Clinical Case Report

Medicine®

OPEN

Poorly controlled type 2 diabetes with no progression of diabetes-related complications and low levels of advanced glycation end products

A Case report

Tomoka Nakamura, MD[a], Tetsuro Tsujimoto, MD, PhD[a,*], Kazuki Yasuda, MD, PhD[b,c], Daisuke Chujo, MD, PhD[a,d], Mitsuru Ohsugi, MD[a,e], Akiyo Tanabe, MD, PhD[a], Kohjiro Ueki, MD, PhD[a,f], Hiroshi Kajio, MD, PhD[a]

Abstract

Rationale: Previous studies have suggested that increased levels of advanced glycation end products (AGEs) and soluble receptor for AGE (sRAGE) are associated with diabetes-related complications. However, there is little evidence on the association between long-term levels of AGEs and sRAGE and progression of diabetes-related complications.

Patient concerns: A 64-year-old man had poorly controlled type 2 diabetes, obesity, smoking, hypertension, and dyslipidemia. He had many risk factors for diabetes-related complications.

Diagnosis: Despite poor glycemic control over 15 years, the patient did not exhibit diabetes-related complications.

Interventions: We examined serum AGEs (CEL and MG-H1) and sRAGE levels in this patient over the past 10 years.

Outcomes: The patient maintained low serum AGEs and sRAGE levels.

Lessons: AGEs and sRAGE levels may be associated with long-term development of diabetes-related complications.

Abbreviations: AGEs = advanced glycation end products, BMI = body mass index, CEL = N-(carboxyethyl) lysine, ELISA = enzyme-linked immunosorbent assay, HbA1c = glycated hemoglobin, MG-H1 = methylglyoxal-derived hydroimidazolone-1, sRAGE = soluble receptor for advanced glycation end products.

Keywords: diabetes mellitus, advanced glycation end products, soluble receptor for advanced glycation end products, diabetes-related complication

1. Introduction

Type 2 diabetes is associated with the development of microvascular complications and cardiovascular diseases. One mechanism for the development and progression of diabetes-related complications is the effect of advanced glycation end products (AGEs) and receptor for AGE (RAGE).[1] AGEs are heterogeneous groups of irreversible adducts formed by nonenzymatic glycation and glyoxidation of proteins, lipids, and nucleic acids with reducing sugars. The main precursors of AGEs are glucose and reactive dicarbonyl compounds, such as glyoxal, methylglyoxal, and deoxyglucosones.[2] For example, methylglyoxal, which is the most reactive dicarbonyl compound, induces the formation of N-(carboxyethyl) lysine (CEL) by reacting with lysine residues. Methylglyoxal also induces the formation of methylglyoxal-derived hydroimidazolone-1 (MG-H1) by reacting with arginine residues.[3] More than 20 AGEs have been identified and are assumed to accumulate continuously with age and hyperglycemia. AGEs may lead to oxidative stress by activating signaling cascades via RAGE, thereby promoting vascular complications.[4,5] One potential marker for the expression of RAGE and activation of the AGE/RAGE axis is circulating soluble RAGE (sRAGE). The sRAGE is also associated with increased risk of renal disease and all-cause mortality in patients with type 2 diabetes.[6] Cross-sectional studies have identified increased levels of baseline AGEs and sRAGE as important predictors of diabetes-related complications.[7,8] However, there is little evidence for a long-term association between the development of AGEs/sRAGE and progression of diabetic complications.

Here, we report the case of a 64-year-old man with poorly controlled type 2 diabetes, no progression of diabetes-related complications, and maintained low serum AGEs and sRAGE levels.

Editor: N/A.

This work was supported by the National Center for Global Health and Medicine Intramural Research Fund 28D1201.

The authors have no conflicts of interest to disclose.

[a] Department of Diabetes, Endocrinology, and Metabolism, Center Hospital, [b] Department of Metabolic Disorders, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, [c] Department of Diabetes, Endocrinology and Metabolism, Kyorin University School of Medicine, Tokyo, [d] Center for Clinical Research, Toyama University Hospital, Toyama, [e] Diabetes and Metabolism Information Center, [f] Department of Molecular Diabetic Medicine, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan.

[*] Correspondence: Tetsuro Tsujimoto, Department of Diabetes, Endocrinology and Metabolism, Center Hospital, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan (e-mail: ttsujimoto@hosp.ncgm.go.jp).

Medicine (2019) 98:30(e16573)

Received: 15 February 2019 / Received in final form: 20 May 2019 / Accepted: 1 July 2019

http://dx.doi.org/10.1097/MD.0000000000016573

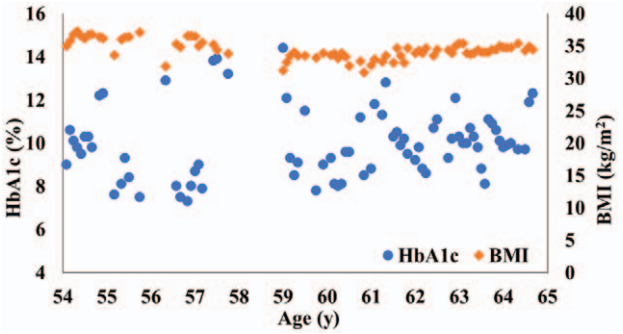

Figure 1. Transition of glycated hemoglobin levels and body mass index for the recent 10 years. BMI = body mass index, HbA1c = glycated hemoglobin.

2. Case report

The patient is a 64-year-old man who first visited our hospital with general fatigue and thirst in 2000 at the age of 47. His blood glucose level was 353 mg/dL, glycated hemoglobin (HbA1c) level was 12.8% (normal reference range: 4.9–6.0%), and he had never been previously diagnosed with diabetes. He was obese, with no islet-specific autoantibodies detected, and was diagnosed with type 2 diabetes. Then, he was treated with antihyperglycemic drugs, but because of his poorly controlled glycemia, he was frequently admitted to our hospital and insulin therapy was started in 2008. His mean HbA1c level from the most recent decade was approximately 10% and his body mass index (BMI) remained above 30 kg/m^2 throughout the period (Fig. 1).

In November 2017, the patient was admitted to our hospital for examination of his diabetes-related complications and control of his hyperglycemia. Self-monitoring of blood glucose showed large glycemic variability from 50 to 400 mg/dL. At the time of admission, his body weight was 92.3 kg and his BMI was 34.5 kg/m^2. He was treated with metformin (1000 mg per day), insulin lispro (25 units before breakfast and 22 units before dinner), and insulin degludec (24 units before sleep). Although the insulin dosage was titrated, the overall treatment regimen of diabetes had not been changed over the 10 years.

The patient was as treated with an angiotensin II receptor blocker, a calcium channel blocker, and diuretics for his hypertension. He also had dyslipidemia, which was treated by statin. He was a former smoker (30 cigarettes per day from ages 20–45 years). Table 1 presents patient characteristics from the hospital admission in November 2017. Regarding the patient's diabetes-related complications, we first evaluated the diabetic microangiopathies of the patient. No diabetic retinopathy was found by the ophthalmologist before admission. His urinary albumin to creatinine ratio at the hospital admission was 10.1 mg/g (normal reference range <30 mg/g) and diabetic nephropathy was not found, but diabetic neuropathy could not be fully assessed because he had abnormal sensations since suffering from traumatic cervical syndrome in 2011. Next, we evaluated macrovascular diseases. He had no history of myocardial infarction or stroke, and neither electrocardiogram nor echocardiogram in hospital showed abnormal findings. Mean common carotid artery intima-media thickness was within normal range (right, 0.5 mm and left, 0.6 mm). Despite poor glycemic control over 15 years, the patient did not exhibit diabetes-related complications including micro- and macrovascular disease. Therefore, we examined serum AGEs (CEL and MG-H1) and sRAGE levels during his hospital stay. The CEL and MG-H1 were measured using OxiSelect CEL Competitive ELISA Kit #STA-813, and OxiSelect MG Competitive ELISA Kit #STA-811 (Cell Biolabs, San Diego, CA), respectively. The sRAGE was measured using sRAGE biotechne Quantikine ELISA Human RAGE #DRG00 (R&D Systems, Minneapolis, MN) according to the manufacturers' instructions. His CEL, MG-HI, and sRAGE levels were 8.3 μg/mL, 1.8 μg/mL, and 401.3 pg/mL, respectively. The serum samples collected during his past admission had been stocked and were examined using the same assay. The AGEs and sRAGE levels were generally stable throughout the past 10 years. We also examined the serum samples from 2 groups of inpatients between 2012 and 2014: those who had HbA1c levels ≥11.0% (Group A, n = 14) and those who had diabetic retinopathy (simple or proliferative) or diabetic nephropathy (exhibiting overt albuminuria) (Group B, n = 25). As shown in Figures 2A–2C, our patient exhibited significantly lower AGEs and sRAGE levels compared to Group A or B.

All participants provided written informed consent to participate. Our study was approved by the Institutional Review Board of the National Center for Global Health and Medicine.

Table 1

Patient characteristics at this hospital admission.

Physical examination		
Body height		163.5 cm
Body weight		92.3 kg
Body mass index		34.5 kg/m^2
Abdominal circumference		109 cm
Blood pressure		129/79 mmHg
Blood laboratory findings		**(Normal range)**
Aspartate aminotransferase	22 IU/L	(13–30 IU/L)
Alanine aminotransferase	25 IU/L	(10–42 IU/L)
Estimated glomerular filtration rate*	66.0 mL/min/1.73 m^2	
Uric acid	7.6 mg/dL	(3.7–7.0 mg/dL)
Triglyceride	114 mg/dL	(40–149 mg/dL)
High-density lipoprotein cholesterol	52 mg/dL	(38–90 mg/dL)
Low-density lipoprotein cholesterol†	144 mg/dL	
Brain natriuretic peptide	6.7 pg/mL	(0.0–18.4 pg/mL)
Fasting plasma glucose	178 mg/dL	(80–110 mg/dL)
Glycated hemoglobin	10.0%	(4.9–6.0%)
Glycoalbumin	30.5%	(11.0–16.0%)
Fasting serum C peptide	1.37 ng/mL	(0.80–2.50 ng/mL)

* Estimated glomerular filtration rate was calculated using the following formula: estimated glomerular filtration rate (mL/min/1.73m^2) = 194 × Creatinine$^{-1.094}$ × Age$^{-0.287}$.

† Calculated by total cholesterol minus high-density lipoprotein cholesterol minus triglyceride/5.

3. Discussion

This case shows 2 important points. First, despite the patient's long-time poor glycemic control and many risk factors, such as aging, male sex, obesity, smoking, hypertension, and dyslipidemia, he had almost no progression of diabetes-microvascular complications and no cardiovascular events. Second, he maintained low serum AGEs and sRAGE levels, which may increase over a lifetime. Based on results of previous studies suggesting no correlation between AGEs/sRAGE levels and glycated hemoglobin levels,[4,6] some factors other than hyperglycemia may regulate AGEs and sRAGE.

Exogenous sources, such as oral intake of AGEs and smoking, are linked to elevation of AGE levels and diabetic vascular

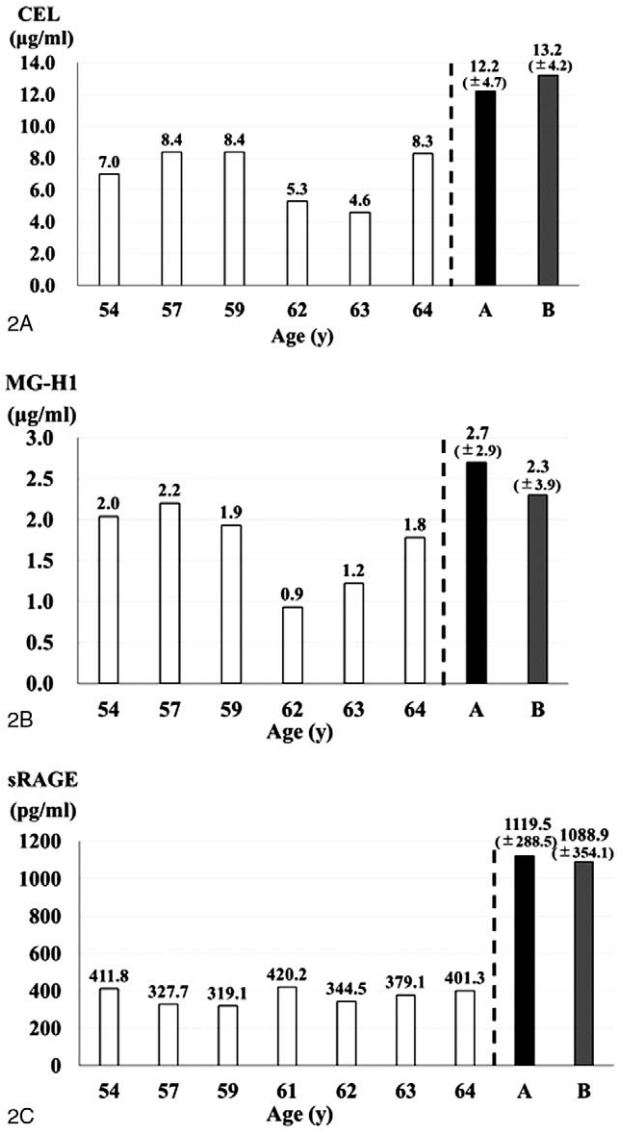

Figure 2. Transition of serum AGEs and sRAGE. White bars represent the patient's serum CEL (2A), MG-H1 (2B), and sRAGE (2C) levels at the time of admission from 2010 to 2017. The CEL, the MG-H1, and sRAGE were measured by ELISA as described in the text. Black bar (A) represents average serum AGEs and sRAGE levels of our 14 cases who were admitted to our hospital from 2012 to 2014 with glycated hemoglobin levels of ≥11% (64% male; age, 57.0 years; body mass index, 25.4 kg/m^2; diabetes duration, 8.1 years; mean glycated hemoglobin, 12.8%). Slashed bar (B) represents average serum AGEs and sRAGE levels of our 25 cases who had diabetic retinopathy (nonproliferative or proliferative retinopathy) or who had albuminuria (urinary albumin to creatinine ratio ≥30 mg/g) (63% male; age, 65.9 years; body mass index, 25.6 kg/m^2; diabetes duration, 15.3 years; mean glycated hemoglobin, 9.6%). AGEs = advanced glycation end products, CEL = N-(carboxyethyl) lysine, ELISA = enzyme-linked immunosorbent assay, MG-H1 = methylglyoxal-derived hydroimidazolone-1, sRAGE = soluble receptor for advanced glycation end product.

dysfunction.[9,10] Several other drugs may also correlate with AGEs accumulation and sRAGE expression.[11] Methylglyoxal levels were significantly lower in subjects taking metformin than in those not taking metformin, despite similar glycemic control, and AGEs in apolipoprotein B100 of low-density lipoprotein were reported lower in patients receiving metformin therapy.[12,13] Statins may inhibit plaque RAGE expression by decreasing AGE generation.[14] Moreover, angiotensin II receptor blockers decrease serum levels of sRAGE and calcium channel blockers reduce RAGE expression in vascular endothelium.[15,16] Furthermore, vitamins such as vitamin B1, B6, C, D, and E may also reduce the formation of AGEs.[17,18] Our patient had been taking metformin, an angiotensin II receptor blocker, a calcium channel blocker, and a statin. However, it should be noted that he kept low levels of serum AGEs and sRAGE throughout the course of his disease. The patient's genetic background and/or lifestyle, which might not be captured by a regular medical interview, may have contributed to his maintenance of low serum AGEs and sRAGE levels. A previous study reported correlations for serum AGE levels in monozygotic twins, suggesting that familial and genetic factors may influence AGEs.[19]

Considering the above information, oral intake of AGEs, smoking, drugs, genetic background, lifestyle and/or unknown factors may regulate AGEs and sRAGE; low levels of serum AGEs and sRAGE may confer protection against diabetes-related complications.

This case report has several limitations. First, there are several methods available to measure AGEs and RAGE, including enzyme-linked immunosorbent assay (ELISA), mass spectroscopy, and autofluorescence. However, there are no single standardized protocols or normal reference ranges established for these measures. Therefore, we examined serum AGEs and sRAGE by ELISA and evaluated these levels compared with our own data from patients with type 2 diabetes in our hospital. Future studies must establish standardized methods for measurements of AGEs and sRAGE. Second, there have been many AGEs identified, but long-term evidence between their accumulation and diabetes-related complications is lacking. In addition, the correlation between serum AGEs/sRAGE levels and tissue AGEs/sRAGE accumulation remains unknown. Third, the association between sRAGE concentrations and diabetes-related complications remains controversial. Some studies have found a negative association between sRAGE and diabetes-related complications.[20] sRAGE may have a counter-regulatory mechanism by acting as a decoy receptor and capturing circulating AGEs.

Here, we report the case of a 64-year-old man with poorly controlled type 2 diabetes, no progression of diabetes-related complications, and maintained low levels of serum AGEs and sRAGE. We occasionally encounter similar cases exhibiting a discrepancy between glycemic control and diabetes-related complications. Activation of the AGE/RAGE axis may contribute to diabetes-related complications, and thus serum AGEs and sRAGE levels may be a useful predictor of diabetes-related complications, independent of glycated hemoglobin. Future studies are needed to reveal the association between AGEs/sRAGE axis and diabetes-related complications in diabetic patients.

Author contributions

Data curation: Kazuki Yasuda.
Supervision: Kazuki Yasuda, Daisuke Chujo, Mitsuru Ohsugi, Akiyo Tanabe, Kohjiro Ueki, Hiroshi Kajio.
Writing – original draft: Tomoka Nakamura.
Writing – review & editing: Tetsuro Tsujimoto.

References

[1] Katakami N. Mechanism of development of atherosclerosis and cardiovascular disease in diabetes mellitus. J Atheroscler Thromb 2018;25:27–39.

[2] Brings S, Fleming T, Freichel M, et al. Dicarbonyls and advanced glycation end-products in the development of diabetic complications and targets for intervention. Int J Mol Sci 2017;18:

[3] Vistoli G, De Maddis D, Cipak A, et al. Advanced glycoxidation and lipoxidation end products (AGEs and ALEs): an overview of their mechanisms of formation. Free Radic Res 2013;47(Suppl 1):3–27.

[4] Saulnier PJ, Wheelock KM, Howell S, et al. Advanced glycation end products predict loss of renal function and correlate with lesions of diabetic kidney disease in american indians with type 2 diabetes. Diabetes 2016;65:3744–53.

[5] Vlassara H, Uribarri J. Advanced glycation end products (AGE) and diabetes: cause, effect, or both? Curr Diab Rep 2014;14:453.

[6] Thomas MC, Woodward M, Neal B, et al. Relationship between levels of advanced glycation end products and their soluble receptor and adverse outcomes in adults with type 2 diabetes. Diabetes Care 2015;38:1891–7.

[7] Koska J, Saremi A, Howell S, et al. Advanced glycation end products, oxidation products, and incident cardiovascular events in patients with type 2 diabetes. Diabetes Care 2018;41:570–6.

[8] Hanssen NM, Beulens JW, van Dieren S, et al. Plasma advanced glycation end products are associated with incident cardiovascular events in individuals with type 2 diabetes: a case-cohort study with a median follow-up of 10 years (EPIC-NL). Diabetes 2015;64:257–65.

[9] Cerami C, Founds H, Nicholl I, et al. Tobacco smoke is a source of toxic reactive glycation products. Proc Natl Acad Scie US A 1997;94:13915–20.

[10] Vlassara H, Cai W, Crandall J, et al. Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for diabetic angiopathy. Proc Natl Acad Sci U S A 2002;99:15596–601.

[11] Spadaccio C, Nenna A, Nappi F, et al. Pharmacologic approaches against Advanced Glycation End Products (AGEs) in diabetic cardiovascular disease. Res Cardiovasc Med 2015;4:5.

[12] Rabbani N, Chittari MV, Bodmer CW, et al. Increased glycation and oxidative damage to apolipoprotein B100 of LDL cholesterol in patients with type 2 diabetes and effect of metformin. Diabetes 2010;59:1038–45.

[13] Beisswenger PJ, Howell SK, Touchette AD, et al. Metformin reduces systemic methylglyoxal levels in type 2 diabetes. Diabetes 1999;48:198–202.

[14] Cuccurullo C, Iezzi A, Fazia ML, et al. Suppression of RAGE as a basis of simvastatin-dependent plaque stabilization in type 2 diabetes. Arterioscler Thromb Vasc Biol 2006;26:2716–23.

[15] Nakamura K, Yamagishi S, Nakamura Y, et al. Telmisartan inhibits expression of a receptor for advanced glycation end products (RAGE) in angiotensin-II-exposed endothelial cells and decreases serum levels of soluble RAGE in patients with essential hypertension. Microvasc Res 2005;70:137–41.

[16] Yamagishi S, Takeuchi M. Nifedipine inhibits gene expression of receptor for advanced glycation end products (RAGE) in endothelial cells by suppressing reactive oxygen species generation. Drugs Exp Clin Res 2004;30:169–75.

[17] Metz TO, Alderson NL, Thorpe SR, et al. Pyridoxamine an inhibitor of advanced glycation and lipoxidation reactions: a novel therapy for treatment of diabetic complications. Arch Biochem Biophys 2003;419:41–9.

[18] Voziyan PA, Hudson BG. Pyridoxamine: the many virtues of a maillard reaction inhibitor. Ann N Y Acad Sci 2005;1043:807–16.

[19] Leslie RD, Beyan H, Sawtell P, et al. Level of an advanced glycated end product is genetically determined: a study of normal twins. Diabetes 2003;52:2441–4.

[20] Kajikawa M, Nakashima A, Fujimura N, et al. Ratio of serum levels of AGEs to soluble form of RAGE is a predictor of endothelial function. Diabetes Care 2015;38:119–25.