Diabetes & Metabolic Syndrome: Clinical Research & Reviews 13 (2019) 1005–1010

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

Original Article

Serum AGEs and sRAGE levels are not related to vascular complications in patients with prediabetes

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ARTICLE INFO

Article history:
Received 15 December 2018
Accepted 17 January 2019

Keywords:
Prediabetes
Vascular complications
sRAGE
Pentosidine

ABSTRACT

Background: While hyperglycemia has a key role in the pathogenesis of microvascular complications of diabetes, it is just one of the many factors contributing to macrovascular damage. The **aim** of the present study is to investigate the link between serum pentosidine and sRAGE levels and vascular complications in patients with prediabetes compared to normal glucose tolerance controls with obesity.
Methods: In this study were included 76 patients with mean age 50.7 ± 10.7 years, divided into two age and BMI-matched groups – group 1 with obesity without glycemic disturbances (n = 38) and group 2 with obesity and prediabetes (n = 38).
Results: There was no significant difference in pentosidine and sRAGE levels between patients with obesity and prediabetes. Patients with hypertension had lower levels of sRAGE compared to non-hypertensive subjects. sRAGE showed a weak negative correlation to blood glucose on 60th min of OGTT and HOMA index. There was no correlation between sRAGE and pentosidine levels and the markers of micro- and macrovascular complications. There was no difference in sRAGE and pentosidine levels between patients with and without endothelial dysfunction.
Conclusions: sRAGE and pentosidine levels are similar in patients with obesity with and without prediabetes and do not correlate to the markers of micro- and macrovascular complications.

1. Introduction

Diabetes mellitus (DM2) comprises a heterogeneous group of metabolic disorders characterized by hyperglycaemia, which is caused by abnormalities in insulin secretion, or action, or both. Diabetes is a chronic disease that requires continuous medical care and education of the patient in order to prevent acute and reduce the risk of chronic complications. Chronic complications of diabetes mellitus include retinopathy with potential loss of vision; nephropathy causing chronic renal failure; peripheral neuropathy and risk of diabetic ulcers on the feet, amputations and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, sudomotor and cardiovascular symptoms and sexual dysfunction. Diabetic patients also have an increased incidence of atherosclerotic cardiovascular, peripheral artery and cerebrovascular disease.

Now it is evident however that chronic diabetic complications begin their development in the earlier stages of impaired glucose homeostasis, because vascular damage in many cases is usually present at diagnosis of type 2 diabetes [1–4] and probably even at prediabetic stage. ***Prediabetes*** represents a metabolic condition, which stands inbetween normal glucose homeostasis and diabetes and includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). These two terms are not synonymous and reflect different disturbances of glucose regulation, although they may occur simultaneously. Patients who have these conditions of impaired glucose homeostasis have an increased risk of developing diabetes [5–7]. While microvascular complications occurring during prediabetes are often mild, they are clinically significant and in some cases can give us information on the mechanisms and pathogenesis of diabetic angiopathy. Until now it was believed that microvascular complications seen in prediabetes are entirely due to hyperglycemia. New studies, however, showed the large contribution of other metabolic factors such as obesity, dyslipidemia and hypertension. Additional evidence in this field came from a study that demonstrated that metabolic syndrome has an additive effect on the risk of microvascular complications of type 2 diabetes [8]. While hyperglycemia undoubtedly has a key role in the

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https://doi.org/10.1016/j.dsx.2019.01.014
1871-4021/

pathogenesis of microvascular complications of diabetes, it is just one of the many factors contributing to the development of macrovascular damage.

Hyperglycemia induces oxidative stress via poliol pathway, advanced glycation end-products (AGEs), proteinkinase C disregulation and hexosamine pathway. AGEs are elevated in case of prolonged hyperglycemia as a result non-enzymatic reaction between glucose residuals and amino groups of proteins, lipids and nucleic acids [9–11], causing irreversible structural changes. Some of the best studied AGEs in patients with diabetes include carboxymethyl-lisine, carboxyethyl-lisine and **pentosidine**, which can serve as markers of AGEs formation and accumulation [12]. At molecular level AGEs, including pentosidine, can induce oxidative stress and endothelial dysfunction [13,14]and some growth factor expression [15]. As a result of this they are linked to many pathological conditions such as ageing, hypertension, kidney failure, diabetes and diabetic retinopathy and nephropathy [16,17].

AGEs affect microvascular homeostasis via interaction with AGEs receptor (RAGE) [18]. There are many data that this interaction has a role in the development of microvascular diabetes complications [19,20]. The soluble form of RAGE (**sRAGE**) is missing its transmebrane domain and is recently identified as an inhibitor of AGE-RAGE mediated pathological changes [21]. sRAGEis linked to some of the metabolic syndrome components (body mass index and insulin resistance) [22] and a negative relationship between sRAGE and HbA1c levels was found [23]. Biological role of sRAGE is not well understood, but it probably acts as a competitive inhibitor of AGE-RAGE interaction. sRAGE can also act as a scavenger receptor for circulating AGEs and other RAGE-ligands [24]. As a result sRAGE is considered a protective factor regarding microvascular damage in type 2 diabetic patients [25]. Until now there is very few data about the role of sRAGE in atherosclerotic changes in humans. In middle-age coronary disease patients without diabetes sRAGE levels are lower compared to subjects without coronary artery disease [26].

The **aim** of the present study is to investigate the link between serumpentosidineand sRAGE levels and vascular complications in patients with prediabetes compared to normal glucose tolerance controls with obesity.

2. Patients and methods

In the present study we included patients that met the following including and excluding criteria:

2.1. Inclusion criteria

- Age 35–74 years
- Impaired glucose tolerance (glucose on 120 min of OGTT between 7.8 and 11.0 mmol/l) and/or impaired fasting glucose (fasting glucose between 6.1 and 6.9 mmol/l) OR
- Obesity (BMI$\geq$ 30 kg/m^2)

2.2. Exclusion criteria

- Metformin or any other antidiabetic drug treatment during the last three months prior to study entry
- Previous cardiovascular or cerebrovascular accident (miocardial infarction, angioplasty, stenting, ischemic stroke)
- Moderate or severe renal (GFR <60 ml/min/1.73m2), or liver disease, heart failure (NYHA class III or IV)
- Malignancies

The project was approved by the University ethics committee for clinical studies and all patients included in the study signed an informed consent for participation in the project.

The following study methods were used:

1. **Anthropometric measurements**
   - Height
   - Weight
   - BMI calculation (weight in kilograms divided by height in meters squared)
   - waist circumference (WC) - measurement is made midway between the 8th rib and the iliac crest
   - Hip circumference - measurement is made at the level of the greater trochanter
   - Calculation of waist-to-hip ratio (WHR)
   - Calculation of the waist-to-height ratio (WSR)
   - Calculation of VAI (visceral adiposity index): VAI = (WC/(36.58 + (1.89 xBMI))) x (TG/0,81) x (1,52/HDL)
2. **Investigation of carbohydrate metabolism**
   - An oral glucose tolerance test (OGTT) with measurement of glucose and immunoreactive insulin (IRI) (electrochemiluminescence immunoassay (ECLIA – Roche Diagnostics™) on 0 min, 60 min and 120 min. HOMA index (fasting glucose X fasting immunoreactive insulin)/22.5) was calculated.

Insulin resistance was assumed at IRI 0 min >17 mU/l, IRI 60 min > 130 mU/l, IRI 120 min > 80 mU/l, HOMA index> 2,6 [27–29].

3. **Laboratory tests**
   - Blood count
   - ESR
   - ASAT, ALAT, GGT
   - Tchol, TG, HDL, LDL, VLDL
   - Creatinine
   - Uric acid
4. **Measurement of serum sRAGE and pentosidine levels** was performed by enzyme-linked immunosorbent assay (ELISA) (BYOVENDOR). The blood was taken after overnight fasting, was immediately centrifuged for 15 min on 4000 rpm and the serum was stored at (−80^{0}C) until the test was performed
5. **Evaluation of the presence of peripheral neuropathy** – evaluation of tactile (10 g monophylament), termal (termal discriminator) and vibration sensation (128 Hz tuning fork and biothesiometer) and tendon reflexes (neurological hammer)
6. **Detection of distal small fiber neuropathy** by the measurement of sudomotor function, usingSudoscan. This is a quick, non-invasive and quantitative method. It is based on an electrochemical reaction between sweat chlorides and stainless-steel electrodes in contact with the palms of the hands and soles of the feet. Results are provided as conductances (microsiemens, μS) for the hands and feet (right and left side) and a score of Diabetic Autonomic Neuropathy (DAN) based on conductance values. SUDOSCAN can detect distal small fiber polyneuropathy with a sensitivity of >75%. SUDOSCAN may be considered as a robust method for the detection of sudomotor dysfunction and is used for clinical and research purposes. It also correlates well with the methods for peripheral neuropathy evaluation - VPT (Vibration Perception Threshold).
7. **Neuropathy disability score calculation** – an easily performed in the clinical setting score that provides an assessment of the risk for neuropathic ulceration. A score of 6/10 or more has been found to indicate an increased risk for foot ulceration.
8. **Evaluation of endothelial function.**

It was analyzed by EndoPat device - EndoPAT is a noninvasive method of assessing vascular reactivity without the disadvantages of the conventional ultrasound measurements. EndoPAT measures the plethysmograph pressure variations of fingers caused by the arterial pulse and transforms it into peripheral arterial tone (PAT - Peripheral Arterial Tone). Endothelium-mediated changes in vascular tone after occlusion of the brachial artery reflect in hyperemic response, which is a measure of arterial endothelial dysfunction (LnRHI). Performing the measurement of the contralateral hand serves as the control of non-endotheliaum dependent changes in vascular tone. In addition, EndoPAT can be used for measuring arterial stiffness: the so-called Augmentation Index (AI). The method has been approved by the US FDA, and is the CE-marked (European regulation) for evaluation of the endothelial dysfunction [30–32].

9. **Intima-media thickness (IMT) of the common carotid artery measurement.**

IMT is a noninvasive ultrasound biomarker of early atherosclerosis. CardioHealth Station performs an automated evaluation of IMT, taking into consideration the characteristics of the individual patient and combining the data from the ultrasound measurement and Framingham risk score (traditional surrogate score for cardiovascular risk calculation). The method is approved by Food and Drug Administration (FDA) [33–35].

10. **Evaluation of Anckle-Brachial Index (ABI).** ABI represents the ratio between the systolic blood pressure at the ankle and the upper arm. It gives information about the presence of peripheral artery disease. Systolic blood pressure on the upper arm was measured using sphygmomanometer and on the ankle – using portative Doppler device.

2.3. Statistical methods

The data were processed using the statistical package SPSS 16.0. The level of significance for rejecting the null hypothesis was $p < 0.05$. The following statistical methods were applied: descriptive analysis, variation analysis, Kolmogorov– Smirnov's one sample non-parametric test, Student's t-test for two independent samples, Mann–Whitney's non-parametric test for two independent samples, one-way analysis of variance between-groups ANOVA, correlation analysis. Data are presented as mean ± SD.

3. Results

In the present study we included 76 patients with mean age 50.7 ± 10.7 years, divided into two groups – group 1 (control group) with obesity without glycemic disturbances (n = 38) and group 2 with prediabetes (n = 38). The characteristics of the two groups are presented on Table 1.

The two groups were similar in age, body weight, fat%, BMI, WHR and WSR, but patients with prediabetes had significantly higher VAI than those without carbohydrate disturbances.

The prevalence of the classical cardiovascular risk factors determined in the study is shown on Table 2. There was no difference in the prevalence of hypertension and dyslipidemia between the groups, although the patients with prediabetes had significantly higher levels of triglycerides compared to controls.

Patients with prediabetes had higher levels of IRI on 0 and 120 min of OGTT and higher HOMA index although similar rates of hyperinsulinemia/insulin resistance were observed between the two groups (Table 3).

The parameters of macrovascular complications are shown on Table 4. There were similar indices of the markers of macrovascular complications between the two groups, although there was a tendency towards lower LnRHI in prediabetic patients, where there was a higher prevalence of endothelial dysfunction. In females LnRHI was statistically lower in prediabetic group compared to female patients without carbohydrate disturbances ($p = 0.033$). IMT showed a significant correlation to patients age, systolic and diastolic blood pressure ($r = 0.573$; 0.467; 0.272; respectively, <0.05), while LnRHI showed a negative correlation to blood glucose levels on 60th minute of OGTT ($r = -0.414$; $p < 0.05$).

The parameters of microvascular complications are shown on Table 5. There were similar indices of the markers of microvascular

Table 1
Anthropometric characteristics of the study groups.

	Group 1 Obesity + NGT	Group 2 Obesity + prediabetes (IGT and/or IFG)
Age (y)	50.8 ± 9.9	50.6 ± 11.5
Weight (kg)	94.5 ± 15.5	99.2 ± 20.5
BMI (kg/m^2)	35.9 ± 4.8	37.5 ± 6.2
% fat tissue	44.3 ± 4.8	44.2 ± 7.0
WHR	0.89 ± 0.07	0.92 ± 0.07
WSR	0.65 ± 0.07	0.67 ± 0.09
VAI	2.5 ± 1.7	3.6 ± 2.0*

* p<0.05.

Table 2
Cardiovascular risk factors.

	Group 1 Obesity + NGT	Group 2 Obesity + prediabetes (IGT and/or IFG)
Systolic BP mmHg	138.5 ± 16.8	132.3 ± 17.3
Diastolic BP mmHg	85.5 ± 10.3	84.1 ± 9.9
Arterial hypertention %	65.8	63.2
Total cholesterol mmol/l	5.9 ± 1.1	5.4 ± 1.1
LDL cholesterolmmol/l	3.9 ± 1.1	3.4 ± 1.1
HDL cholesterol mmol/l	1.3 ± 0.4	1.1 ± 0.3
Trygliceridesmmol/l	1.6 ± 0.8	1.9 ± 0.9*
Dyslipidemia %	67.6	70.3
Smoking %	47.4	24.3*

* p<0.05.

Table 3
Markers of insulin resistance.

	Group 1 Obesity + NGT	Group 2 Obesity + prediabetes (IGT and/or IFG)
IRI 0 min (mU/l)	16.3 ± 6.9	21.9 ± 12.8*
IRI 60 min (mU/l)	128.6 ± 83.9	118.3 ± 65.5
IRI 120 min (mU/l)	68.7 ± 66.3	117.4 ± 82.7*
HOMA index	3.7 ± 1.7	5.5 ± 3.3*
Prevalence of insulin reistance (%)	67.6	77.8

* p<0,05.

Table 4
Markers of macrovascular complications.

	Group 1 Obesity + NGT	Group 2 Obesity + prediabetes (IGT and/or IFG)
Mean intima media thickness(IMT)mm	0,63 ± 0,11	0,62 ± 0,11
Reactive hyperemia index (LnRHI)	0,64 ± 0,26	0,58 ± 0,26
Prevalence of endothelial dysfunction (LnRHI<0,51)	38,9%	60%
AI – augmentation Index	4,3 ± 13,1	4,0 ± 7,8
Ankle-brachial index (ABI)	1,07 ± 0,09	1,08 ± 0,17

* p<0,05.

Table 5
Markers of microvascular complications.

	Group 1 Obesity + NGT	Group 2 Obesity + prediabetes (IGT and/or IFG)
Neuropathy disability score (NDS)	1.7 ± 2.2	1.9 ± 2.1
Vibration perception treshold(VPT)	9.9 ± 3.5	10.9 ± 5.5
Autonolic neuropathy risk (Sudoscan) %	32.5 ± 11.5	34.2 ± 12.3

* p<0.05.

complications between the two groups, although there was a tendency towards higher NDS, VPT and higher autonomic neuropathy risk in patients with prediabetes. NDS, VPT and autonomic neuropathy risk showed a strong correlation to patients age (r = 0.477; 0.602; 0.542 respectively; p<0.05), and mean IMT (r = 0.333; 0.283; 0.315 respectively; p<0.05). Autonomic neuropathy risk, unlike the other parametres, correlated also to the markers of visceral obesity – BMI, waist circumference, WSR and fat% (r = 0.445; 0.341; 0.366; 0.367 respectively; p<0.05).

There was no significant difference in pentosidine and sRAGE levels between patients with obesity and prediabetes (1229.7 ± 350.3 vs 1195.9 ± 324.5 pmol/ml and 462.6 ± 161.5 vs. 480.5 ± 186.8 pg/ml respectively). There was no difference in patients with different types of carbohydrate disturbances (IFG only, IGT only and IFG + IGT). There was no difference between patients with and without metabolic syndrome and insulin resistance. Patients with hypertension had lower levels of sRAGE compared to nonhypertensive subjects (436.1 ± 154.0 vs 528.1 ± 189.8 pg/ml, p = 0.032). sRAGE showed a weak negative correlation to blood glucose on 60th min of OGTT (r = −0.254, p = 0.036) and HOMA index (r = −0.269, p = 0.029). There was no correlation between sRAGE and pentosidine levels and the markers of micro- and macrovascular complications and patients age. There was no difference in sRAGE and pentosidine levels between patients with and without endothelial dysfunction.

4. Discussion

Hyperglycemia is major factor for micro-and macrovascular complications development in all stages of impaired glucose homeostasis. Advanced glycation end-products formation plays a role in the pathogenesis of diabetic nephropathy, retinopathy, neuropathy and macroangiopathy.

The interaction between AGEs and RAGE induces mesangial proliferation and production of transforming factor-beta in the kidney and eventually contributes to the mycroalbuminuria and glomerulosclerosis progression [36]. Many studies find elevated pentosidine levels in patients with overt nephropathy or chronic kidney disease [37–39], with even higher levels in end stage kidney failure [40].

Elevated levels of AGEs are found retinal blood vessels, serum and corpus vitreum of diabetic patients and they correlate with the severity of diabetic retionopathy [41,42]. Pentosidine levels are an independent predictor of retinopathy, hypertention and dislipidemia and its levels rise even higher with the progression of microangiopathy [43].

Many data support the significant role of RAGE in the progression of atherosclerosis and atherosclerotic plaque vulnerability. In patients with type 2 diabetes atherosclerotic plaques show higher expression of RAGE compared to nondiabetic controls [44]. Serum sRAGE levels are investigated as a predictive marker for coronary artery disease risk in type 2 diabetes patients [45] and as a marker linked to intima media thickness in type1 diabetics [46]. Not much is known however about the role of RAGE and sRAGE for vascular complications in the early stages of impaired glucose homeostasis.

Similar to other studies [47] we didn't find a difference in sRAGE levels between patients with and without prediabetes or any correlation to insulin resistance markers. Other studies however show lower levels of sRAGE in patients with prediabetes and newly diagnosed diabetes compared to controls [48]. The possible reason for these discrepancies could be that the role of hyperglycemia and RAGE formation in those early stages is variable and there are many confounding factors such as metabolic syndrome, chronic inflammation, insulin resistance etc. An interesting finding is the difference between sRAGE between patients with and without hypertension. In nondiabetic patients with obstructive sleep apnea a relationship between endogenous secretory RAGE but not sRAGE and blood pressure was found [49].

In our study we included obese patients with IFG/IGT and patients with obesity without glycemic disturbances as control group in order to investigate the effect of glycemic disturbances on sRAGE and pentosidine levels that is independent of body weight and other vascular risk factors. We deliberately did not include patients with newly diagnosed diabetes, because diabetes is sometimes diagnosed after a long-standing hyperglycemia which can significantly affect RAGE levels and vascular diabetes complication development. The small number of the included patients is a possible reason for lack of statistical significance of the results.

5. Conclusions

sRAGE and pentosidine levels are similar in patients with obesity with and without prediabetes and do not correlate to the markers of micro- and macrovascular complications.

Declaration of interest

The authors declare that they have no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contributions

Antoaneta Gateva performed the study, collected the data and wrote the paper.

Yavor Assyov performed the study and collected the data.

Adelina Tsakova performed the laboratory tests.

Zdravko Kamenov designed the study.

Funding

The study was conducted with the financial support of Medical University Sofia, Medical Sciences Council – Project 6007/11.09.2013/Contract 1-C/10.12.2013. The sponsor had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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