Altered serum glyceraldehyde-derived advanced glycation end product (AGE) and soluble AGE receptor levels indicate carbonyl stress in patients with schizophrenia

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Abstract

Recent cross-sectional and longitudinal studies indicate that measurements of peripheral blood carbonyl stress markers such as the advanced glycation end product (AGE) pentosidine and the reactive carbonyl-detoxifying B6 vitamin pyridoxal could be used as therapeutic biological markers in subpopulations of schizophrenia patients. Glyceraldehyde-derived AGEs (Glycer-AGE) have strong neurotoxicity, and soluble receptors for AGEs (sRAGE) may ameliorate the effects of AGEs. In the present study, we measured Glycer-AGEs and sRAGE levels to determine their potential as diagnostic, therapeutic, or clinical biological markers in patients with schizophrenia. After enrollment of 61 admitted Japanese patients with acute schizophrenia and 39 healthy volunteers, 54 patients were followed up from the acute stage to remission. Serum biomarkers were measured in blood samples taken before breakfast using competitive enzyme-linked immunosorbent assays, and Glycer-AGEs were significantly higher and sRAGE levels were significantly lower in patients with acute schizophrenia than in healthy controls. Moreover, Glycer-AGEs/sRAGE ratios were considerably higher in schizophrenia patients and were stable during the clinical course. However, these markers of carbonyl stress markers were not correlated with clinical features, including disease severity, or with daily chlorpromazine doses. These data indicate the potential of

Glycer-AGEs, RAGEs, and their relative ratios as diagnostic markers for patients with schizophrenia.

Keywords: carbonyl stress, clinical course, Glycer-AGEs, schizophrenia, sRAGE

Abbreviations: AGE, advanced glycation end product; Glycer-AGE, glyceraldehyde-derived AGE; RAGE, AGE receptors; sRAGE, soluble AGE receptors; esRAGE, endogenous secretory RAGE; ANCOVA, analysis of covariance; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders-IV; ELISA, enzyme-linked immunosorbent assay; MMP, matrix metalloproteinase

1. Introduction

Carbonyl stress has been identified as an environmental factor [1, 8-10] in the pathophysiology of schizophrenia. During carbonyl stress, excess glucose and lipids are converted to irreversible advanced glycation end products (AGEs) and advanced lipoxidation end products (Supplementary material Fig. 1). Recent cross-sectional and longitudinal studies suggest the potential of peripheral blood carbonyl stress markers as therapeutic biomarkers in subpopulations of patients with schizophrenia [1, 8-10]. In particular, the AGE pentosidine is significantly more abundant in the peripheral blood of patients with clinically severe schizophrenia [1, 9, 10]. Conversely, low levels of vitamin B6 (pyridoxal), which detoxifies RCOs, are often observed in these patients [1, 8]. Although decreases in pyridoxal levels have been demonstrated in multiple studies [1, 8-10], serum pentosidine levels were not increased in serum from the present patients [8].

Among multiple identified AGEs glyceraldehyde-derived AGEs (Glycer-AGEs) has strong neurotoxicity [24] and are considered central to the pathogenesis of neurodegenerative diseases [26, 27]. AGEs interact with AGE receptors (RAGE) on the membrane, which then induce deleterious effects relating to increases in oxidative and carbonyl stress [17]. AGEs also bind circulating soluble receptors, including

endogenous secretory RAGE (esRAGE) and soluble receptor for RAGE (sRAGE). Accordingly, sRAGE serum levels are five times higher than those of esRAGE in healthy subjects, suggesting that sRAGE levels are more indicative of carbonyl stress than esRAGE [17]. In the present study, we measured Glycer-AGE and sRAGE levels in patients with schizophrenia and assessed their roles as diagnostic, therapeutic, or clinical biomarkers of disease status.

2. Materials and Methods

2.1 Patients

Japanese patients with schizophrenia (paranoid, disorganized, or catatonic types) who met the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) diagnosis of schizophrenia were enrolled following clinical interviews by at least three experienced psychiatrists. All patients were admitted to the Juntendo Koshigaya Hospital (Saitama) or Juntendo University Hospital (Tokyo) because of deteriorating symptoms. Clinical data, including serum measurements, were obtained for patients who could be followed up from the time of admission to discharge in paired samples. Patients were excluded if they had diabetes mellitus, chronic renal disease, or other physiological diseases according to tests of glucose, glycosylated hemoglobin A1C,

creatinine, and urea nitrogen, because these can increase AGE levels. Renal function was also assessed according to glomerular filtration rates (normal, > 60 ml/min) and urinalyses. Times of discharge were thoroughly discussed with patients and their families, and were determined according to sufficient improvements for treatment on an outpatient basis.

Data were also collected from 39 healthy controls who did not meet current or past criteria for any Axis I DSM-IV disorder. These subjects had no systemic or neurologic disease, no past head trauma with loss of consciousness, and no lifetime history of alcohol or substance dependence. No healthy controls had diabetes mellitus or chronic renal disease.

2.2 Evaluation of Clinical Symptoms

Clinical symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS) on a scale of 1–7 [16]. BPRS scores were based on direct interviews that were conducted independently by experienced psychiatrists, and overall total ratings and scores for positive and negative symptom clusters were generated [2].

Because the Juntendo University Schizophrenia Project [14] prioritizes improvements in patient symptoms, the use of drug therapy was not controlled for

ethical reasons. The Ethics Committee of the Juntendo University Faculty of Medicine approved the present study (2012083). All participants provided written informed consent prior to participating in the study.

2.3 Measurements of Carbonyl Stress Markers

Serum Glycer-AGE levels were measured using competitive enzyme-linked immunosorbent assay (ELISA) with immunopurified Glycer-AGE antibodies [25]. Details of the measurement procedures are available on request. RAGE levels were determined using commercially available ELISA kits (R&D systems, Minneapolis, MN, USA) with reliable intra-assay and inter-assay coefficients of variation [12, 30].

2.4 Statistical Analysis

Chi-square tests were used to assess differences in frequency distributions of basic parameters such as sex. Differences in the serum carbonyl stress marker levels between unpaired groups were identified using two-tailed Mann–Whitney *U*-tests for two-group comparisons, and using Kruskal–Wallis tests for comparisons of three or more groups. One-way analysis of covariance (ANCOVA) was used to assess the effect of schizophrenia diagnosis (schizophrenia versus healthy controls) with relevant

covariates. Differences in serum carbonyl stress marker levels in paired patient serum samples from admission and discharge were examined using the Wilcoxon matched-pairs signed-rank test. Correlations between clinical features such as the duration of hospitalization and serum metabolite levels were analyzed using Pearson's correlation test. Correlations between BPRS scores and serum metabolites were assessed using Spearman's correlation test.

3. Results

3.1 Participants

Subjects included 61 Japanese patients with paranoid, disorganized, or catatonic type schizophrenia and 39 healthy controls (Table 1). No first-episode drug-naïve patients were included, and 11 patients were not taking any antipsychotic agents (medication free) at the time of disease recurrence and admission (Supplementary Table 1). The mean ± standard deviation (SD) duration of drug discontinuation before admission was 34.3 ± 67.8 months (range, 1–264 months). Among 61 patients, 54 were followed from admission to discharge (Supplementary material Table 2) and clinical data were used for analyses of paired samples. No significant differences in gender distribution or age were identified between healthy controls and patients with

schizophrenia. However, body mass index (BMI) was significantly higher among patients with schizophrenia (Table 1).

3.2 Carbonyl Stress Markers in Patients with Acute Stage Schizophrenia

Serum Glycer-AGE levels were significantly higher in patients with schizophrenia at admission than in healthy controls. In contrast, serum sRAGE levels were significantly lower in patients at admission than in healthy controls (Table 1 and Fig. 1A and 1B). Significant negative correlations were identified between serum Glycer-AGE and sRAGE levels ($r = -0.329$, $P = 0.001$) in all participants. In agreement, Glycer-AGEs/sRAGE ratios were reportedly more sensitive markers of carbonyl stress [7], and differed significantly between the present subject groups, with approximately 2-fold higher ratios in patients with schizophrenia than in healthy controls (Table 1, Fig. 2C). Carbonyl stress marker levels did not differ significantly between medicated patients and 11 medication free patients (Supplemental Table 1).

3.3 Nutrition Status and Lifestyle

To identify potential confounding factors in patients with schizophrenia at admission, we correlated the nutritional variables BMI, hemoglobin A1C, creatinine,

glucose, total cholesterol, triacylglycerol, and total protein with carbonyl stress markers. Only BMI was associated with Glycer-AGEs (r = 0.293, P = 0.048) and Glycer-AGEs/sRAGE ratios (r = 0.304, P = 0.040; Supplementary Table 3). Lifestyle factors, including smoking status (yes, 23; no, 36; unknown, 2) and alcohol consumption (yes, 8; no, 51; unknown, 2) were not associated with carbonyl stress markers. To confirm associations of these factors with serum Glycer-AGE levels and Glycer-AGEs/sRAGE ratios in patients with schizophrenia, we performed one-way ANCOVA with BMI as a covariate. When BMI was controlled, the main effect of diagnosis remained significant for both serum Glycer-AGE levels (F = 10.34, df = 1, P = 0.002) and Glycer-AGEs/sRAGE ratios (F = 11.44, df = 1, P = 0.001).

3.4 Clinical Variables

Any clinical variables (Table 1) excepting BMI as mentioned-above were not significantly correlated with carbonyl stress markers (Supplementary material Table 3). However, Glycer-AGEs/sRAGE ratios of > 2 SD higher than control ratios (ratios of > 13; 23 cases) were more common among patients with schizophrenia. Thus, in subsequent analyses, clinical variables such as symptom severity were compared between patients with high (> 2 SD above normal) and normal ratios (within 2 SD of

control ratios), but no significant differences were identified (Supplementary material Table 4).

3.5 Temporal Changes in Levels and Ratios of Carbonyl Stress Markers

Fifty-four patients with schizophrenia were followed from admission to discharge and paired comparisons of serum biomarkers were performed (Supplementary material Table 2). As expected, total BPRS and positive and negative symptoms were significantly improved between admission and discharge, reflecting significantly increased daily chlorpromazine doses in these patients. However, Glycer-AGEs and sRAGE levels and their relative ratio did not differ between admission and discharge (Supplementary material Table 2). Moreover, changes (Δ) in carbonyl stress markers, which were calculated as $\Delta_{\text{carbonyl stress markers}}$ = [(discharge level − admission level)/admission level], were not significantly correlated with changes in clinical symptoms (Supplementary material Table 3).

4. Discussion

In the present cross-sectional longitudinal study, we confirmed previous observations of altered carbonyl stress markers levels in schizophrenia by using the

other putative marker Glycer-AGEs and sRAGE. The present data are the first to show significant increases in Glycer-AGE levels in patients with acute schizophrenia. Among AGEs, altered levels and neurotoxicity of Glycer-AGEs have been reported in association with various neurodegenerative diseases [20, 26]. Accordingly, Glycer-AGEs rather than non-toxic AGEs such as pentosidine are reportedly involved in the pathophysiology of neurodegenerative diseases [28]. However, schizophrenia has been considered a functional disease in neuropathological studies of patients with schizophrenia who lack evidence of prominent neurodegeneration [21], indicating differing roles of increased Glycer-AGEs levels in schizophrenia and neurodegenerative diseases [27].

In the present study, sRAGE levels were significantly decreased in patients with acute schizophrenia. Although the pathophysiological roles of sRAGE in humans remain controversial, sRAGE has a reported counter-regulatory mechanism that abolishes the effects of the AGEs–RAGE axis [7]. In contrast, interactions of Glycer-AGEs with RAGE have been related to neurotoxicity through alterations of intracellular signaling [19]. Serum levels of sRAGE have only been investigated in two conflicting reports of patients with schizophrenia, with increased sRAGE levels in one [22] and decreased levels in the other [3]. The former study, which contradicts the present data,

also investigated longitudinal changes and higher sRAGE levels in the acute stage were associated with severe and deteriorating symptoms [22]. In contrast, sRAGE levels were not increased during convalescence in the present cohort. Because AGEs are irreversible end products of Amadori products such as hemoglobin A1C that only change after months of treatment, changes in sRAGE levels are not expected to be dramatic for at least the first few months. In addition. reduced serum sRAGE levels have been associated with cerebrovascular disease [5], hypertension [4], and hypercholesterolemia [18], whereas elevated serum sRAGE levels are reportedly associated with diabetes [11, 13]. Increases in sRAGE require increased expression of matrix metalloproteinase (MMP), because total sRAGE comprises both esRAGE and that shed from cell-bound RAGE via MMP [31]. Notably, MMP expression was not increased in schizophrenia patients. Thus, the present significant negative correlations of serum sRAGE with Glycer-AGEs levels suggests that decrease sRAGE levels might due to combine with the increased Glycer-AGE levels in schizophrenia.

In a previous postmortem study [15], we showed that the pathophysiology of schizophrenia causes minimal changes in these receptor and transporter biomarkers. However, use of the present ratio of opposing receptor/transporter magnified these changes to produce a significant index of schizophrenia related carbonyl stress.

Accordingly, the present Glycer-AGEs/sRAGE ratios were approximately 2-fold higher in schizophrenic patients than in controls, and reportedly differed significantly between patients with acute schizophrenia (13.6 ± 9.4 U/ng), diabetic mellitus (17.8 ± 8.1 U/ng) [7], and patients with a high risk of cardiovascular disease (18.3 ± 1.4 U/ng) [23]. In contrast, Glycer-AGE levels alone did not distinguish between patients with acute schizophrenia (12.3 ± 3.5 U/ml), chronic renal failure (13.2 ± 4.4) [29], or non-alcoholic steatohepatitis (13.2 ± 4.4 U/ml) [6], indicating that the Glycer-AGEs/sRAGE ratio is a superior marker of carbonyl stress in schizophrenia, as in other diseases [7, 23]. However, Glycer-AGEs, sRAGE, and Glycer-AGEs/sRAGE ratios were not significantly related with clinical features of acute schizophrenia, including symptom severity. Potentially, this reflects limitations of the present study, including the small changes in these parameters, and the small heterogeneous cohort of schizophrenia patients. Nonetheless, the present data warrant further assessment of these Glycer-AGEs, sRAGE, and their ratios in larger studies, which may resolve these problems and clarify the pathophysiology of carbonyl stress in schizophrenia. In addition, types of drug therapy were not controlled and control subjects were not matched in terms of BMI or age in the present study. Thus, more detailed nutritional and/or environmental

information such as numbers of pack-years may facilitate demonstrations of these effects in future studies.

5. Conclusion

The present results indicate that carbonyl stress is present in some patients with acute schizophrenia and adds key observations to the study of the pathogenesis and treatment of schizophrenia. Specifically, Glycer-AGE and sRAGE levels were significantly higher and lower, respectively, in acute schizophrenia and remained stable over the clinical course. Moreover, the ratio of Glycer-AGEs/sRAGE was significantly greater in patients with schizophrenia than in healthy control subjects.

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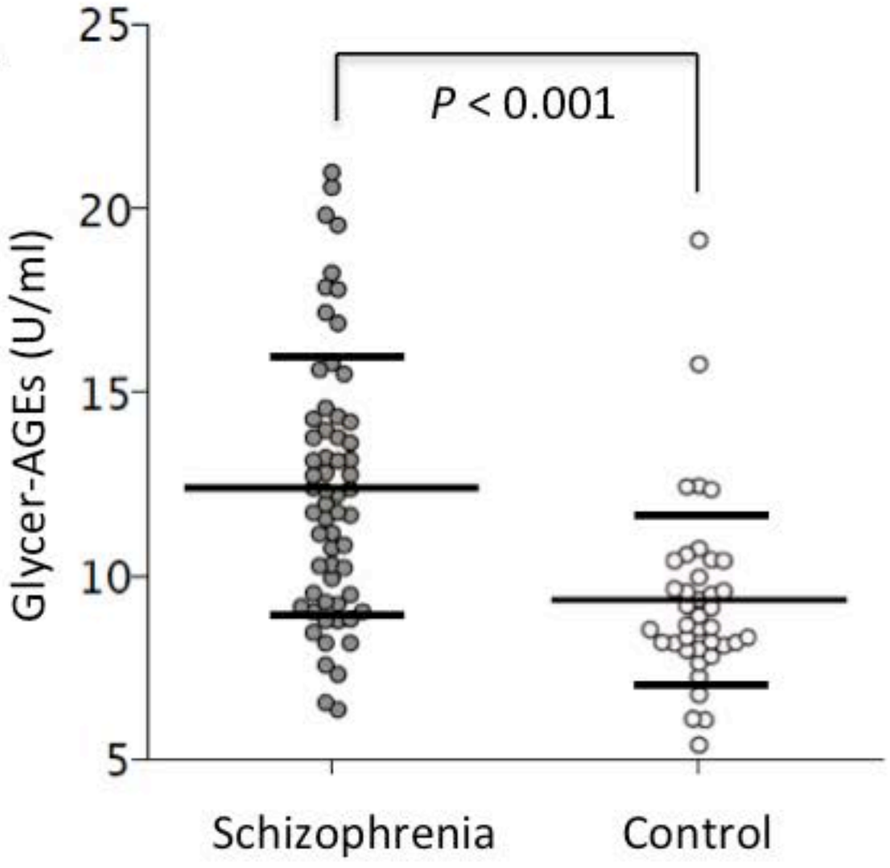
Figure Legends

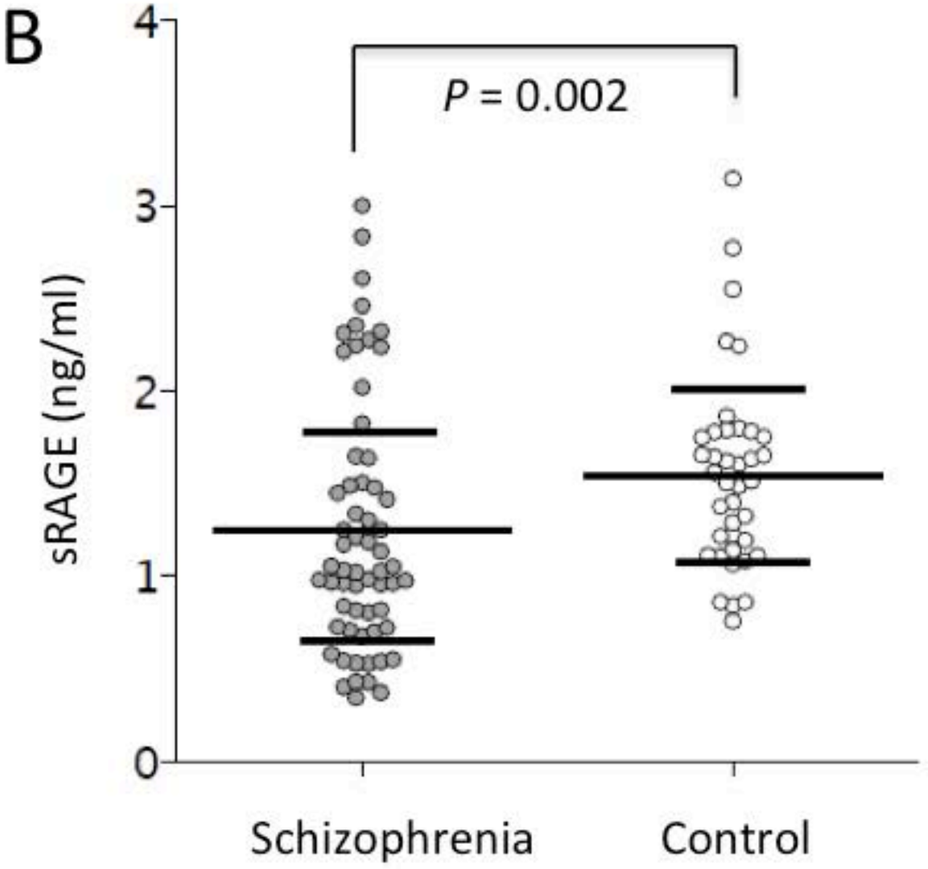
Figure 1. Serum Levels of Carbonyl Stress Markers and their Ratios at Admission

(A) Glycer-AGEs, (B) sRAGE, and (C) the Glycer-AGEs/sRAGE ratio are compared between patients with schizophrenia and normal healthy control subjects. Data are presented as means and standard deviations and were compared using two-tailed Mann–Whitney *U*-test.

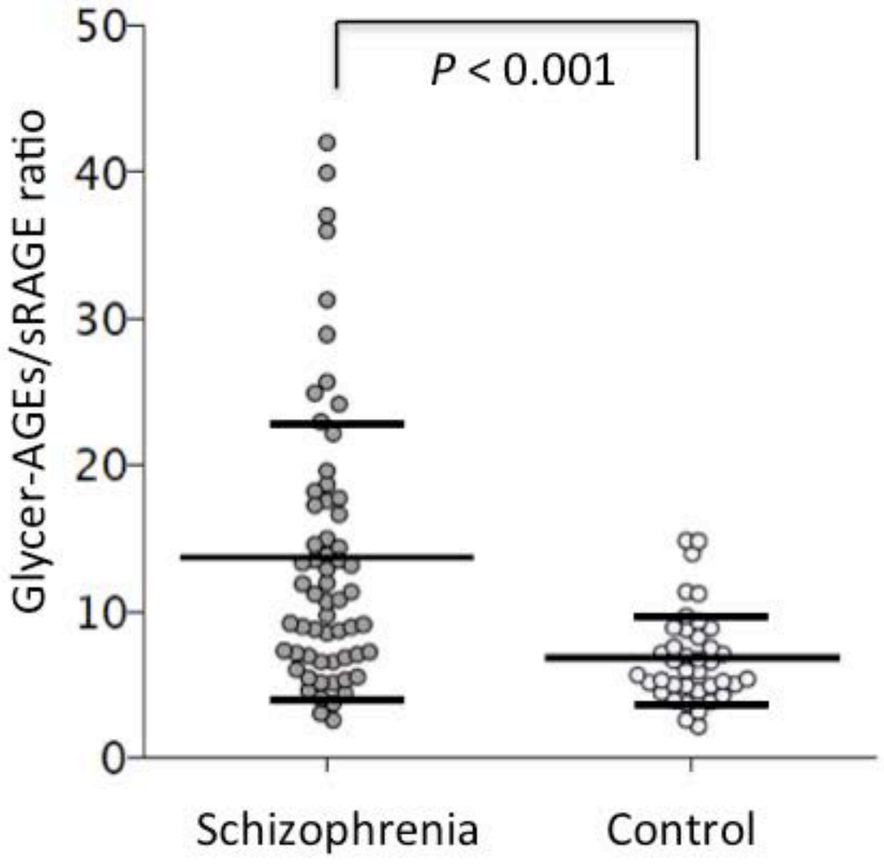
A

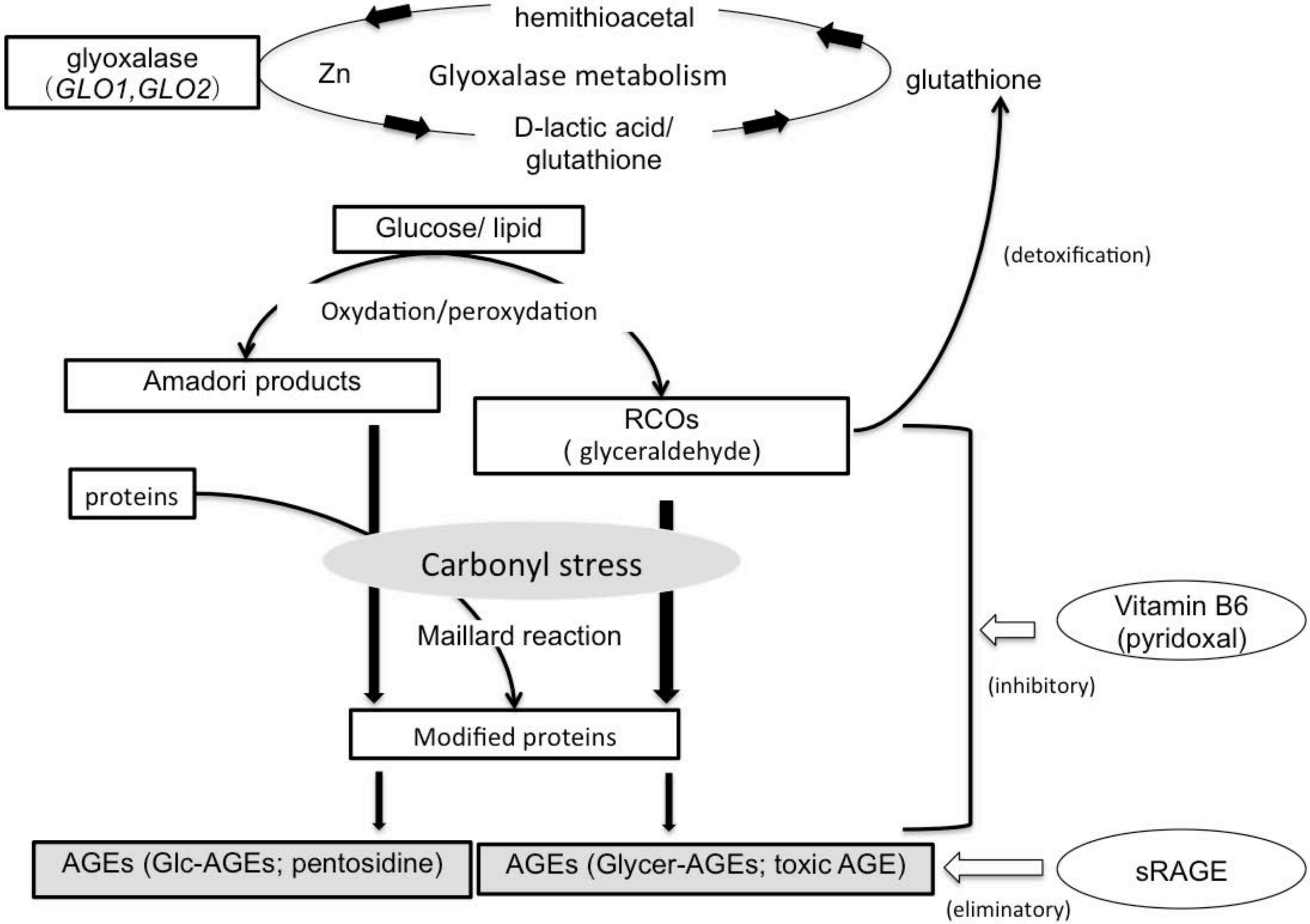

25
20
15
10
5
Glycer-AGEs (U/ml)
P < 0.001
Schizophrenia
Control

B


4
3
2
1
0
sRAGE (ng/ml)
P = 0.002
Schizophrenia
Control

C


50
40
30
20
10
0
Glycer-AGEs/sRAGE ratio
P < 0.001
Schizophrenia
Control



Supplementary Figure 1. Mechanism of Carbonyl Stress and Detoxification

Reactive carbonyl compounds (RCOs) cause carbonyl stress and are detoxified by degradation into lactic acid and glutathione by glyoxalase enzymes. Inhibition of RCO generation and the Maillard reaction by vitamin B6 suppresses AGEs accumulation, whereas AGEs are eliminated by sRAGE. This figure is adapted from a previous publication (Katsura et al., 2014).

Table 1. Comparison of patients with schizophrenia versus controls at admission

Variables	Patients with schizophrenia (*n* = 61)	Controls (*n* = 39)	Statistical test and *P*-value Mann-Whitney *U*	
			χ^2	*P*
Sex, M/F	31/30	17/22	0.498	0.541
Age, mean (years)	35.5 ± 12.1(17–73)	31.8 ± 4.5 (22–42)	−1.163	0.245
BMI	24.1 ± 5.4 (13.0–47.0)	21.3 ± 4.8 (17.4–31.2)	−2.917	**0.004**
Onset (years)	23.7 ± 9.1(12–53)	NA		
Duration of education (years)	12.5 ± 2.5 (9–20)	NA		
Family history (yes/no)	14/47	NA		
Duration of illness (years)	13.9 ± 10.0 (0–48)	NA		
DUP (months)	22.1 ± 37.6 (0–264)	NA		
Number of admissions	1.9 ± 1.4 (1–7)	NA		
CP dose (mg/day)	647.1 ± 711.1 (0–3162)	NA		
BPRS (Total)	55.1 ± 17.3 (9–96)	NA		
(Positive)	15.3 ± 4.9 (6–24)	NA		
(Negative)	9.9 ± 3.4 (3–18)	NA		
Glycer-AGEs, U/ml	12.3 ± 3.5 (6.3–20.9)	9.3 ± 2.5 (5.3–19.1)	–4.63	**<0.001**
sRAGE, ng/ml	1.2 ± 0.6 (0.3–3.0)	1.5 ± 0.5 (0.7–3.1)	3.099	**0.002**
Glycer-AGEs/sRAGE ratio, U/ng	13.6 ± 9.4 (2.5–42.0)	6.8 ± 3.1 (2.1–14.8)	–4.357	**<0.001**

Data are presented as the mean ± standard deviation (SD) and range. Glycer-AGEs, glyceraldehyde-derived AGEs; sRAGE, soluble receptors for AGEs; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CP dose, chlorpromazine equivalent dose; DUP, duration of untreated psychosis; NA, not applicable. *P*-values that indicate statistical differences are presented in bold.

Supplementary Table 1. Comparisons of medicated and non-medicated patients at admission

Variables	Medication-free patients (*n* = 11)	Medicated patients (*n* = 50)	Statistical test and *P*-value Mann-Whitney *U*	
			χ^2	*P*
Sex, M/F	5/6	29/21	0.575	0.448
Age, mean (years)	34.7 ± 10.4 (18–53)	36.7 ± 12.9 (18–73)	0.285	0.775
BMI	20.6 ± 3.2 (16.0–27.0)	23.8 ± 7.4 (13.0–47.0)	1.114	0.285
Onset (years)	24.0 ± 10.0 (13–46)	23.7 ± 9.1 (12–53)	-0.011	0.992
Duration of education (years)	13.0 ± 2.0 (9–16)	12.6 ± 2.7 (9–20)	-0.552	0.581
Family history (yes/no)	3/8	11/39	0.142	0.707
Duration of illness (years)	12.0 ± 9.1 (1–33)	15.4 ± 10.5 (0–48)	1.152	0.249
DUP (months)	34.2 ± 67.7 (1–264)	17.7 ± 17.6 (0–72)	-0.499	0.618
Number of admissions	1.5 ± 0.7 (1–3)	2.0 ± 1.5 (1–7)	0.714	0.475
CP dose (mg/day)	0	804.7 ± 618.6 (50–2497)	5.524	**<0.0001**
BPRS (Total)	59.1 ± 19.4 (23–85)	53.0 ± 16.9 (0–96)	-1.362	0.173
(Positive)	15.7 ± 5.6 (6–24)	14.8 ± 4.7 (6–24)	-0.657	0.511
(Negative)	9.7 ± 3.8 (3–16)	10.0 ± 3.1 (3–18)	0.032	0.975
Glycer-AGEs, U/ml	11.0 ± 2.9 (7.3–17.8)	12.8 ± 3.6 (6.5–20.9)	1.604	0.109
sRAGE, ng/ml	1.4 ± 0.6 (0.6–3.0)	1.2 ± 0.7 (0.3–2.8)	-0.844	0.399
Glycer-AGEs/sRAGE ratio, U/ng	9.1 ± 4.3 (2.5–17.5)	13.8 ± 9.3 (2.9–39.9)	1.456	0.145

Data are expressed as the mean ± standard deviation (SD) and range. Glycer-AGEs, glyceraldehyde-derived AGEs; sRAGE, soluble receptors for AGEs; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CP dose, chlorpromazine equivalent dose; DUP, duration of untreated psychosis. *P*-values that indicate significant differences are presented in bold.

Supplementary Table 2. Characteristics and test scores of schizophrenia patients at admission and discharge

Variables	Paired-sample Schizophrenia Patients (n = 54)			
Sex, M/F	27/27			
Age, mean ± SD, years	36.2 ± 12.2 (18–73)			
Onset (range), years	23.8 ± 9.3 (12–53)			
Duration of illness (range), years	14.4 ± 10.2 (0–48)			
DUP (range), months	22.3 ± 38.3 (0–264)			
Duration of hospitalization (range), days	120.1± 96.4 (7–438)			
			Wilcoxon test	
	at Admission	at Discharge	Z	P
CP dose, mg/day	583.7± 638.0 (0–2497)	880.7 ± 529.8 (50–2223)	−5.96	<**0.001**
BPRS scores (Total)	54.7 ± 17.6 (0–96)	38.0 ± 9.8 (18–63)	−4.55	<**0.001**
(Positive)	15.1 ± 4.9 (6–24)	9.8± 3.6 (4–20)	−5.38	<**0.001**
(Negative)	9.9 ± 3.3 (3–18)	7.7 ± 2.7 (3–16)	2.95	**0.003**
Glycer-AGEs, U/ml	12.3 ± 3.5	11.9 ± 3.5	−1.14	0.254
sRAGE, ng/ml	1.2 ± 0.6	1.2 ± 0.6	0.50	0.613
Glycer-AGEs/sRAGE ratio, U/ng	13.1 ± 8.5	12.0 ± 7.6	−1.01	0.312

Glycer-AGEs, glyceraldehyde-derived AGEs; sRAGE, soluble receptors for AGEs; BPRS, Brief Psychiatric Rating Scale; CP dose, chlorpromazine equivalent dose; DUP, duration of untreated psychosis. *P*-values with statistical significance are indicated in bold.

Supplementary Table 3. Correlations between clinical variables and markers of carbonyl stress

Variables	Patients at admission (n = 61)			Paired samples (n=54) $\Delta_{\text{carbonyl stress markers}}$		
	Glycer-AGEs	sRAGE,	Glycer-AGEs/sRAGE ratio	$\Delta_{\text{Glycer-AGEs,}}$	$\Delta_{\text{sRAGE,}}$	$\Delta_{\text{Glycer-AGEs/sRAGE ratio}}$
Age, mean (years)	-0.077	-0.188	0.128		NA	
BMI	**0.293**	-0.280	**0.304**		NA	
Onset (years)	-0.139	-0.021	-0.039		NA	
Duration of education (years)	-0.140	0.097	-0.232		NA	
Duration of illness (years)	0.166	-0.072	0.147		NA	
DUP (months)	0.081	-0.109	0.028		NA	
Number of admissions	-0.061	0.064	0.127		NA	
CP dose (mg/day)	0.262	-0.101	0.137	-0.170*	-0.008*	-0.114*
BPRS (Total)	-0.166	0.024	-0.084	-0.20*	-0.170*	0.033*
(Positive)	-0.109	0.136	-0.115	-0.115*	-0.073*	-0.044*
(Negative)	0.087	-0.044	0.150	-0.046*	-0.115*	0.197*

Data are presented as correlation coefficients. Glycer-AGEs, glyceraldehyde-derived AGEs; sRAGE, soluble receptors for AGEs; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CP dose, chlorpromazine equivalent dose; DUP, duration of untreated psychosis; NA, not applicable. *P*-values that indicate significant differences ($P < 0.05$) are presented in bold**.**

*Regression analyses were performed for $\Delta_{\text{carbonyl stress markers}}$, $\Delta_{\text{CP dose}}$, and $\Delta_{\text{BPRS (Total, Positive and Negative)}}$.

Supplementary Table 4. Comparison of patients with extremely high Glycer-AGEs/sRAGE ratios versus patients with normal ratios at admission

Variables	Extremely high Glycer-AGEs/sRAGE ratio (*n* = 23)	Normal Glycer-AGEs/sRAGE ratio (*n* = 38)	Statistical test and *P*-value Mann-Whitney *U*	
			χ^2	*P*
Sex, M/F	12/11	19/19	0.027	0.869
Age, mean (years)	35.6 ± 12.4 (24–57)	36.8 ± 12.4 (18–73)	0.285	0.775
BMI	25.0 ± 4.8 (17–31)	22.1 ± 7.1 (13–47)	1.578	0.115
Onset (years)	22.5 ± 10.9 (12–53)	24.6 ± 8.9 (13–47)	-1.025	0.305
Duration of education (years)	12.2 ± 3.2 (9–20)	13.0 ± 2.3 (9–16)	-1.237	0.261
Family history (yes/no)	6/17	8/30	0.205	0.650
Duration of illness (years)	17.7 ± 11.4 (4–37)	13.5 ± 9.8 (0–48)	1.095	0.274
DUP (months)	21.8 ± 21.2 (1–72)	23.0 ± 43.5 (0–264)	0.655	0.512
Number of admissions	1.9 ± 0.9 (1–3)	1.92 ± 1.48 (1–7)	0.823	0.410
CP dose (mg/day)	735.0 ± 638.1 (0–1951)	473.4 ± 561.8 (0–2350)	1.376	0.169
BPRS (Total)	53.6 ± 25.8 (0–96)	55.5 ± 14.9 (23–85)	-0.186	0.852
(Positive)	15.9 ± 5.9 (6–24)	14.8 ± 4.8 (6–24)	0.572	0.567
(Negative)	10.7 ± 3.2 (5–18)	9.7 ± 3.4 (3–16)	0.878	0.380

Patients with extremely high Glycer-AGEs/sRAGE ratios were categorized as those with ratios of > 2 standard deviations (SD) higher than the mean of controls (ratios of > 13). Patients with normal ratios were categorized as those with ratios within 2 SD of the mean control ratio (ratios of ≤ 13).

Data are presented as the mean ± standard deviation (SD) and range. Glycer-AGEs, glyceraldehyde-derived AGEs; sRAGE, soluble receptors for AGEs; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CP dose, chlorpromazine equivalent dose; DUP, duration of untreated psychosis.