthy obese adolescents had higher markers of inflammation and insulin resistance, but not ε-N-carboxymethyl-lysine (CML) or soluble receptor for advanced glycation end products (sRAGE).
- Metabolically unhealthy obese adolescents had higher CML and sRAGE independent of body mass index.

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may result from this enhanced inflammatory and oxidative stress status (6). In contrast to RAGE, the advanced glycation end product receptor 1 (AGER1) is an AGE receptor that binds, internalises and degrades AGEs (7). AGEs have also been shown to be associated with insulin resistance, which may be reversed by a low AGE diet (8,9). A study in a group of adults with metabolic syndrome showed that levels of serum AGEs were only increased in obese subjects who had at least one other feature of metabolic syndrome (10). In addition, a study in adolescents showed that soluble receptor for advanced glycation end products (sRAGE) was inversely correlated with the increasing number of components of metabolic syndrome in males but not in females (11). It has also been reported that a reduction in sRAGE precedes the development of metabolic syndrome (12). Few studies have been carried out in adolescents, which is a strategically important population, to establish long-term lifestyle changes aimed at avoiding chronic medical conditions such as diabetes and cardiovascular disease. However, it is interesting that circulating AGE levels were found to be decreased in a group of obese adolescents compared with their lean counterparts in at least two cohorts (13,14). These results were counterintuitive, as a positive association between obesity and markers of inflammation and oxidative stress such as AGEs would have been expected. A study in adolescents with obesity showed less sRAGE and greater insulin resistance and cardiovascular risks (15).

The prevalence of obesity and its comorbidities is particularly prevalent in Mexico (16) and a clear understanding of the potential role of AGEs, especially those of dietary origin, is critical to help establish public health policies. In this study, we tried to determine the relationship between circulating AGEs and the expression of AGE receptors, markers of inflammation and insulin resistance in a group of healthy adolescents with either normal or above normal weight in a Mexican community. We hypothesised that metabolically healthy adolescents with obesity would have had higher levels of AGEs, such as $^{\varepsilon}$N-carboxymethyl-lysine (CML) and RAGE, and lower levels of sRAGE and AGER1.

METHODS

This cross-sectional study was performed on 80 adolescents who had normal weight and stated that they were healthy and 80 with obesity. They were recruited from schools in the city of Leon, Mexico. The two groups were classified based on their body mass index (BMI) according to published tables by Cole et al. (17), using dataset-specific centiles linked to adult cut-off points of 25 and 30. Insulin resistance was defined as a HOMA-IR >3.0 (18) and was calculated using the Matthews' formula (19). The participants were grouped according to the homeostatic model assessment for insulin resistance (HOMA-IR) into metabolically healthy (HOMA-IR <3.0) or unhealthy (HOMA-IR >3.0).

There were 68 metabolically healthy obese subjects and 79 metabolically healthy normal weight subjects included in this study (20). We did not include the 12 metabolically unhealthy obese adolescents and one metabolically unhealthy normal weight adolescent in the analysis.

The inclusion criteria included the following: stage five of the Tanner scale; no history of kidney diseases, hormonal imbalance, therapy with steroids or growth hormone; normal menstrual cycle for females; no tobacco smoking and no evidence of any acute infection. At the initial study visit, all participants received an evaluation that included their medical history and a physical examination and they provided a fasting blood sample. Plasma was processed the same day and glucose was measured using the (insert name of product) enzymatic method (Lakeside, Mexico City, Mexico), together with triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-C) using the standard (CHOD-POD, liquid) enzymatic method (Spinreact, Girona, Spain). Serum aliquots were stored at −80°C until the further determination of a number of biomarkers. CML was measured in serum by an enzyme-linked immunosorbent assay using noncross-reactive monoclonal antibodies (4G9) raised against a synthetic standard; $^{\varepsilon}$N-carboxymethyl-lysine bovine serum albumin was measured as previously described (21) and insulin was measured by immunoradiometric assay (Cisbio Bioassays, Minneapolis, MN, USA). We also measured soluble receptor for AGEs and interleukin-6 (IL-6) high sensitivity and tumour necrosis factor-α (TNF-α) by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA).

In addition, we obtained extra blood from 48 participants – 27 with normal weight and 21 who were obese – to separate peripheral mononuclear cells so that RAGE and AGER1 expression could be measured.

Peripheral blood mononuclear cells

Peripheral blood mononuclear cells were separated from fasting, ethylenediaminetetraacetic acid anticoagulated blood by Ficoll-Hypaque Plus gradient (Amersham Biosciences, Uppsala, Sweden) and used to isolate messenger ribonucleic acid (RNA). Total RNA was extracted by Trizol (Molecular Probes, Inc, Eugene, OR, USA). The extracted RNA had an optical density 280:260 ratio between 1.8 and 2.0. Total RNA was reversed transcribed using Superscript III Real Time (Invitrogen, Carlsbad, CA, USA).

Polymerase chain reaction (PCR) assay

The quantitative SYBR Green real-time assay (Roche, Indianapolis, IN, USA) was performed to analyse the expression of messenger RNA for AGER1 and RAGE. Briefly, 7.5 μL of template complementary deoxyribonucleic acid (cDNA) was added to a final volume of 20 μL containing 1× SYBR Green PCR master mix and 5 pmol/L of the primers. Amplification was performed with 40 cycles of denaturation at 95°C for 15 seconds, annealing at 52°C for 20 seconds and elongation at 72°C for 30 seconds. Sequences of the primers used for real-time PCR were AGER1, forward primer, 5′-CTGGGGCTCTTCATCTTCAG-3′; reverse primer 5′-GTTGCATCTCCCACAGAGGT-3′; RAGE, forward primer, 5′-AGGAGCGTGCAGAACTGAAT-3′; reverse primer

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5′-TTGGCAAGGTGGGGTTATAC-3′. The messenger RNA levels were acquired from the value of the threshold cycle of AGER1 and RAGE and normalised against the threshold cycle of glyceraldehyde-3-phosphate dehydrogenase (22).

Statistical analysis

Data are presented as means and standard deviations. The Kolmogorov–Smirnov goodness-of-fit test was used to test for normal distribution. Differences between the groups were analysed by the Student *t*-test or Mann–Whitney *U* test for nonparametric variables. Correlation analyses were examined by Pearson's correlation coefficients. Significant differences were defined as a p value of <0.05 and are based on two-sided tests. The data were analysed using SPSS statistical program, version 18.0 for Windows (SPSS Inc, Chicago, IL, USA) and Statistica 7 software (StatSoft Inc, Tulsa, OK, USA).

The study was approved by the Institutional Ethical Committee at the University of Guanajuato, Guanajuato, Mexico, and all subjects and their parents or tutors signed a consent form before enrolment.

RESULTS

General findings

The clinical and biochemical characteristics of both groups are shown in Table 1. There were no differences in age, gender distribution or height between both groups, but, as expected by study design, the obese group had a much higher weight, BMI and waist circumference than the nonobese group. The main differences were in higher triglycerides, very low density lipoprotein, glucose, insulin, insulin resistance, TNF-α and IL-6 in the obese group. There were no significant differences in serum CML, sRAGE, RAGE or AGER1 between both groups. There were no statistically significant differences between gender for any one of the parameters in Table 1, except for weight, height and BMI, which were all higher in males than females: 70.5 ± 14 kg versus 61 ± 12 kg, 169 ± 6 cm versus 159 ± 6 cm and 24.5 ± 5 versus 24.1 ± 4, respectively. More specifically, serum CML was 12.6 ± 3.8 U/mL versus 13.0 ± 3.9 U/mL and sRAGE was 1912 ± 949 pg/mL versus 1745 ± 821 pg/mL in males and females, respectively.

Of note, that 12 metabolically unhealthy obese (six males) had higher serum CML (15.5 ± 2.7 U/mL, $p < 0.028$) and sRAGE (3123 ± 1363.6 pg/mL, $p < 0.001$) than the metabolically healthy obese subjects described in Table 1.

There was only one subject with normal weight, a woman with HOMA-IR $\geq$3.0, and both her serum CML (22.9 U/mL) and sRAGE (4688 pg/mL) were higher than those in metabolically healthy normal weight subjects in Table 1.

Associations between the different parameters

Table 2 shows results of the univariate correlation in metabolically healthy obese adolescents between the main parameters. BMI correlated positively with HOMA-IR, IL-6 and the TG/HDL-C index; IL-6 correlated positively with HOMA-IR and TNF-α correlated negatively with CML and positively with the TG/HDL-C index. No correlations were found between CML and any of the AGE receptors, namely RAGE and AGER1. There were no correlations between BMI and CML.

DISCUSSION

In this cohort of healthy community-dwelling adolescents, we did not find any correlation between markers of obesity, such as BMI or waist circumference, and circulating levels of CML or sRAGE, two commonly measured parameters of the AGE-RAGE axis. This was in contrast to previous studies that showed decreased levels of CML and sRAGE when obese and lean children and adolescents were compared (12–14,23).

On average, our obese subjects had higher circulating levels of triglycerides, fasting glucose, insulin and HOMA-IR than the normal weight adolescents and this was similar to findings in previously published studies in other countries (24). However, the averages of these levels were still within normal limits, because we excluded those few subjects with insulin resistance.

In adults, there is still controversy about the relationship between anthropometric parameters and levels of serum CML, as some studies have found a direct relationship (10) and others have reported an inverse association (25,26). In those studies that found an inverse association between BMI and CML levels, it was assumed that lower levels of serum CML in obese subjects resulted from trapping CML in the inflamed, enlarged fat tissue (25,26). As these different studies dealt with different populations of different ages and used different methods to measure CML, it is difficult to interpret the differences. Of note, the current study measured serum CML using the same technique performed by the same technician and using the same antibody that was used in a previously published study of adults with and without metabolic syndrome (10). That study found that BMI on its own did not correlate with serum CML, but levels of serum CML were much higher when obesity was present together with at least one other feature of metabolic syndrome. Of interest, when we compared the 12 obese subjects excluded from the analyses because of a HOMA-IR of >3.0 with the metabolically healthy obese subjects, the first subjects also had higher levels of CML and sRAGE and the only normal weight adolescent with a HOMA-IR that was greater than 3.0 also had higher levels of CML and sRAGE. The findings support the concept that when obesity is combined with other manifestations of metabolic syndrome, in particular high HOMA-IR, it is associated with higher serum AGE levels (10). In fact, if we were to extrapolate from the only normal weight subject with high HOMA-IR, the conclusion would be that insulin resistance, as determined by HOMA-IR, was the main determinant of CML levels, regardless of body mass.

A study of adolescents with obesity and metabolic syndrome (11) found an association between sRAGE and waist circumference, BMI and HOMA-IR and concluded

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Table 1 Clinical and biochemical characteristics of the two metabolically healthy study groups

Variable	Normal weight (n = 79)	Obese (n = 68)	p
Sex (%) (male/female)	22/31	18/28	0.80
Age (years)*	16.0 (16.0–17.0)	16.0 (15.0–18.0)	0.81
Weight (kg)	56.9 ± 7.8	74.7 ± 13.1	0.001
Height (cm)	164.1 ± 0.08	163.1 ± 0.07	0.39
Waist (cm)	78.1 ± 9.5	84.1 ± 11.2	0.001
BMI (kg/m^2)	21.1 ± 1.9	28.0 ± 4.0	0.001
Glucose (mmol/L)	4.79 ± 0.48	4.97 ± 0.41	0.01
Cholesterol (mmol/L)	39.23 ± 6.76	37.70 ± 7.07	0.18
Triglycerides (mmol/L)	1.10 ± 0.39	1.24 ± 0.37	0.03
HDL-C (mmol/L)	1.69 ± 0.18	1.65 ± 0.22	0.20
LDL-C (mmol/L)	1.70 ± 0.52	67.2 ± 1.62	0.66
VLDL-C (mmol/L)*	0.46 (0.39–0.59)	0.52 (0.44–0.63)	0.01
TG/HDL index	1.55 ± 0.6	1.75 ± 0.6	0.02
Insulin (μU/mL)	5.7 ± 2.5	7.2 ± 2.9	0.001
HOMA-IR	1.2 ± 0.5	1.6 ± 0.6	0.001
IL-6 (pg/mL)	0.8 ± 0.5	1.1 ± 0.7	0.002
TNF-α (pg/mL)*	33.2 (17.3–62.1)	42.0 (29.0–70.1)	0.04
sRAGE (pg/mL)*	1601 (1290–1932)	1601 (1296–1919)	0.74
CML (U/mL)	12.8 ± 4.0	12.8 ± 3.8	0.99
RAGE†	27 ± 3	28 ± 2	0.54
AGER1†	27 ± 2	28 ± 1	0.18

AGER1 = Advanced glycation end product receptor 1; BMI = Body mass index; CML = $^{\varepsilon}$N-carboxymethyl-lysine; RAGE = Receptor for advanced glycation end products; sRAGE = Soluble advanced glycation end product receptor.
All data with normal distributions are expressed as means and standard deviations (±).
*Nonparametric variables not parametric are expressed as medians and interquartile ranges.
†RAGE and AGER were only analysed in 26 subjects without obesity and in 20 obese subjects.

Table 2 Univariate correlations between selected biochemical parameters and BMI in metabolically healthy obese adolescents

	BMI	HOMA	TG/HDL	TNF-α	IL-6	CML	sRAGE	RAGE	AGER1
BMI	1								
HOMA	r = 0.323*	1							
	p = 0.007								
TG/HDL	r = 0.334*	0.346*	1						
	p = 0.005	0.004							
TNF-α	r = −0.064	0.204	0.326*	1					
	p = 0.602	0.095	0.007						
IL-6	r = 0.368*	0.320*	0.131	−0.068	1				
	p = 0.002	0.008	0.287	0.583					
CML	r = 0.146	0.090	0.067	−0.251*	−0.045	1			
	p = 0.233	0.0464	0.587	0.039	0.713				
sRAGE	r = −0.290	0.111	−0.165	0.110	−0.016	0.073	1		
	p = 0.215	0.367	0.177	0.372	0.900	0.556			
RAGE	r = −0.290	−0.132	−0.067	0.104	−0.325	0.094	0.020	1	
	p = 0.215	0.578	0.780	0.662	0.162	0.693	0.197		
AGER1	r = 0.280	0.026	0.048	−0.401	0.045	0.263	0.250	−0.020	1
	p = 0.232	0.913	0.842	0.080	0.722	0.263	0.295	0.932	

AGER1 = Advanced glycation end product receptor 1; BMI = Body mass index; CML = $^{\varepsilon}$N-carboxymethyl-lysine; HOMA = Homeostatic model; IL-6 = Interluikin-6; RAGE = Receptor for advanced glycation end products; sRAGE = Soluble advanced glycation end product receptor; TG/HDL = Triglycerides/high-density lipoproteins – cholesterol.
*Statistically significant p values.

that BMI may be the most important determinant of sRAGE. Another study (15) also found that adolescents with obesity had less sRAGE and greater HOMA-IR, which are associated with cardiovascular risk.

Of interest, serum CML levels in the current cohort were significantly higher than those of obese male adults in another study who had an average age of 43 years ($p < 0.001$) (27). They were also only slightly lower than

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patients newly diagnosed with diabetes, reported by our group, who had an average age of 48.5 years ($p < 0.036$) (28). That study used the same methodology for measuring CML as this study and comprised participants of the same region and country. This suggests that, at least in this particular community, serum CML levels decreased somewhat from adolescence to adulthood. Moreover, the sRAGE levels in our cohort seemed to be higher than adult subjects from the same population and using the same measurement kits (unpublished results). The factors involved in these changes were not within the scope of the current study.

We did not find any correlation between serum CML and RAGE and other markers of inflammation in this cohort, in contrast to the findings of several previous studies (3). This may result, at least partly, from the cross-sectional nature of the study as well as the fact that most of the obese participants did not have evidence of significant inflammation when compared with their nonobese counterparts, as reflected by only minimal elevation of inflammation markers. With regard to AGER1, we observed only a marginal correlation with TNF-α, which agreed with the concept that AGER1 is a receptor that opposes AGEs and oxidative stress and RAGE overexpression (29) and may therefore represent a unique candidate for the AGE defence intended for tissue protection against AGE toxicity (30). There was no association between serum CML and sRAGE in this study, although we previously found a very good positive correlation between these two parameters when they were assessed by the same methodology in a group of patients with recently diagnosed diabetes (24). That finding yet again highlighted the challenges of interpreting the AGE-RAGE axis status from isolated values of sRAGE in the absence of serum AGE levels, which is frequently done in studies.

Dietary AGE intake and renal function have been reported to be important determinants of circulating CML levels. Unfortunately, we did not measure dietary AGE intake or kidney function in our participants and this was a limitation of the current study. Other study limitations included the relatively small sample size and the cross-sectional nature, which only allowed us to establish associations but not causality. The fact that the population was limited to a specific community in Mexico may limit the generalisability of the conclusions. However, by decreasing population heterogeneity, it may have obviated important genetic factors at the same time.

CONCLUSION

Measurements of serum CML and AGE receptors, such as sRAGE, RAGE and AGER1, in a population of metabolically healthy adolescents with different BMIs did not show any association between any of these parameters and anthropometric markers of obesity. However, these parameters were higher in a small group of adolescents with high HOMA-IR, independent of BMI. This emphasises the need to clearly define the study population and methodology used to assess different parameters when trying to compare results with other studies in this area.

CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

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