Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Original Paper | Praca oryginalna
Pediatr Endocrinol Diabetes Metab 2015;21,4:162-170
DOI: 10.18544/PEDM-21.04.0038

Postprandial sRAGE levels in type 1 diabetes mellitus in children and adolescents

Poposiłkowe stężenie sRAGE u dzieci i młodzieży z cukrzycą typu 1

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Abstract

Introduction. Hyperglycaemia state increases the accumulation of the advanced glycation end-products (AGEs) in the body, which, in turn, induce the development of micro – and macroangiopathic lesions through binding with their receptor, RAGE (Receptor for Advanced Glycation Endproducts). Soluble isoform of RAGE receptor (sRAGE), circulating in the serum, binds with AGEs, and inhibits their attachment to the surface receptor. In turn, the above mentioned interaction inhibits the activation of the surface receptor. Previous studies did not provide a clear answer to the question about the importance and role of sRAGE in the development and maintaining of inflammation in children and adolescents with type 1 diabetes mellitus (T1DM). Studies assessing the role of the above mentioned eproteins in postprandial period are scarce. **Aim** to compare sRAGE levels in T1DM children vs. the control group, and to assess sRAGE postprandial levels in T1DM children and adolescents. **Material and methods.** The study involved 71 patients (35 girls and 36 boys) aged 7–17 years, diagnosed with T1DM, with treatment duration from 6 to 60 months. The control group consisted of 20 children (9 girls and 11 boys) aged 6.5–16 years. Due to a potential impact on study results, patients with other diseases were excluded. sRAGE levels were measured in the morning on fasting (at blood glucose levels within 80–120mg% range), and also at 1, 2 and 4 hours after a standard meal. **Results.** In the T1DM group, statistically significant **higher** sRAGE levels were measured at 0', 1 and 4h of the study compared to the control group. In the T1DM children with HbA1c level <8 % and diabetes mellitus duration <2 years, statistically significant **higher** sRAGE levels were observed on fasting, and at 1 and 4h of the study compared to the control group. In patients with T1DM, sRAGE fasting levels were statistically significanty **higher** compared to 1, 2 and 4h measurements. The results show a significant negative correlation between glucose and sRAGE levels measured at the 2nd hour of the study. However, no correlation between sRAGE and HbA1c levels as well as between diabetes mellitus duration were observed. **Conclusions.** The inflammation is more pronounced in the T1DM group and hyperglycaemia episodes increase inflammatory processes.

Key words

sRAGE, postprandial hyperglycaemia, type 1 diabetes mellitus, metabolic memory

Streszczenie

Wstęp. Hiperglikemia nasila gromadzenie końcowych produktów glikacji białek – AGEs (Advanced Glycation End-products), które poprzez łączenie się ze swoim receptorem – RAGE (Receptor for Advanced Glycation End-products) prowadzą do mikro i makroangiopatii cukrzycowej. Krążąca w surowicy krwi rozpuszczalna izoforma receptora – sRAGE (soluble Receptor for AGEs) łącząc się z AGEs uniemożliwia ich przyłączanie się do receptora powierzchniowego i w konsekwencji jego aktywację. Przeprowadzone dotychczas badania nie dały jednoznacznej odpowiedzi na pytanie o znaczenie i udział sRAGE w rozwoju i podtrzymywaniu stanu zapalnego u dzieci i młodzieży z cukrzycą typu 1. Niewiele jest badań dotyczących roli tych cytokin w okresie poposiłkowym. **Cel.** Porównanie stężenia sRAGE u dzieci z cukrzycą typu 1 i w grupie kontrolnej oraz ocena stężenia sRAGE w okresie poposiłkowym u dzieci i młodzieży z cukrzycą typu 1. **Materiał i metody.** Badaniami objęto 71 pacjentów w wieku od 7 do 17 lat leczonych z powodu cukrzycy typu 1 od 6 do 60 miesięcy. Grupę kontrolną stanowiło 20 dzieci w wieku od 6,5 do 16 lat. Z badań wykluczono osoby z chorobami infekcyjnymi oraz chorobami przewlekłymi mogącymi mieć wpływ na wyniki badania. Stężenie sRAGE oznaczane było rano na czczo przy poziomie cukru we krwi mieszczącym się w przedziale 80–120mg%, a także w 1, 2 i 4 godzinie po podaniu posiłku standardowego. **Wyniki.** W grupie dzieci z cukrzycą typu 1 stwierdzono istotnie statystycznie wyższe stężenia sRAGE w 0',1 i 4 godzinie badania w porównaniu do grupy kontrolnej. U dzieci z cukrzycą typu 1, u których stężenie HbA1c było <8% oraz u których czas trwania cukrzycy był krótszy niż 2 lata, stwierdzono istotnie statystycznie wyższe stężenia sRAGE na czczo oraz w 1 i 4 godzinie badania w porównaniu do grupy kontrolnej. Stężenia sRAGE u pacjentów z cukrzycą typu 1 oznaczone na czczo były

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Received: 2015-12-10.
Accepted: 2016-03-01.
Conflict of interests: none declared.

statystycznie istotnie wyższe w porównaniu z oznaczeniami w 1, 2 i 4 godzinie badania. Wykazano istotnie statystycznie ujemną korelację stężeń glukozy ze stężeniami sRAGE w 2 godzinie badania. Nie stwierdzono korelacji stężeń sRAGE ze stężeniami HbA1c jak również z czasem trwania cukrzycy. **Wnioski.** 1.Poposiłkowe zmiany w stężeniach sRAGE różnią się u dzieci z cukrzycą typu 1 w porównaniu do grupy kontrolnej. 2. Stężenia sRAGE u dzieci z cukrzycą typu 1 nie zależą od długotrwałego wyrównania metabolicznego pomimo stwierdzenia ujemnej korelację między stężeniem sRAGE a aktualną glikemią.
Słowa kluczowe
sRAGE, hiperglikemia poposiłkowa, cukrzyca typu 1, pamięć metaboliczna

Introduction

Hyperglycaemia is an established factor involved in the pathogenesis of progressive lesions in blood vessels. It has been proven that even a short-term increase of postprandial glycaemia promotes glycation of proteins, and accumulation of advanced glycation end-products (AEGs) responsible for the development of long-term complications [1]. Previous studies demonstrated that AEGs, by binding with their specific receptor, stimulate release of inflammatory cytokines and promote procoagulant activity in blood [2,3]. RAGE was discovered in 1992 [3]. It is a surface receptor located on macrophages, monocytes, smooth muscle cells, endothelial cells, astrocytes and microglial cells. RAGE is a member of the immunoglobulin-like cell surface receptor superfamily encoded by the gene located on chromosome 6, within the major histocompatibility complex (MHC) class III region. RAGE consists of three fragments – N-terminal extracellular fragment (332aa), transmembrane portion (23aa), and C-terminal intracellular fragment (43aa). N-terminal fragment contains 3 domains: two C-set and one V-set. V-domain binds ligand, while transmembrane portion of the RAGE receptor attaches to the C-terminal intracellular fragment, and is responsible for signal transduction into the cellular nucleus. The RAGE receptor recognizes three dimensional structures of the ligand, and not the amino acid sequence, which, in turn, increases the scale of the activated signalling pathways responsible for many inflammatory processes [4,5].

esRAGE (endogenous secretory receptor for AGEs) is a soluble isoform of the RAGE receptor present in blood serum. It is created through an alternative gene transcription process or cleavage of the transmembrane portion of the cRAGE isoform by the matrix metalloproteinases (MMPs) [6]. Both soluble forms create the so-called sRAGE (soluble receptor for AGEs) pool that binds AGEs circulating in blood serum. As a result, this interaction inhibits binding of AGEs to the surface receptor, thus prevents its activation. Therefore, sRAGE exhibits an antagonistic action with regard to RAGE [5,7]. The available literature data do not allow for a clear determination of sRAGE role in development and maintaining of inflammation in children and adolescents with type 1 diabetes mellitus, especially during postprandial period.

Aim of the paper

The study aimed to compare sRAGE levels in children with T1DM and in the control group, and to assess sRAGE postprandial levels in children and adolescents with T1DM.

Material and methods

The study involved 71 patients (35 girls and 36 boys) aged 7–17 years, diagnosed with T1DM, with treatment duration from 6 to 60 months. Children were receiving an intensive insulin therapy with the use of personal insulin pump (PIP) or multiple injections with insulin pens. Due to a potential impact on study results, patients with infectious and chronic diseases were excluded. The control group consisted of 20 children (9 girls and 11 boys) aged 6.5–16 without carbohydrates metabolism disorders or any other diseases. Children and adolescents with T1DM received the possibility to use a 24h continuous glucose monitoring system (CGMS) that was connected on admission. The blood samples were drawn on fasting from the basilic vein in accordance with commonly followed standards. The following parameters were tested: fasting glucose level, HbA1c, and sRAGE levels. On the second day of hospitalization, the trial was initiated only in patients with fasting glucose levels falling within 80–120mg% range, and without nocturnal hypoglycaemia episodes in CGMS measurements. Patients/parents were trained to use the CGMS device. Based on the retrospective data taken from parents/children, each subject received calculations of the amount of insulin needed per carbohydrate exchange, insulin/carbohydrate exchange ratio, and insulin sensitivity. All children were receiving a balanced formula type Nutridrink [Nutricia], in order to obtain a standardized meal. Additional blood samples for sRAGE levels measurement were drawn at 1, 2 and 4h after administration of a standard meal. sRAGE levels were measured with the use of an immunoenzymatic assay, i.e. ready-to-use ELISA kits manufactured by Bio-Vendor Research and Diagnostic Products (Modrice, Czech Republic). The study was approved by the Ethics Committee. Parent/legal representative and individuals over 16 years of age had to provide a signed copy of an informed consent form (ICF) before any study procedure could start.

Statistical analysis

In groups with heterogeneous variance, a hypothesis concerning equivalence of means for particular samples was verified with the use of the analysis of variance (ANOVA). In case of small size groups, a non-parametric Kruskal-Wallis test was used (homoscedasticity was verified with the use of Bartlett's test).

With regard to discrete parameters, the prevalence of a given characteristic within groups was analysed with the use of c^2 test with Yates' correction. The correlation analyses were performed for the selected parameters pairs, and allowed for calculation of Pearson's correlation (r). In case of p value <0.05, the observed difference was statistically significant.

Table I. Clinical characteristics of T1DM and control groups
Tabela I. *Charakterystyka kliniczna grupy T1DM i grupy kontrolnej*

Characteristic	Patient group N=71	Control group N=20	P value
Sex (F/M)	35/36	9/11	0.931
Age (years)	7–17.5 M=13	6.5–16 M=12	0.459
BMI (kg/m^2)	14–28.1 M=18.7	13.9–24.4 M=18.5	0.783
HbA1c (%)	5.6–13.9 M=7.2	--	--

Table II. Comparison of inflammatory markers and glucose levels – T1DM children vs. control group
Tabela II. *Porównanie markerów stanu zapalnego i stężeń glukozy – grupa T1DM i grupa kontrolna*

Parameter	Number of tests	Study group		Number of tests	Control group		P value
		X±SD	M		X±SD	M	
Glucose mg/dL 0'	71	113.7±19.8	117.0	20	84.3±8.2	83.0	0.0000
Glucose mg/dL 1h	71	211.1±53.1	216.0	20	89.7±22.5	85.5	0.0000
Glucose mg/dL 2h	70	180.3±57.8	180.0	20	76.3±14.1	74.0	0.0000
Glucose mg/dL 4h	71	123.0±56.3	108.0	20	84.5±9.9	81.5	0.0019
sRAGE pg/mL 0'	71	866.5±253.3	832.8	19	687.3±214	650.1	0.0068
sRAGE pg/mL 1h	71	788.3±220.3	759.6	20	681.7±191.6	644.9	0.0412
sRAGE pg/mL 2h	63!	805.5±257.6	744.6	20	705.4±215.7	600.0	0.0905
sRAGE pg/mL 4h	70	788.5±224.5	770.7	20	654.1±200.1	577.9	0.0121

X – mean; SD – standard deviation; M – median

Statistical analysis was performed with the use of computer packages of statistical programs EPIINFO version 7.1.1.14 (from 02.07.2013).

Results

Patients' clinical characteristics are presented in Table I. In the T1DM group, statistically significant **higher** sRAGE levels were measured at 0', 1 and 4h of the study compared to the control group ($p < 0.05$). Tests results are presented in Table II.

The T1DM children were divided in two groups:

Taking into account of\\the level of HbA1c, the patients were divided into two subgroups:

HbA1c ≤8%, N=54 – *Subgroup 1;* HbA1c >8%, N=17 – *Subgroup 2*.

Taking into account the T1DM duration, the patients were divided into two subgroups:

≤2 years, N = 35 – Subgroup A; >2 years, N = 36 – Subgroup B.

Statistically significant **higher** sRAGE levels on fasting and at 1, 4h of the study were observed only in the subgroup 1 compared to the control group ($p < 0.05$). Comparing the results of children in subgroup 2 to the control group and results of children in both groups divided in regard to the HbA1c level, statistically significant differences have not been observed. Results are presented in Table III–V.

Statistically significant **higher** sRAGE levels on fasting and at 1, 4h of the study were observed in children from subgroup A compared to the control group. The results are presented in Tables VI. Statistically significant **higher** sRAGE levels at 1 and 4h of the study were observed in children from subgroup B compared to the control group. The results are presented in Tables

Table III. Comparison of inflammatory markers and glucose levels – subgroup 1 T1DM children vs. control group
Tabela III. *Porównanie markerów stanu zapalnego i stężeń glukozy – podgrupa 1 T1DM i grupa kontrolna*

Parameter	Number of tests	Subgroup 1		Number of tests	Control group		P value
		X±SD	M		X±SD	M	
Glucose mg/dL 0'	54	114.7±19	117.0	20	84.3±8.2	83.0	0.0000
Glucose mg/dL 1h	54	212.2±55.8	217.5	20	89.7±22.5	85.5	0.0000
Glucose mg/dL 2h	53	184.7±63.7	191.0	20	76.3±14.1	74.0	0.0000
Glucose mg/dL 4h	54	122.7±58	105.5	20	84.5±9.9	81.5	0.0058
sRAGE pg/mL 0'	54	885.8±265.4	839.2	19	687.3±214	650.1	0.0046
sRAGE pg/mL 1h	54	805.6±226.2	783.5	20	681.7±191.6	644.9	0.0251
sRAGE pg/mL 2h	46	818.1±264.3	767.5	20	705.4±215.7	600.0	0.0861
sRAGE pg/mL 4h	53	798.3±226.8	771.3	20	654.1±200.1	577.9	0.0087

Table IV. Comparison of inflammatory markers and glucose levels – subgroup 2 T1DM children vs. control group
Tabela IV. *Porównanie markerów stanu zapalnego i stężeń glukozy – podgrupa 2 T1DM i grupa kontrolna*

Parameter	Number of tests	Subgroup 2		Number of tests	Control group		P value
		X ± SD	M		X ± SD	M	
Glucose mg/dl 0'	17	110,6 ± 22,4	116,0	20	84,3 ± 8,2	83,0	0,0001
Glucose mg/dl 1h	17	207,4 ± 44,7	210,0	20	89,7 ± 22,5	85,5	0,0000
Glucose mg/dl 2h	17	166,6 ± 30,9	177,0	20	76,3 ± 14,1	74,0	0,0000
Glucose mg/dl 4h	17	124,1 ± 52	115,0	20	84,5 ± 9,9	81,5	0,0031
sRAGE pg/ml 0'	17	805,4 ± 205,6	813,3	19	687,3 ± 214	650,1	0,128
sRAGE pg/ml 1h	17	733,5 ± 196,9	675,3	20	681,7 ± 191,6	644,9	0,377
sRAGE pg/ml 2h	17	771,5 ± 242,8	736,7	20	705,4 ± 215,7	600,0	0,273
sRAGE pg/ml 4h	17	757,7 ± 220,9	738,7	20	654,1 ± 200,1	577,9	0,156

VII. Comparing the results of children in both groups divided in regard to the T1DM duration, no statistically significant differences was noticed. The results are presented in Tables VIII.

Next, sRAGE levels were measured at particular time points in children with T1DM. Fasting sRAGE levels were statistically significant **higher** compared to measurements at 1, 2, and 4h of the study ($p = 0.000$). The results are presented in Table IX and Fig. 1.

This study evaluated the correlation between sRAGE levels and blood glucose at particular time points of the study. The study revealed a significantly negative correlation between glucose and sRAGE levels measured at the 2nd hour of the study. The results are summarized in Table X. However, no correlation between sRAGE and HbA1c levels as well as between diabetes mellitus duration were observed (Table XI).

Discussion

Hyperglycaemia is the strongest inducer of the protein glycation process [6–8]. Endo- and exogenous AGEs, directly through molecular modification or indirectly via binding with multiple receptors, induce irreversible changes in the endothelium [2,8]. Transmembrane RAGE is the most known receptor for AGEs [9]. The interaction between AGEs and an endothelial cell results in an increase of endothelial permeability, decrease

Table V. Comparison of inflammatory markers and glucose levels – subgroup 1 vs. subgroup 2 T1DM children
Tabela V. *Porównanie markerów stanu zapalnego i stężeń glukozy – podgrupa 2 T1DM i grupa kontrolna*

Parameter	Number of tests	Subgroup 1		Number of tests	Subgroup 2		P value
		X ± SD	M		X ± SD		
Glucose mg/dl 0'	54	114,7 ± 19	117,0	17	110,6 ± 22,4	116,0	0,599
Glucose mg/dl 1h	54	212,2 ± 55,8	217,5	17	207,4 ± 44,7	210,0	0,558
Glucose mg/dl 2h	53	184,7 ± 63,7	191,0	17	166,6 ± 30,9	177,0	0,175
Glucose mg/dl 4h	54	122,7 ± 58	105,5	17	124,1 ± 52	115,0	0,590
sRAGE pg/ml 0'	54	885,8 ± 265,4	839,2	17	805,4 ± 205,6	813,3	0,293
sRAGE pg/ml 1h	54	805,6 ± 226,2	783,5	17	733,5 ± 196,9	675,3	0,163
sRAGE pg/ml 2h	46	818,1 ± 264,3	767,5	17	771,5 ± 242,8	736,7	0,472
sRAGE pg/ml 4h	53	798,3 ± 226,8	771,3	17	757,7 ± 220,9	738,7	0,498

Table VI. Comparison of inflammatory markers and glucose levels – subgroup A T1DM children vs. control group
Tabela VI. *Porównanie markerów stanu zapalnego i stężeń glukozy – podgrupa 1 T1DM i grupa kontrolna*

Parameter	Number of tests	Subgroup A		Number of tests	Control group		P value
		X±SD	M		X±SD	M	
Glucose mg/dL 0'	35	113.2±22.2	113.0	20	84.3±8.2	83.0	0.0000
Glucose mg/dL 1h	35	204.3±48.9	208.0	20	89.7±22.5	85.5	0.0000
Glucose mg/dL 2h	35	175.1±60.2	184.0	20	76.3±14.1	74.0	0.0000
Glucose mg/dL 4h	34	113.1±47.0	100.0	20	84.5±9.9	81.5	0.0111
sRAGE pg/mL 0'	35	885.1±298.9	846.1	19	687.3±214	650.1	0.0214
sRAGE pg/mL 1h	35	810.7±257.1	788.9	20	681.7±191.6	644.9	0.0612
sRAGE pg/mL 2h	35	821.3±289.3	759.5	20	705.4±215.7	600.0	0.158
sRAGE pg/mL 4h	32	812.1±254.7	792.6	20	654.1±200.1	577.9	0.0172

of thrombomodulin expression, increase of tissue factor (TF) synthesis and expression, and an increase of production of inflammatory markers [8,9]. sRAGE prevent the connection between AGEs and the transmembrane receptor, therefore it may play a role of an anti-inflammatory agent [10]. In patients with an early stage diabetic retinopathy, it was demonstrated that the use of sRAGE limits processes of neoangiogenesis and atrophy of pericytes in the retina [11]. In this paper, statistically significant higher sRAGE levels in children with type 1 diabetes mellitus compared to the control group were observed. The statistically significant difference was observed on fasting as well as at 1 and 4h after a standard meal administration (Table II). Other authors also have observed higher sRAGE levels in children with type 1 diabetes mellitus [12]. In authors' opinion, this condition may provide a temporary protection, and prevent the initiation of the inflammatory cascade by capturing the circulating AGEs [13]. This may indicate the presence of an inflammatory reaction, during which sRAGEs exhibit the protective action. It is because the amount of surface receptors for AGEs increases in places of damaged and inflamed tissues. It was demonstrated that an increased activation of signalling pathways in the long-term treated diabetic patients may result from RAGE receptors activation [14]. In many papers, sRAGE is presented as a factor binding the marked amount of RAGE-

Table VII. Comparison of inflammatory markers and glucose levels – subgroup B T1DM children vs. control group
Tabela VII. *Porównanie markerów stanu zapalnego i stężeń glukozy – podgrupa B T1DM i grupa kontrolna*

Parameter	Number of tests	Subgroup B		Number of tests	Control group		P value
		X	M		X	M	
Glucose mg/dl 0'	36	114,2 ± 17,4	118,0	20	84,3 ± 8,2	83,0	0,0000
Glucose mg/dl 1h	36	217,7 ± 56,8	218,5	20	89,7 ±2 2,5	85,5	0,0000
Glucose mg/dl 2h	36	185,1 ±55,8	180,0	20	76,3 ± 14,1	74,0	0,0000
Glucose mg/dl 4h	36	132,6 ± 63,3	116,5	20	84,5 ± 9,9	81,5	0,0023
sRAGE pg/ml 0'	36	848,5 ± 202,1	818,0	19	687,3 ± 214	650,1	0,0095
sRAGE pg/ml 1h	36	766,5 ± 178,6	743,3	20	681,7 ± 191,6	644,9	0,0699
sRAGE pg/ml 2h	31	789,3 ± 23,9	736,7	20	705,4 ± 215,7	600,0	0,105
sRAGE pg/ml 4h	36	766,1 ± 192,6	721,8	20	654,1 ± 200,1	577,9	0,0319

Table VIII. Comparison of inflammatory markers and glucose levels – subgroup A vs. subgroup B T1DM children
Tabela VIII. *Porównanie markerów stanu zapalnego i stężeń glukozy – podgrupa A T1DM i podgrupa B T1DM*

Parameter	Number of tests	Subgroup A		Number of tests	Subgroup B		P value
		X± SD	M		X ± SD	M	
Glucose mg/dl 0'	35	113,2 ± 22,2	113,0	36	114,2 ± 17,4	118,0	0,825
Glucose mg/dl 1h	35	204,3 ± 48,9	208,0	36	217,7 ± 56,8	218,5	0,291
Glucose mg/dl 2h	34	175,1 ± 60,2	184,0	36	185,1 ± 55,8	180,0	0,474
Glucose mg/dl 4h	35	113,1 ± 47,0	100,0	36	132,6 ± 63,3	116,5	0,145
sRAGE pg/ml 0'	35	885,1 ± 298,9	846,1	36	848,5 ± 202,1	818,0	0,547
sRAGE pg/ml 1h	35	810,7 ± 257,1	788,9	36	766,5 ± 178,6	743,3	0,402
sRAGE pg/ml 2h	32	821,3 ± 289,3	759,5	31	789,3 ± 223,9	736,7	0,626
sRAGE pg/ml 4h	34	812,1 ± 254,7	792,6	36	766,1 ± 192,6	721,8	0,395

Table IX. Characteristics of sRAGE levels change at particular time points in T1DM children
Tabela IX. *Charakterystyka zmian w stężeniach sRAGE w wybranych punktach czasowych w grupie T1DM*

	Number of tests	Median	Minimum	Maximum
sRAGE 0'	71	**832.8**	413.0	1691.8
sRAGE 1h	71	759.6	384.5	1582.9
sRAGE 2h	63	744.6	375.5	1627.1
sRAGE 4h	70	770.7	416.0	1537.1

specific ligands. Therefore, sRAGE level reduction indicates an increase of the inflammation, progression of diabetic vascular complications, and an increase of cardiovascular (CV) incidents risk [14–16]. Higher sRAGE level may be a strong marker of CV diseases risk, both in type 1 and type 2 DM patients, as well as in subjects without carbohydrates metabolism disorders [17]. Higher sRAGE levels were also observed in patients with advanced micro- and macrovascular complications [18]. Nevertheless, there have been calls that sRAGE is not a AGEs scavenger, and its level may only reflect the tissue RAGE expression [19]. However, a study demonstrating an increase of AGEs level accompanied by an increase of expression and thus the amount of transmembrane RAGE receptor, with

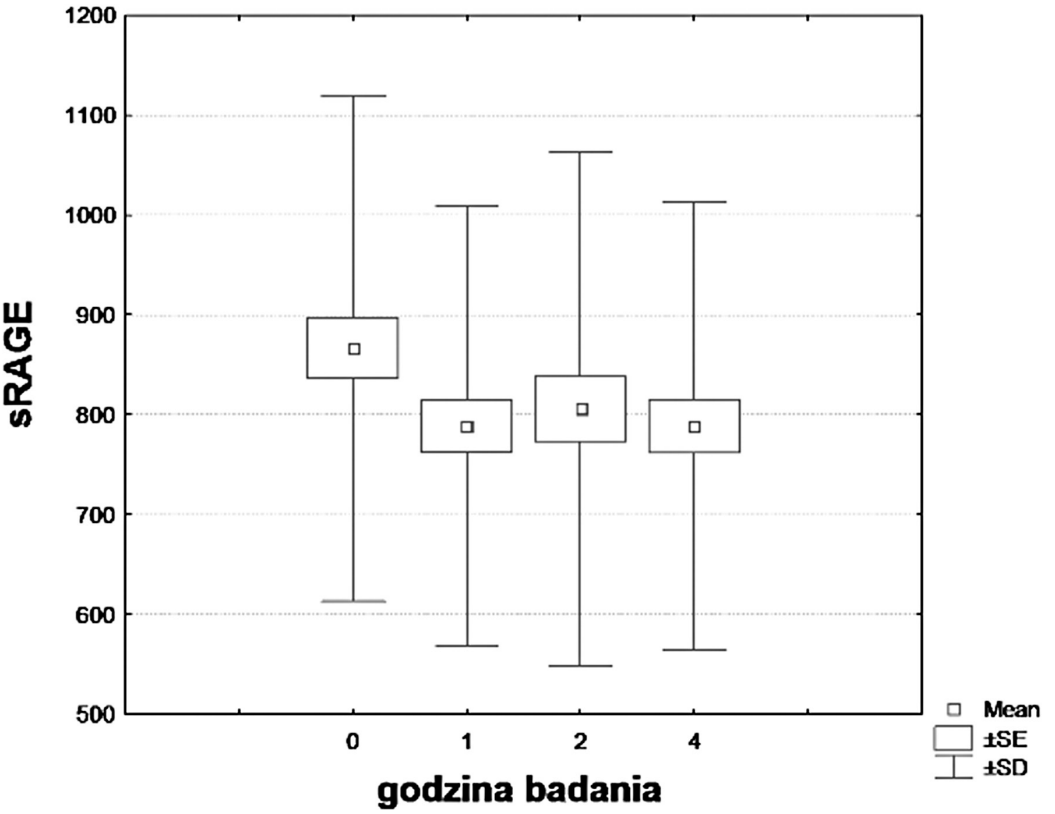

Fig. 1. Characteristics of sRAGE levels change at particular time points in T1DM children
Ryc. 1. *Charakterystyka zmian w stężeniach sRAGE w wybranych punktach czasowych w grupie T1DM*

Table X. Correlation of glucose and sRAGE levels at particular time points in T1DM children
Tabela X. *Korelacja glukozy i stężeń sRAGE w wybranych punktach czasowych w grupie T1DM*

	sRAGE 0'	s RAGE 1h	sRAGE 2h	sRAGE 4h
Blood glucose 0'	- 0,08	- 0,07	- 0,03	0,02
	N = 71	N = 71	N = 63	N = 70
	P = 0,485	P = 0,541	P = 0,799	P = 0,855
Blood glucose 1h	- 0,09	- 0,14	- 0,10	- 0,03
	N = 71	N = 71	N = 63	N = 70
	P = 0,435	P = 0,253	P = 0,441	P = 0,806
Blood glucose 2h	- 0,37	- 0,39	- 0,39	- 0,34
	N = 70	N = 70	N = 63	N = 69
	P = 0,002	P = 0,001	P = 0,002	P = 0,004
Blood glucose 4h	- 0,12	- 0,15	- 0,10	- 0,16
	N = 71	N = 71	N = 63	N = 70
	P = 0,307	P = 0,208	P = 0,428	P = 0,178

Table XI. Correlation of HbA1c and sRAGE levels in T1DM children
Tabela XI. *Korelacja stężenia HBA1c i sRAGE w grupie T1DM*

HbA1c	sRAGE 0'	sRAGE 1h	sRAGE 2h	sRAGE 4h
r	- 0,14	- 0,18	- 0,13	- 0,08
N	N = 71	N = 71	N = 63	N = 70
p	0,231	0,131	0,328	0,523

concomitant sRAGE level decrease, provides contrary results [20]. On the other hand, Katakami et al. demonstrated that in T1DM patients sRAGE level is higher compared to the healthy controls; however, this difference was insignificant [21]. However, no relationship between the degree of metabolic control in diabetes mellitus, expressed as HbA1c percentage, and sRAGE level was observed [21]. In our studies, sRAGE levels in children with HbAc1 ≤8% were statistically significant higher, both on fasting and at 1 and 4h post meal, compared to the control group (Table III). Therefore, reports on a potential relationship between sRAGE level and metabolic control of diabetes mellitus are divergent [22,23]. Motawi *et al.* demonstrated that higher HbA1c levels were statistically significant correlated with lower sRAGE levels [22]. In my own study, I have not observed any statistically significant correlation between HbA1c and sRAGE levels. Other authors also did not confirm such a relationship [23].

In the present study, the highest sRAGE levels were observed in children with DM duration ≤2 and >2 years. In the above mentioned subgroup, fasting as well as 1- and 4-hour postprandial sRAGE levels were statistically significant higher compared to the control group (Table VI,VII). Koutroumani *et al.* have observed higher sRAGE levels in children with T1DM duration >5 years compared to the children with disease duration below 5 years [24]. According to other authors, sRAGE level increases from the beginning of the disease, and remains stable thereafter [25]. However, the recent studies also demonstrate a strong impact of an exogenous insulin on sRAGE levels [26]. Perhaps, such a type of insulin therapy impacts the increase of the RAGE expression on cell surface, and sRAGE level increase [27]. According to available literature, postprandial hyperglycaemia episodes, regardless of global patient's metabolic control, may independently impact the development of diabetic complications [28]. However, it was demonstrated that the underlying inflammation responsible for long-term diabetic complications is induced to a greater extent rather by postprandial blood glucose increase than by chronic hyperglycaemia [28]. Moreover, it has been proven that metabolic reactions activated by persisting high blood glucose levels modify inflammatory response, and in part may compensate the toxic effects of chronic hyperglycaemia [28,29]. According to the established principle of the metabolic memory, even short-term hyperglycaemia episodes during and early phases of T1DM, despite good metabolic control in subsequent years, may adversely impact the risk of vascular complications development through epigenetic modifications [29]. We have also found studies that did not observe any relationship between postprandial hyperglycaemia and sRAGE levels [30]. sRAGE stability has been already described by Bower et al. During a 3-year follow-up, the authors concluded that single measurements of sRAGE levels were not significantly different [31]. In our studies, the highest sRAGE levels were observed before Nutridrink administration, and were decreasing thereafter. Differences between measurements performed on fasting and at 1 hour after a meal, and between 2 and 4 hours after a meal were statistically significant lower (Table IX, Fig. 1). This situation indicates high dynamics of metabolic changes during the postprandial period. It is suggested that sRAGE level decrease during the postprandial period probably results from AEGs binding, whose levels increases along with the change of postprandial blood glucose concentrations [32]. The results show a significant negative correlation between glucose and sRAGE 2-hour postprandial levels (Table X). The tests results demonstrate a complex role of sRAGE in the inflammatory reaction. Therefore, further studies enabling explanation of its role in the inflammation observed in T1DM children and adolescents are warranted.

Conclusions

1. Postprandial changes in sRAGE concentrations have a different profile comparing healthy controls to T1DM children.

2. They are not dependent on a long term diabetes control, however for diabetic children there are negative correlations of sRAGE and contemporary glycemia.

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