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

A Case report

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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.
Therefore, we examined serum AGEs (CEL and MG-H1) over 15 years, the patient did not exhibit diabetes-related carotid artery intima-media thickness was within normal range at hospital admission in November 2017. Regarding the patient statin. He was a former smoker (30 cigarettes per day from ages 45 years). Table 1 presents patient characteristics from the recent 10 years. BMI remained above 30kg/m2 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 400mg/dL. At the time of admission, his body weight was 92.3kg and his BMI was 34.5kg/m2. He was treated with metformin (1000mg 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 changed over the 10 years. BMI started in 2008. His mean HbA1c level from the most recent decade was approximately 10% and his body mass index (BMI) remained above 30kg/m2 throughout the period (Fig. 1).

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 353mg/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 30kg/m2 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. 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 <30mg/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, 0.5mm and left, 0.6mm). 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 (CellBiolabs, 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-H1, and sRAGE levels were 8.3μg/mL, 1.8μg/mL, and 401.3pg/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.

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

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/m² |
| Abdominal circumference                           | 109 cm   |
| Blood pressure                                    | 129/70 mmHg |
| **Blood laboratory findings**                     |
| **Normal range**                                  |
| Aspartate aminotransferase                        | 22 IU/L  |
| Alanine aminotransferase                          | 25 IU/L  |
| Estimated glomerular filtration rate*             | 66.0 mL/min/1.73 m² |
| Uric acid                                         | 7.6 mg/dL |
| Triglyceride                                      | 114 mg/dL |
| High-density lipoprotein cholesterol              | 52 mg/dL |
| Low-density lipoprotein cholesterol†              | 144 mg/dL |
| Brain natriuretic peptide                         | 6.7 mg/mL |
| Fasting plasma glucose                            | 178 mg/dL |
| Glycated hemoglobin                               | 10.0%    |
| Glycated albumin                                  | 16.0%    |
| Fasting serum C peptide                           | 1.37 ng/mL |
| Estimated glomerular filtration rate (mL/min/1.73 m²) = 194 × Creatinine (mg/dL) × Age (yr) / 8.0. |

Fig. 1. Transition of glycated hemoglobin levels and body mass index for the recent 10 years. BMI = body mass index, HbA1c = glycated hemoglobin.
Several other drugs may also correlate with AGEs accumulation and sRAGE expression. 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. Furthermore, vitamins such as vitamin B1, B6, C, D, and E may also reduce the formation of AGEs. 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.

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 spectrometry, 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, but 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.

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/m²; 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/m²; 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.

Author contributions

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