Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 2457–2461

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

Advanced glycation end products (AGEs) and their soluble receptors (sRAGE) as early predictors of reno-vascular complications in patients with uncontrolled type 2 diabetes mellitus

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ARTICLE INFO

Article history:
Received 22 May 2019
Accepted 27 June 2019

ABSTRACT

Aim: To evaluate the role of advanced glycation end-products (AGEs) and their soluble receptors (sRAGE) expression levels as predictors of vascular complications in uncontrolled type 2 diabetes mellitus (T2DM).

Methods: Cross-sectional study was conducted on T2DM adults of both sexes who attended the outpatient service of Al-Karak Teaching Hospital, Jordan during the period from June 2017 to August 2018. Participants were categorized in two groups according to their glycemic control and the presence of reno-vascular complications. Twenty healthy subjects were recruited as control group. Blood sample was obtained from all participants and used for the assessment of FBG, HbA1c, serum AGEs and sRAGE, serum urea and creatinine; 24 h urine was also collected for the determination of urinary albumin.

Results: Diabetic subjects with vascular complication had a significantly higher serum AGEs 50.3 ± 13 *vs.* 28.9 ± 8 pg/ml) and AGEs/sRAGE ratio (0.058 ± 0.02 *vs.* 0.037 ± 0.02) associated with significantly lower serum sRAGE (868.7 ± 50.8 *vs.* 912.8 ± 294.3) compared to those with no complications. Serum AGEs and sRAGE showed weak negative and non-significant association in both groups of patients. However, the AGEs/sRAGE ration was inversely and significantly associated with the urinary albumin/creatinine ratio ($r = -0.51$, $P = 0.009$) only in DM patients with reno-vascular complications.

Conclusion: We found an association between AGEs/sRAGE ratio and urinary albumin/serum creatinine ratio in T2DM patients with reno-vascular complications; providing evidence that serum AGEs and sRAGE can be considered as predictors of vascular complications in uncontrolled T2DM patients.

1. Introduction

Advanced glycation end products (AGEs) are stable metabolic end products [1] resulted from the slow non-enzymatic glycation of proteins (Maillard reaction) occurred mostly during chronic diseases like diabetes [2,3]. Nevertheless, AGEs are also rapidly formed during various conditions of oxidative stress, which potentially involved in the pathogenesis of sepsis [4,5]. Moreover, the inflammation-induced oxidative stress leads to the formation of a highly reactive carbonyl compounds, which are partially converted into AGEs [6,7]. Cumulative aggregation of AGEs may also be demonstrated in various pathophysiological conditions like Alzheimer's disease, atherosclerosis and systemic lupus erythematosus [8–10]. In addition, the exogenously formed AGEs may act as a source of chemically reactive toxins (e.g., heated food) and absorbed through the intestine to the systemic circulation [11]. AGEs played a role through the signal transduction cascade of the inflammatory response and can bind to multiple receptors, including the membrane-bound receptor for AGEs (RAGE) that activates the proinflammatory nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) cascade. This leads to excessive expression of RAGEs, which produce more NF-κB, resulting in chronic inflammation [12]. RAGE was expressed in human plasma as two soluble isoforms; the first one is created as a membrane bound receptor and cleaved by metalloproteinases [13], while the other is produced by alternative splicing of the RAGE gene [14]. Both constituted the plasma soluble RAGE (sRAGE). Moreover, many recent data have focused on the association between the expression of sRAGE and the microvascular injury in complicated

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https://doi.org/10.1016/j.dsx.2019.06.019
1871-4021/

DM, which increased the risks of cardiovascular diseases and other vascular complications [15,16]. The present study aims to evaluate the role AGEs and sRAGE expression as predictors of vascular complications in uncontrolled diabetes mellitus.

2. Subjects and methods

2.1. Study design and patient selection

This cross-sectional study was performed at the out-patient clinic, Al-Karak Teaching Hospital, Jordan June 2017 to August 2018. All the participants provided their signed written informed consent before enrollment in the study. The research protocol was approved by the Research Ethics Committee of the Faculty of Pharmacy, Al-Rafidain University College, Iraq and the local Medical Ethics at Al-Karak Teaching Hospital. The study was conducted on 50 patients previously diagnosed with type 2 diabetes mellitus (T2DM) and poor glycemic control, who are attending the daily clinic for routine follow-up. Based on the results of renal function markers (creatinine, urea and urinary albumin levels), they are allocated into 2 groups (each of 25 patients); group I, T2DM patients without vascular complications; and group II, T2DM patients with vascular complications. Twenty healthy subjects, matched for age with the T2DM patients, were selected as a control group (group III) for comparison of the biomarkers. The diabetic patients were recruited to participate when they attended the hospital during their regular screening visit for diabetic complications and were ranked, according to their urinary albumin level, into two groups: those with normal albuminuria (group I, <30 mg/day) and those with microalbuminuria (group II, ≥30 mg/day).

2.2. Evaluation of biomarkers

In all participants, fasting blood samples (10 ml) were obtained and divided into two parts; the first part was kept in heparinized tube and used for the evaluation of blood glucose and HbA1c; while the other part was kept in plain tube and left to clot for obtaining the serum which is utilized for measurement of urea, creatinine, AGEs and sRAGE. Meanwhile, the participants were asked to collect 24 h urine for measurement of urinary albumin secretion. Serum AGEs were assessed using a competitive ELISA kit (MyBiosource, USA) according to a standardized method [17]. Briefly, the 96-well plates were coated with 50 μl/well of AGE-RNase (3.75 μg/ml) and 50 μl of serum (1:4 dilution) added, followed by 50 μl of 1:500 diluted anti-AGE antibody. Alkaline phosphate conjugated anti-rabbit IgG (1:2000) in dilution buffer was then added to each well and incubated for 1 h at 37 °C. After washing, color was developed by adding 100 μl *p*-nitrophenyl phosphate substrate. The optical density (OD) was measured at 405 nm by an ELISA reader. Serum sRAGE levels were measured using ELISA kit (MyBiosource, USA) according to the manufacturer's protocol [18]. Briefly, after washing, plates were incubated with streptavidin horseradish peroxidase, developed with appropriate substrate and OD 450 nm was determined using an ELISA plate reader. HbA1c was measured in whole blood using ion-exchange high-performance liquid chromatography with the Bio-Rad Variant Haemoglobin Testing System (Bio-Rad Laboratories, CA, USA). Urinary albumin was measured by rate nephelometry using the Beckman Array 360 Analyser (Beckman-Coulter, CA, USA). Serum urea and creatinine were analyzed using ready-made kits for spectrophotometric methods.

2.3. Statistical analysis

The data were statistically analyzed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA) and Graph Pad Prism 5.1 (GraphPad Software Inc., CA, USA). All the followed tests were two-sided, and p value < 0.05 was considered for statistical significance. Unpaired Student's *t*-test and ANOVA were utilized for normally distributed variables, and the nonparametric Mann-Whitney U and Kruskal-Wallis tests were employed for asymmetrically distributed variables. Pearson or Spearman rank correlation analysis and logistic regression analysis were performed to explore the relationships between the serum sRAGE and AGEs levels and the markers of vascular complications.

3. Results

Table 1 showed revealed non-significant differences between the ages of the participants in the 3 groups ($P = 0.6$).The gender distribution in all groups is comparable and significantly not different ($P = 0.918$). Regarding disease duration, the T2DM patients with disease-related complications (group III) are presented with significantly longer duration (109%; $P < 0.0001$) compared with that reported in group I. Table 1 also showed that the patients in group II are presented with significantly lower glycemic control, in terms of FBG and HbA1c markers, compared with the values reported in groups I and III ($P < 0.001$). Moreover, the serum levels

Table 1
The patient characteristic and the biochemical markers of the T2DM patients and health subjects enrolled in the study.

variables	Groups			*p* value
	I	II	III Control	
Sample size	(25) 35.7%	(25) 35.7%	(20)28.6%	
Age (year)	55.8 ± 4.1	55.6 ± 4.2	56.8 ± 3.9	0.6
Gender				
Male *n*(%)	13 (52%)	14 (56%)	10 (50%)	0.918
Female *n*(%)	12 (48%)	11(44%)	10 (50%)	
Disease Duration (year)	3.2 ± 1	6.7 ± 0.9	0	<0.001*
Fasting Blood glucose (mg/dl)	192.3 ± 12.4	227.2 ± 11.3	86.9 ± 5.1	<0.001*,#
HbA1c (%)	6.7 ± 0.4	7.9 ± 0.7	4.3 ± 0.2	<0.001*,#
AGEs (pg/ml)	28.9 ± 8	50.3 ± 13	9.8 ± 0.9	<0.001*,#
sRAGE (pg/ml)	912.8 ± 294.3	868.7 ± 50.8	1718.3 ± 455.7	<0.001*,#
AGEs/sRAGE ratio	0.037 ± 0.02	0.058 ± 0.02	0.006 ± 0.001	<0.001*,#
S. Creatinine (mg/dl)	1.04 ± 0.14	1.26 ± 0.08	0.81 ± 0.08	<0.001*,#
S. Urea (mg/dl)	28.5 ± 2.8	43.4 ± 5.0	23.4 ± 2.1	<0.001*,#
U. Albumin (mg/24 h)	14.4 ± 1.1	223.5 ± 7.1	19.5 ± 3.4	<0.001*,#

Categorical parameters were expressed as number and percentage; continuous variables were expressed as mean ± SD; *n*: number of subjects; * significantly different ($p < 0.05$) when compared all groups; # significantly different ($p < 0.05$) when compared groups I and II.

of AGEs and sRAGE in group II patients were significantly higher than those reported in both group II patients and healthy subjects (group III) ($P < 0.001$). Similarly, the AGEs/sRAGE ratio was significantly greater in group II compared with group I and group III (32.2% and 89.7%; $P < 0.001$, respectively). In this regard, Table 1 also showed that serum levels of urea and creatinine and the daily urinary albumin elimination were significantly elevated in T2DM patients in groups I and II compared with the healthy subjects (group III); however, these values in group II patients were extremely greater than those reported in group I patients ($P < 0.001$). Fig. 1 (A and B) showed that serum levels of AGEs and sRAGE were negatively and non-significantly correlated in both group I and II ($r = -0.075$ and -0.254, respectively); however, those markers demonstrated non-significantly positive correlation ($r = 0.26$, $P = 0.27$) in the healthy subjects (Fig. 1C). In Table 2, correlation studies showed the weak association between serum levels of AGEs and sRAGE with the markers of glycemic control and vascular complications in non-complicated T2DM patients (group I). Meanwhile, the glycemic indices were significantly correlated with the markers of vascular changes at this stage of the disease. In Table 3, serum sRAGE levels demonstrated non-significant negative association with the serum AGEs level ($r = -0.25$), while a highly negative and significant association was reported with the glycemic control and vascular complication markers. Meanwhile, the serum level of AGEs was positively and significantly associated with the HbA1c levels ($r = 0.51$) in this group. Fig. 2A showed a weak negative and non-significant association between AGEs/sRAGE ratio and the marker of reno-vascular complications (U. Albumin/S. Creatinine ratio) ($r = -0.011$, $P = 0.95$) in group I patients. Meanwhile, Fig. 2B clearly showed a highly negative and significant association between the AGEs/sRAGE ratio and the renal complication index ($r = -0.51$, $P = 0.009$) in the T2DM patients of group II. However, in this regard Fig. 2C revealed a weakly negative and non-significant association between these markers in the group of healthy subjects (group III) ($r = -0.11$, $P = 0.64$).

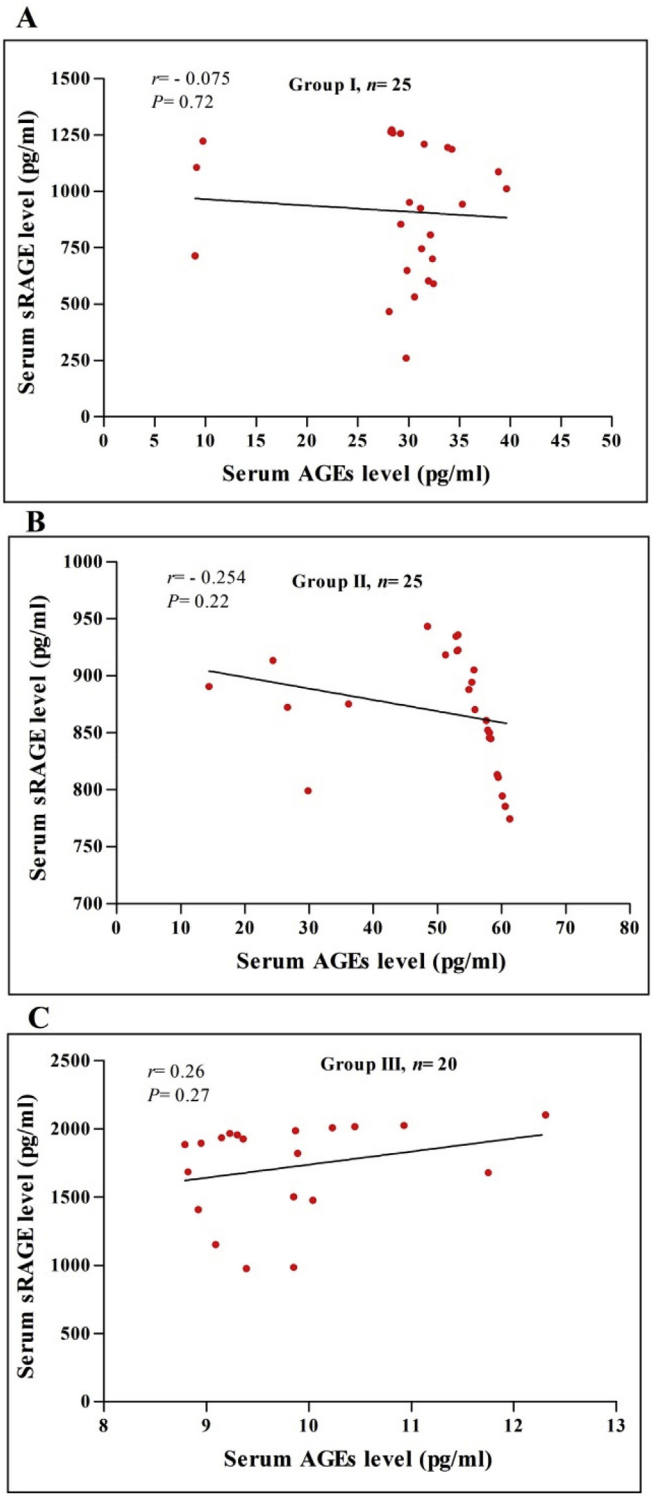

Fig. 1. Pearson's correlation between serum levels of AGEs and sRAGE in A) T2DM patients without vascular complications (group I); B) T2DM patients with vascular complications (group II); C) healthy subjects (group III).

4. Discussion

In Arab countries, the elevated rates of obesity, metabolic dysregulations and diabetes mellitus and their consequences threaten seriously the people health and quality of life. Many studies are conducted to characterize the etiology of various metabolic diseases in a prospective manner and to identify predictive

Table 2
Correlation between the biochemical markers of T2DM patients in group I.

Variables	AGEs	sRAGE	HbA1c	FBG	Cr	Urea	U. Alb
AGEs		−0.08	0.17	0.15	0.15	0.12	0.22
sRAGE	−0.08		0.13	0.11	0.12	0.09	0.17
HbA1c	0.17	0.13		0.97[a]	0.89[a]	0.87[a]	0.96[a]
FBG	0.15	0.11	0.97[a]		0.94[a]	0.91[a]	0.97[a]
Cr	0.15	0.12	0.89[a]	0.94[a]		0.91[a]	0.89[a]
Urea	0.12	0.09	0.87[a]	0.91[a]	0.91[a]		0.85[a]
U. Alb	0.22	0.17	0.96[a]	0.97[a]	0.89[a]	0.85[a]	

[a] Significantly different ($p < 0.05$); AGEs: advanced glycation end products; sRAGE: soluble receptor of AGE; HbA1c: glycated hemoglobin; FBG: fasting blood glucose; Cr: creatinine; U. Alb: urinary albumin.

Table 3
Correlation between the biochemical markers of T2DM patients in group II.

Variables	AGEs	sRAGE	HbA1c	FBG	Cr	Urea	U. Alb
AGEs		−0.25	0.51[a]	0.25	0.34	0.12	0.26
sRAGE	−0.25		−0.68[a]	−0.97[a]	−0.85[a]	−0.89[a]	−0.96[a]
HbA1c	0.51[a]	−0.68[a]		0.75[a]	0.65[a]	0.63[a]	0.75[a]
FBG	0.25	−0.97[a]	0.75[a]		0.83[a]	0.91[a]	0.99[a]
Cr	0.34	−0.85[a]	0.65[a]	0.83[a]		0.82[a]	0.80[a]
Urea	0.12	−0.89	0.63[a]	0.91[a]	0.82[a]		0.88[a]
U. Alb	0.26	−0.96	0.75[a]	0.99[a]	0.80[a]	0.88[a]	

[a] Significantly different ($p < 0.05$); AGEs: advanced glycation end products; sRAGE: soluble receptor of AGE; HbA1c: glycated hemoglobin; FBG: fasting blood glucose; Cr: creatinine; U. Alb: urinary albumin.

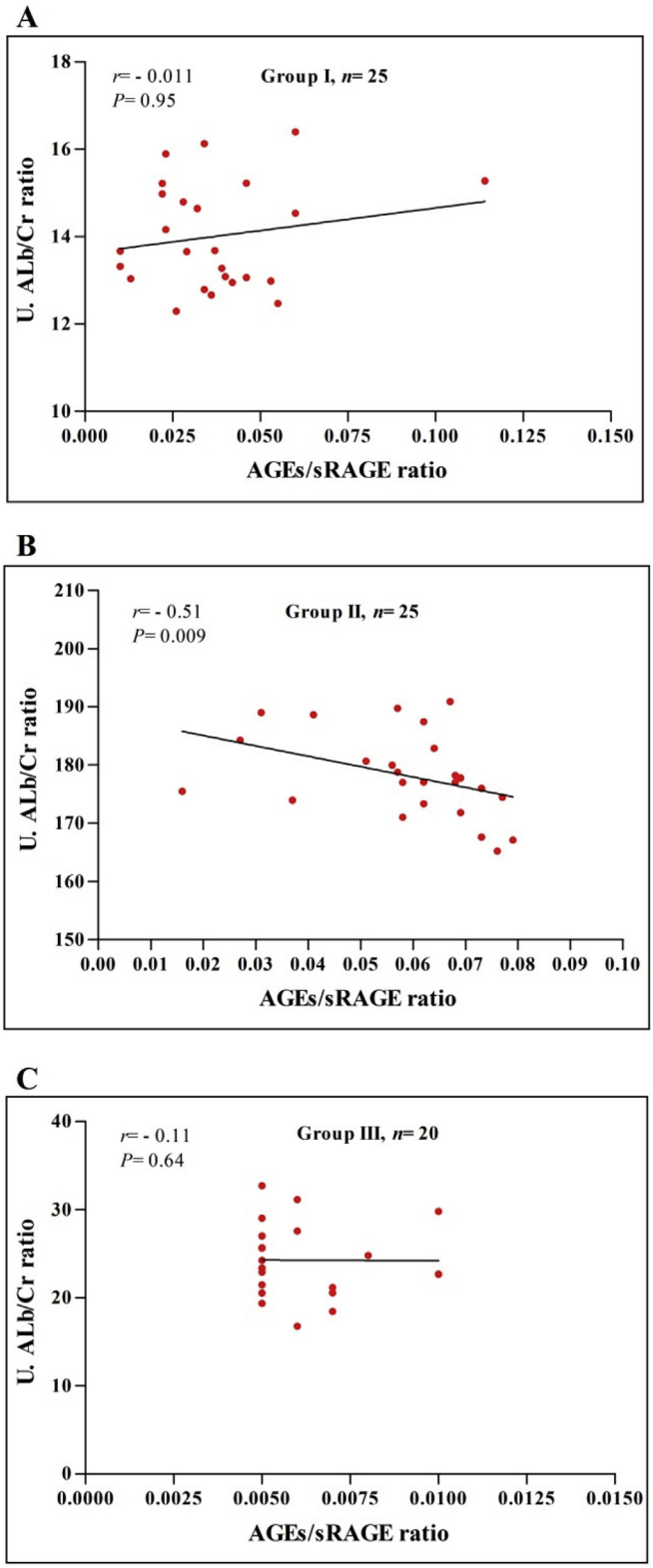

Fig. 2. Spearman's correlation between AGEs/sRAGE ratio and U. Albumin/S. creatinine ration in A) T2DM patients without vascular complications (group I); B) T2DM patients with vascular complications (group II); C) healthy subjects (group III).

biomarkers. Regarding the AGE-sRAGE axis, the published data suggested that in T2DM and obese patients undergoing bariatric surgery, higher baseline levels of sRAGE predicted weight reduction and remission from T2DM three years post-intervention [19,20]. Accordingly, the present study aimed to evaluate the feasibility of this approach in relation with predictors of T2DM in an Arab population. The present study clearly showed the significantly negative correlation between sRAGE and the diabetes-induced deterioration of renal function in complicated T2DM. It has been reported that circulating AGEs were elevated in DM and predict the development of DM-associated complications [21,22]; however, the capability of sRAGE isoforms to be involved similarly was equivocal. It has been reported that AGEs directly influence the initiation of DM complications via the alteration of functional proteins with consequent activation of RAGE signaling pathway. However, sRAGE acts to trap AGEs; therefore, it is highly expected that administration of sRAGE both in vitro and in vivo attenuates AGE/RAGE-mediated complications like atherosclerosis [23], and insulin resistance [24]. In the present study, the reported weak correlation between the changes in plasma sRAGE and AGEs suggest that sRAGE may be depleted with disease progression and no more capable to trap more AGEs. Moreover, with progressive DM-related complications, the rate of decline in sRAGE was highly associated with the severity of vascular damage in the renal tissue. The capacity of sRAGE to trap circulating AGEs in a physiologically meaningful way may be conflicted because of the high difference in the concentrations between the decoy and the ligand [25,26]. Although the results of the present study my conflict with other reports [25], it is important to recognize that many studies have mentioned that lower plasma sRAGE levels may be associated with poor health outcomes [27,28]. In this regard, in children who later progressed to type 1 diabetes, manifested a decrease in their plasma sRAGE levels at seroconversion to positivity for DM-predictive autoantibodies [29]. However, it is also possible that during DM-induced renal complications the reduced renal clearance of sRAGE may dramatically uncover the induction of RAGE expression that might not be recognized in uncomplicated DM and healthy adults. The reported decline in the plasma sRAGE level in complicated DM might reflect a failure of its protective mechanism, which could be clearer among patients with a relatively fast disease progression [30]. The presented data, although limited by small sample size, suggest that the plasma concentrations of AGEs and AGEs/sRAGE ratio are elevated in patients who have high or low serum sRAGE. Accordingly, both AGEs and the AGEs/sRAGE ratio should serve as a universal biomarker. However, this not true because the AGE-RAGE axis includes three players: AGEs, RAGE, and sRAGE. AGEs are only one player in the scheme of the AGE-RAGE axis. All three players in the scheme of the AGE-RAGE axis should be involved in formula that represents a universal biomarker/risk indicator.

5. Conclusion

The study demonstrated an association between AGEs/sRAGE ratio and urinary albumin/serum creatinine ratio in T2DM patients with reno-vascular complications; providing evidence that serum AGEs and sRAGE may be considered as predictors of vascular complications in uncontrolled T2DM patients.

Conflicts of interest

Nothing declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.06.019.

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