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Research article

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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HIGHLIGHTS

- Advanced glycation end product (AGE) is a carbonyl stress marker of schizophrenia.
- Glycer-AGE and receptors for AGE (sRAGE) were involved in neurotoxic pathology.
- We compared serum these markers levels between schizophrenia and controls.
- Glycer-AGEs and sRAGE levels were significantly higher and lower in schizophrenia.
- The Glycer-AGEs/sRAGE ratio was altered more in 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. Glycer-AGEs/sRAGE ratios were also higher in schizophrenia patients and were stable during the clinical course. Furthermore, discriminant analyses confirmed that Glycer-AGEs and Glycer-AGEs/sRAGE ratios are significant diagnostic markers for schizophrenia, and distinguished between patients and healthy controls in 70.0% of cases. However, these markers of carbonyl stress 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.

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.

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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) have 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 receptors 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 misorders-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 recorded from 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].

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.