Increased Silent Brain Infarction Accompanied With High Prevalence of Diabetes and Dyslipidemia in Psychiatric Inpatients: A Cross-Sectional Study

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ABSTRACT

Objective: Patients with schizophrenia have increased risk of atherosclerotic diseases. It is already known that lifestyle-related disorders and the use of antipsychotics are closely related with the progression of atherosclerosis in psychiatric patients. Stroke as well as coronary heart disease play an important role in the cause of death in Asia and Japan. Thus, we studied the prevalence of cerebrovascular disease in psychiatric inpatients in Japan using brain magnetic resonance imaging (MRI).

Method: This cross-sectional study was performed from January 2012 to December 2013. Study participants were 152 hospitalized patients (61 men and 91 women) in the Department of Psychiatry at Kohnodai Hospital, National Center for Global Health and Medicine, Ichikawa City, Japan. Mean ages were 50.0 and 57.1 years old for men and women, respectively. The diagnoses (*DSM-IV-TR* criteria) of participants were schizophrenia (69.1%), mood disorder (18.4%), and other mental disorders (12.5%). We checked physical status, metabolic status of glucose and lipid levels, and brain MRI within 1 week of admission.

Results: The study group showed a significantly high prevalence of diabetes and low high-density lipoprotein (HDL) cholesterolemia in both sexes (n = 61 in men, n = 91 in women, $P < .05$). In the study group, serum fasting plasma glucose and hemoglobin A_{1c} levels were significantly high (n = 152, $P < .05$), but serum HDL cholesterol and total cholesterol were significantly low in both sexes (n = 61 in men, n = 90 in women, $P < .05$), and triglycerides were low in men (n = 61, $P < .05$). Silent brain infarction was recognized at a higher rate (n = 98, $P < .05$) compared with healthy controls.

Conclusions: Participants in this study had an increased ratio of silent brain infarction compared with Japanese healthy controls, accompanied with higher ratios of diabetes and low HDL cholesterol.

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The average life expectancy of patients with schizophrenia is approximately 15 years shorter than that of the general population in the United States.[1] Coronary heart disease is the cause of more than 50% of deaths in patients with schizophrenia in the United States.[1] Crump et al[2] reported that the leading causes of death in people with schizophrenia in Sweden were cardiovascular disease and cancer. These results indicate that patients with schizophrenia have the tendency to suffer from atherosclerotic diseases.

Hypertension, diabetes mellitus, dyslipidemia, visceral-type obesity, and smoking are risk factors for atherosclerosis. There are many reports of a high prevalence of diabetes in patients with schizophrenia.[3–6] The causes of diabetes are thought to be related to these patients' lifestyles, which include unhealthy eating habits, shortage of exercise, and smoking.[7–9] Schizophrenic patients also have a high incidence of dyslipidemia.[10] Sasaki et al[11] reported that serum high-density lipoprotein (HDL) cholesterol (HDL-C) decreased in patients with schizophrenia. Furthermore, Sugawara et al[12] reported that the prevalence of metabolic syndrome was higher in Japanese schizophrenic patients under age 60 years old compared with the general population. It is also reported that the prevalence of smoking is higher in these patients than in the general population.[1,13]

Most schizophrenic patients are administered typical or atypical antipsychotics. Prah et al[14] reported that, in 2007 in the United Kingdom, 15.0% of the prescriptions were for typical antipsychotics and 51.2% were for atypical antipsychotics among schizophrenic patients in primary care. It was also reported that antipsychotic prescriptions changed from typical antipsychotics (1997: 71.7%, 1999: 25.2%, 2002: 5.7%) to atypical antipsychotics for patients with mental disorders among Texas veterans.[15] In Japanese schizophrenic inpatients in 2008,[16] 44.2% received typical antipsychotics and 55.8% received atypical antipsychotics. Some atypical antipsychotics cause adverse effects on metabolism, such as diabetes and dyslipidemia.[4,17] These side effects also increase risks for atherosclerosis.

Cancer, heart disease, and cerebrovascular disease are main causes of death in the general population in Japan. Saku et al[18] reported that the standardized mortality ratio of cancer in Japanese patients with schizophrenia, followed up from 1982 to 1985, was almost the same as the general population. However, there are no reports that state the mortality rates of coronary heart disease and strokes in schizophrenic patients in Japan. Schizophrenic patients under 45 years old demonstrated a 2-fold increased risk of developing strokes compared with controls in Taiwan.[19] Therefore, it is probable that

Clinical Points

- Psychiatric patients in this study had increased silent brain infarction accompanied with atherosclerotic risk factors, such as high diabetes prevalence and low high-density lipoprotein cholesterolemia.
- The causes of high prevalence of risk factors in psychiatric patients are thought to be related to their lifestyles and antipsychotics administrated.
- Clinicians need to check and treat risk factors to prevent atherosclerotic diseases when examining psychiatric patients.

strokes as well as coronary heart disease have an essential role in cause of death and quality of life in the schizophrenic patients of Japan and the Asia-Pacific region.[20]

Magnetic resonance imaging (MRI) of the brain is commonly used in the diagnosis of stroke in Japan. Silent brain infarction (SBI) is described as lesions imaged by MRI as cerebral infarctions but without any recognized clinical symptoms and signs. SBI frequently occurs in healthy elderly individuals and is thought to more than double the risk of subsequent stroke, dementia, and cognitive decline.[21,22]

In the present study, we investigated brain MRI and lipid and glucose metabolism of psychiatric inpatients in Japan. High prevalence of SBI with diabetes and dyslipidemia was reported.

METHOD

Study Subjects

This study was performed from January 2012 to December 2013 at Kohnodai Hospital, National Center for Global Health and Medicine, Ichikawa City, Japan. Study participants were 152 hospitalized patients (61 men and 91 women) in the Department of Psychiatry at Kohnodai Hospital. The psychiatric diagnoses (per *DSM-IV-TR* criteria) of participants were schizophrenia, brief psychiatric disorders, and schizoaffective disorders (n = 105, 69.1%); mood disorders (n = 28, 18.4%); and other mental disorders (Alzheimer's disease, stimulant psychosis, and somatoform disorders) (n = 19, 12.5%). Ninety-seven patients were diagnosed with schizophrenia, 6 with brief psychiatric disorders, 2 with schizoaffective disorders, 18 with bipolar disorders, and 10 with major depressive disorders. Mean ages of the patients were 50.0 and 57.1 years for men and women, respectively.

The study protocol was approved by the Ethics Committees of Chiba Institute of Science, Choshi City, Japan, and National Center for Global Health and Medicine, Ichikawa City, Japan. All participants were provided with a written informed consent form, and explanation and participation agreement were performed in accordance with the Declaration of Helsinki principles.

Diagnosis of Study Participants

The psychiatric diagnoses were made using *DSM-IV-TR* criteria. The definition of hypertension was systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg. Diabetes mellitus was defined as hemoglobin A1c (HbA_{1c}) ≥ 6.5% and fasting plasma glucose ≥ 126 mg/dL. High low-density lipoprotein (LDL) cholesterolemia (fasting serum LDL cholesterol [LDL-C] ≥ 140 mg/dL) or low high-density lipoprotein (HDL) cholesterolemia (fasting serum HDL cholesterol [HDL-C] < 40 mg/dL) or hypertriglyceridemia (fasting serum triglyceride ≥ 150 mg/dL) are described as dyslipidemia. Patients are also counted as having hypertension, diabetes, or dyslipidemia if they use antihypertensive (Ca antagonists, angiotensin receptor blockers, diuretics, and β-blockers) or hypoglycemic (insulins, biguanides, sulfonylureas, α-glucosidase inhibitors, thiazolidines, and dipeptidyl peptidase-4 [DDP-4] inhibitors) or antidyslipidemic drugs (statins, fibrates, and ezetimibe), respectively.

The diagnosis of metabolic syndrome was made using the definition of the Japan Society for the Study of Obesity.[23] Metabolic syndrome was diagnosed when waist circumference (male ≥ 85 cm, female ≥ 90 cm) plus 2 of the following criteria were met: high blood pressure (≥ 130/85 mm Hg), reduced HDL-C (< 40 mg/dL) and/or raised triglycerides (≥ 150 mg/dL), and raised fasting hyperglycemia (≥ 110 mg/dL).[23] Cerebral infarction was diagnosed by the presence of neurologic symptoms and signs corresponding to brain imaging. We counted a past history of coronary intervention as coronary heart disease. The definition of smokers was patients who smoked until 1 month before admission.

Data Collection

Patients' demographic data and medical history were obtained from their medical records. Body mass index (BMI) was calculated by their height and weight. Waist circumference was measured at a level midway between the lowest rib and the iliac crest. Hospital staff measured blood pressure on the right arm of a patient before breakfast. Blood samples were obtained from patients after 12-hour starvation. We collected these data from patients within a week of admission.

Total cholesterol and triglycerides were assayed by enzymatic method, and HDL-C was assayed by direct method. LDL-C was calculated using the Friedewald formula from total cholesterol, triglycerides, and HDL-C (total cholesterol – triglycerides ÷ 5 – HDL-C). HbA_{1c} was measured by the high-performance liquid chromatography method, and plasma glucose was measured by the enzymatic method.

To find the difference in glucose and lipid metabolism and risk factors of atherosclerosis between psychiatric patients and the healthy Japanese standard population, we used The National Health and Nutrition Survey in Japan 2011 produced by the Japanese Ministry of Health, Labor, and Welfare as the control group.[26] This survey was performed in 7,047 people (3,230 were male, 3,817 were female) chosen at random from all districts of Japan in November 2011. The age range of the target population was from 1 to over 70 years old.

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Table 1. Profile of Study Patients

Variable	Total	Men	Women
Patients, n	152	61	91
Age, mean ± SD, y	54.3 ± 13.9	50.0 ± 13.5	57.1 ± 13.5
Diagnosis of mental disorders, n (%)			
Schizophrenia, brief psychiatric disorders, and schizoaffective disorders	105 (69.1)	43 (70.5)	62 (68.1)
Mood disorders	28 (18.4)	9(14.8)	19 (20.9)
Other	19 (12.5)	9 (14.8)	10 (11.0)
Diagnosis of physical disorders, n (%)			
Hypertension	50 (32.9)	24 (39.3)	26 (28.6)
Diabetes mellitus	28 (18.4)	12(19.7)	16 (17.6)
Dyslipidemia[a]	81 (55.1)	31 (53.4)	50 (56.2)
High LDL cholesterolemia	32 (21.8)	12 (20.7)	20 (22.5)
Low HDL cholesterolemia	36 (24.5)	21 (36.2)	15 (16.9)
Hypertriglyceridemia	30 (20.4)	13 (22.4)	17 (19.1)
Metabolic syndrome[b]	20 (15.9)	11 (22.0)	9 (11.8)
Smokers, n (%)[c]	47 (33.3)	27 (48.2)	20 (23.5)
Cerebral infarction, n (%)	11 (7.2)	3(4.9)	8(8.8)
Past history of coronary heart disease, n (%)	3 (2.0)	1 (1.6)	2 (2.2)

[a]Total: N = 147, men: n = 58, and women: n = 89.
[b]Total: N = 126, men: n = 50, and women: n = 76.
[c]Total: N = 141, men: n = 56, and women: n = 85.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Table 2. Physical Disorders of Study Participants[a]

	Study Group		95% CI		Sex- and Age-Adjusted Ratio of
Variable	n	Ratio[a]	Lower	Upper	Standard Group
Hypertension					
Men	61	0.393 (24/61)	0.271	0.527	0.424
Women	91	0.286 (26/91)	0.196	0.390	0.417*
Diabetes mellitus					
Men	61	0.197 (12/61)	0.103	0.328	0.099*
Women	91	0.176 (16/91)	0.104	0.270	0.073*
High LDL cholesterolemia					
Men	58	0.207 (12/58)	0.116	0.326	0.318
Women	89	0.225 (20/89)	0.147	0.321	0.230
Low HDL cholesterolemia					
Men	58	0.362 (21/58)	0.240	0.499	0.141*
Women	89	0.169 (15/89)	0.098	0.263	0.032*
Hypertriglyceridemia					
Men	58	0.224 (13/58)	0.125	0.353	0.442*
Women	89	0.191 (17/89)	0.115	0.288	0.264
Metabolic syndrome					
Men	50	0.220 (11/50)	0.115	0.360	0.208
Women	76	0.118 (9/76)	0.056	0.213	0.099
Smoking					
Men	56	0.482 (27/56)	0.355	0.615	0.377
Women	85	0.235 (20/85)	0.154	0.335	0.102*

[a]Parentheses indicate the real numbers of physical disorders/cases.
*Indicates significant difference ($P < .05$) between the study and standard groups.
Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Imaging

The MRI examinations were performed in 5-mm thickness with 2-mm slice gap using a 1.5 Tesla MRI system (Siemens Magnetom Symphony, Siemens Medical Solutions USA Inc, Malvern, Pennsylvania). Ninety-eight patients underwent T1- and T2-weighted MRI and fluid-attenuated inversion recovery (FLAIR) of the brain as described previously.[24] The FLAIR images were used to distinguish infarcts from dilated perivascular spaces. We diagnosed SBI as follows: (1) spotty area ≥ 3 mm in diameter showing high density in T2 and FLAIR images and low density in T1 image, (2) lack of neurologic signs explained by MRI lesions, and (3) no medical history of clinical symptoms of stroke.

The control group for SBI included 790 elderly volunteers (330 women and 460 men; mean age = 61.0 years; range, 40–88 years).[25] All of the volunteers were living independently at home with no apparent history of stroke or dementia.

Statistics

Means or ratios in the control group were calculated by adjusting sex and age configuration to the patient group. Next, we estimated means or ratios with 95% CIs of the patient group. Then, we compared the patient group with the control group. All analyses were conducted using statistical software SAS, version 9.3 (SAS Institute, Inc, Cary, North Carolina).

RESULTS

Demographic Data

Table 1 shows the profile of study patients. We calculated the rate of hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome as complicated lifestyle-related diseases. The ratio of hypertension was significantly low in women compared with the Japanese standard (Table 2). Sex and age–adjusted diabetic ratio of the standard group was 0.099 and 0.073 in men and women, respectively. The 95% CI of diabetic ratio in the study group was 0.103–0.328 in men and 0.104–0.270 in women, indicating that prevalence of diabetes mellitus was significantly higher than the Japanese standard in both sexes (Table 2).

It is difficult to say whether the ratio of dyslipidemia is high or not because the definition of dyslipidemia is low HDL cholesterolemia (HDL-C < 40 mg/dL) or administration of antidyslipidemic agents in the National Health and Nutrition Survey in Japan 2011. However, the prevalence of low HDL-C was significantly higher in the study group than in the Japanese standard in both sexes as shown in Table 2. The ratio of high LDL-C was not significantly different between the study group and the Japanese standard population in both sexes, but the ratio of hypertriglyceridemia was significantly lower in men in the study group. The prevalence of metabolic syndrome in the study group was almost the same as the Japanese standard in both sexes as defined by the Japan Society for the Study of Obesity[23] (Table 2).

Sex and age-adjusted prevalence of smoking in the standard group was 0.377 and 0.102 in men and women, respectively. The 95% CI of prevalence of smoking in the study group was 0.355–0.615 in men and 0.154–0.335 in women, indicating that prevalence of smoking was significantly higher in the study group than in the Japanese standard in women (Table 2).

Table 3. Psychiatric Medications Administrated to Patients[a]

Drug	Patients
Atypical antipsychotics	108 (71.1)
Risperidone	38 (25.0)
Olanzapine	36 (23.7)
Quetiapine	15 (9.9)
Clozapine	8 (5.3)
Aripirazole	4 (2.6)
Paliperidone	3 (2.0)
Perospirone	2 (1.3)
Blonanserine	2 (1.3)
Typical antipsychotics	29 (19.1)
Haloperidol	15 (9.9)
Zotepine	6 (3.9)
Pipamperone	3 (2.0)
Perphenazine	2 (1.3)
Timiperone	2 (1.3)
Bromperidol	1 (0.7)
Other	13 (8.6)
Mirtazapine	5 (3.3)
Lithium carbonate	2 (1.3)
Yokukansan	2 (1.3)
Valproate	1 (0.7)
Amoxapine	1 (0.7)
Lamotrigine	1 (0.7)
Sulpiride	1 (0.7)
None	2 (1.3)

[a]All values are presented as n (%).

Table 4. Physical and Metabolic Characteristics of Study Participants

Physical and Metabolic Characteristics	Study Group n	Study Group Mean	95% CI Lower	95% CI Upper	Sex- and Age-Adjusted Mean of Standard Group
Height (cm)					
Men	55	169.1	167.3	170.9	168.9
Women	81	154.7	153.5	155.7	154.2
Body weight (kg)					
Men	54	69.9	65.1	74.8	68.3
Women	82	56.8	54.2	59.4	53.8*
Body mass index (kg/m^2)					
Men	54	24.3	22.9	25.7	23.9
Women	81	23.8	22.7	24.9	22.6*
Waist circumference (cm)					
Men	50	88.1	84.0	92.2	86.1
Women	76	83.0	80.0	86.0	81.4
Systolic blood pressure (mm Hg)					
Men	58	125.5	121.5	129.5	130.8*
Women	90	125.3	121.8	128.7	128.8*
Diastolic blood pressure (mm Hg)					
Men	58	79.3	76.3	82.3	82.4*
Female	90	75.6	73.2	78.1	77.8
LDL-C (mg/dL)					
Men	58	111.7	103.9	119.5	116.3
Women	89	117.8	109.8	125.7	120.2
Total cholesterol (mg/dL)					
Men	61	183.1	172.1	194.1	203.4*
Women	90	195.9	187.0	204.9	209.1*
HDL-C (mg/dL)					
Men	58	47.1	43.0	51.3	55.1*
Women	89	55.1	51.3	58.9	64.2*
Triglycerides (mg/dL)					
Men	61	119.5	96.9	142.1	171.0*
Women	90	116.1	100.6	131.6	124.8
Fasting plasma glucose (mg/dL)	151	120.9	112.7	129.0	100.5*
HbA_{1c} (%)	152	5.89	5.73	6.05	5.66*

*Indicates significant difference ($P < .05$) between the study and standard groups.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Antipsychotics Mainly Administered to Patients and Other Drugs Used

In the study group, 71.1% of patients took atypical antipsychotics, mainly risperidone, olanzapine, quetiapine, and clozapine; 19.1% took typical antipsychotics and 8.6% took other psychiatric medications (antidepressants and mood stabilizers) (Table 3). Therefore, over 90% of patients were treated with antipsychotics.

Twenty-four patients were treated with antihypertensive drugs. Eighteen patients were treated with Ca antagonists, 12 with angiotensin receptor blockers, 3 with β-blockers, and 1 with diuretics. Hypoglycemic drugs were administrated to 16 diabetic patients. Insulins were administered to 2 patients, DDP-4 inhibitors to 10 patients, thiazolidines to 5 patients, biguanides to 4 patients, and sulfonylureas and α-glucosidase inhibitors to 2 patients each. Eighteen patients took antidyslipidemic drugs, 15 took statins, 5 took ezetimibe, and 2 took fibrates. These drugs were used for more than 3 months.

Physical Characteristics of Study Patients

Table 4 shows physical characteristics of study patients. Body weight and BMI were significantly higher in female study group patients compared with the controls ($P < .05$). Waist circumference was not significantly different between the study group and the control group. Blood pressure was significantly lower ($P < .05$) in the study group except for diastolic blood pressure in women, suggesting that blood pressure was well controlled in the Kohnodai Hospital. Increased BMI often accompanies abnormal metabolism of lipid and glucose.

Variations in Blood Levels of Lipid and Glucose

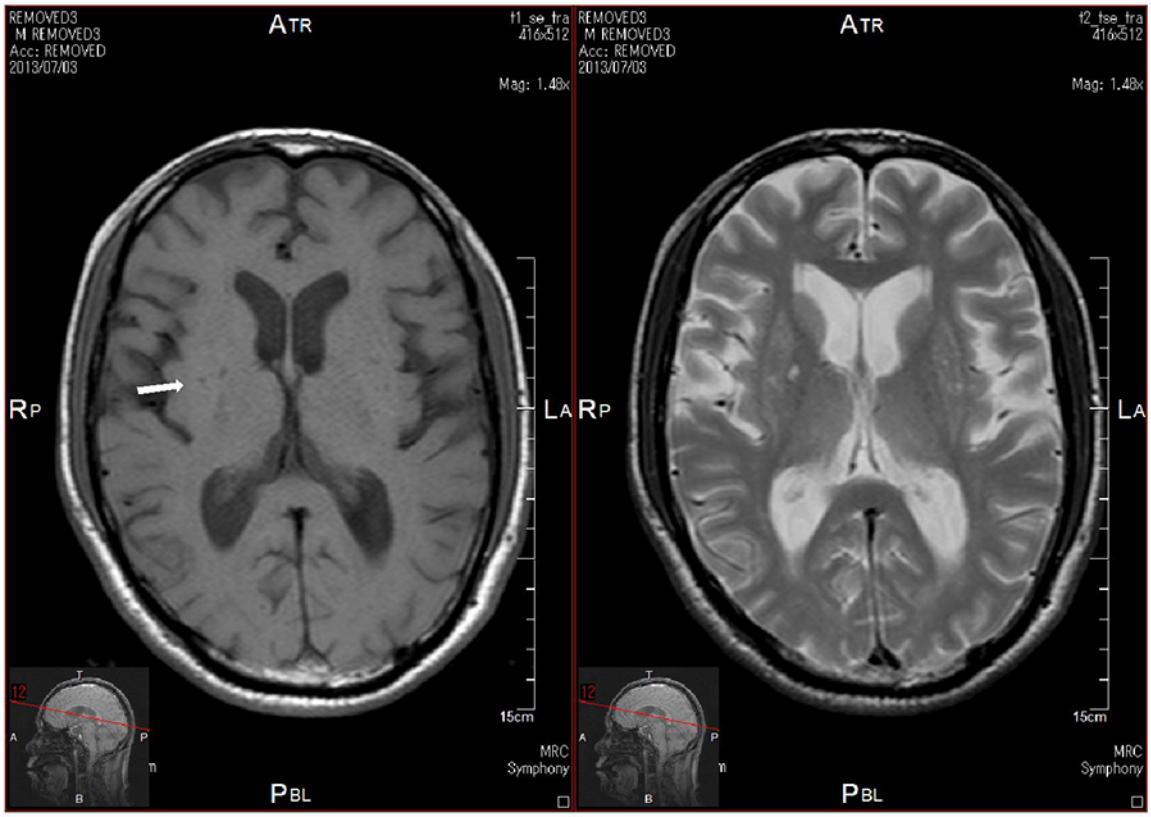
Table 4 shows serum blood levels of lipid and glucose. Patients had significantly lower serum levels of total cholesterol and HDL-C compared with the controls, in accordance with a high ratio of low HDL cholesterolemia. Serum LDL-C levels were not significantly different between patients and controls. Male patients had significantly lower triglycerides than the male controls, but female patients did not. Fasting plasma glucose and HbA_{1c} were significantly higher in patients than controls. This finding is in accordance with a high ratio of diabetes. Diabetes and low HDL cholesterolemia are well known to enhance atherosclerosis.

Increased Silent Brain Infarction in Psychiatric Patients

Figure 1 shows typical SBI in a 54-year-old schizophrenic female patient with no neurologic symptoms and signs. We can detect several low-density areas in the T1 image and corresponding high-density areas in the T2 image of the right lateral lobe.

Eleven patients were diagnosed with cerebral infarction by the presence of neurologic symptoms and signs corresponding to brain imaging. Ninety-eight of 152 patients agreed to undergo brain MRI (Table 5). Age-adjusted ratios of SBI plus cerebral infarction and SBI in

Figure 1. Brain Magnetic Resonance Imaging of a 54-Year-Old Female Schizophrenic Patient With No Neurologic Symptoms and Signs[a]



[a]Several low-density areas are detected in the right lateral lobe in the T1 image (left panel of this figure), corresponding to high-density areas in the T2 image (right panel). An arrow shows one of the low-density areas in the T1 image.

Table 5. Brain Magnetic Resonance Imaging (MRI) of Study Participants

	Study Group		95% CI		Age-Adjusted Ratio	
Brain MRI	n	Ratio	Lower	Upper	of Control Group	Significance
Ratio of cerebral infarction and SBI	98	0.439 (43/98)	0.347	0.539	0.236	*
Ratio of SBI	98	0.327 (32/98)	0.236	0.429	0.235	*

[a]Parentheses indicate the real numbers of cerebral infarctions plus SBI or SBI/cases with brain MRI.
*Indicates significant difference ($P < .05$) between the study and control groups.
Abbreviation: SBI = silent brain infarction.

the healthy control group were 0.236 and 0.235, respectively. The SBI ratio of the Japanese healthy controls is 0.076 in 40–49 years, 0.116 in 50–59 years, 0.313 in 60–69 years, and 0.542 in > 70 years as described by Yoshida et al.[25] The 95% CIs of SBI plus cerebral infarction and SBI in the study group were 0.347–0.539 and 0.236–0.429, respectively, indicating that these ratios were significantly higher in psychiatric patients.

DISCUSSION

The present study shows that psychiatric inpatients have increased SBI accompanied with high prevalence of diabetes and low HDL cholesterolemia. However, dyslipidemia, especially LDL-C and triglycerides, is different in each study. Tschoner et al[27] and Murashita et al[28] describe high serum levels of LDL-C and triglycerides in psychiatric patients. There are reports of low serum LDL-C and triglycerides in schizophrenic patients.[29] These differences in LDL-C and triglyceride levels may be dependent on the situations of patients. Patients took different antipsychotics and had varied lifestyles, factors which were difficult to control in outpatients. Patients had no significant difference in LDL-C in both sexes in this study. Male patients showed significant low serum triglyceride levels, but female patients had no significant difference in serum triglycerides compared with controls. The level of serum triglycerides is greatly influenced by diet and alcohol.[30] Triglyceride metabolisms may have changed in psychiatric patients with hospital admission through proper diet and exercise during their stay. Furthermore, the serum triglyceride level of the male Japanese standard was 171.0 mg/dL, higher than that of women (124.8 mg/dL). These findings are due to the decrease of serum triglyceride level in male patients.

There are many surveys on the causes of low HDL cholesterolemia.[17,28] Lifestyle-related conditions such as diabetes, obesity, shortage of exercise, and smoking are causes of low HDL-C.[31] Liver cirrhosis, malnutrition, and administration of probucol (antidyslipidemic agent) are also known to induce low HDL cholesterolemia,[32] but this is not the case in our study because few patients had liver cirrhosis (1 patient) and malnutrition (1 patient had chronic obstructive pulmonary disease and colon carcinoma), and probucol was not used (data not shown). Serum HDL-C in patients with diabetes (total of 28 patients, 12 male and 16 female) is 50.1 mg/dL. Sex-adjusted HDL-C is 51.9 mg/dL in nondiabetic patients, indicating that approximately 2 mg/dL of serum HDL-C is decreased by diabetes. Obesity may not be the cause of low HDL cholesterolemia in male patients because BMI in male patients was not significantly different from the Japanese standard in our study. It is reported that smoking decreases serum HDL-C by 3.5 mg/dL and walking 6,000 steps/d increases HDL-C by 3 mg/dL.[33,34] According to The National Health and Nutrition Survey in Japan 2011, 20.1% of the general Japanese population are smokers compared to 33.3% of patients in this study. Also, male patients were 8.0 mg/dL lower in HDL-C than the Japanese controls, and female patients were 9.1 mg/dL lower in our study. These findings suggest that it is difficult to explain low HDL cholesterolemia in psychiatric patients by lifestyle-related conditions only. Serum total cholesterol was lower in psychiatric patients compared with the Japanese controls. Serum total cholesterol level is calculated by LDL-C, HDL-C, and triglycerides. Psychiatric patients had low serum HDL-C in both sexes, almost the same levels of LDL-C, and low serum triglycerides in men, indicating that serum total cholesterol was low in psychiatric patients.

It is reported that antipsychotic users have an increased risk of cardiac mortality and all-cause mortality.[35,36] In general, atypical antipsychotics have less neurologic side effects (extrapyramidal symptoms) but greater metabolic effects compared with typical antipsychotics.[37] Several clinical studies showed that atypical antipsychotics, especially olanzapine and clozapine, had increased risks of diabetes and dyslipidemia, which are dependent on insulin resistance accompanied with weight gain or increase of visceral fat.[4,17] However, there are some cases that have shown increased blood glucose and dyslipidemia without weight gain. Houseknecht et al[38] reported that atypical antipsychotics directly induced whole-body insulin resistance in animal models, in accordance with diabetes and dyslipidemia without weight gain. Over 70% of patients used atypical antipsychotics in our study (Table 3). It is probable that atypical antipsychotics play an important role in the high rate of diabetes and dyslipidemia.

Coronary heart disease is the main cause of death in psychiatric patients in the United States and Western Europe.[1,2] However, only 3 patients had a past history of coronary heart disease in our study. Smith et al[3] reported that cardiovascular diseases are likely to be underrecognized and undertreated in people with schizophrenia. It is possible that symptoms related with coronary heart disease were masked in psychiatric patients in our study. Enhanced ratio of SBI is an important finding for future care of psychiatric patients because SBI increases the risk of subsequent cerebral infarction, dementia, and cognition decline.[21,22] Cerebral infarction is known to be related with hypertension, diabetes, low HDL-C, and smoking.[39–42] However, there is no clear evidence on the relation between SBI and low HDL-C.[43] Indeed, this study does not show a significant difference of HDL-C between patients with and without SBI (52.4 mg/dL in HDL-C with SBI and 47.4 mg/dL in HDL-C without SBI). Most SBIs were lacunar infarction, which is closely related with hypertension but very little with cholesterol metabolism.[43,44] In this study, systolic blood pressure was significantly low in patients with schizophrenia compared with the control group. The relationship between low HDL-C, diabetes, smoking, and SBI remains to be elucidated.

This current study also has some limitations. First, it was a cross-sectional study. It is necessary to perform a prospective study to clarify the cause-effect relationship between serum HDL-C, diabetes, smoking, and SBI in brain imaging. Second, patients in this study were inpatients. It is possible that lipid profiles in hospitalized patients, especially LDL-C and triglycerides, are different from profiles in outpatients. Third, the number of patients is too small to classify our results under each psychotic disorder, such as schizophrenia, bipolar disorders, depressive disorders, and anxiety disorders. Fourth, it is difficult to explain the mechanism of increased SBI in the study group, because it contains several kinds of psychotic disorders that have various backgrounds with mental and physical treatments. Finally, we need to check other atherosclerotic markers in psychotic patients for prevention of atherosclerosis.

In conclusion, psychiatric patients in this study had increased ratio of SBI and SBI plus cerebral infarction compared with the Japanese controls. Patients also showed high ratios of diabetes and low HDL cholesterolemia, mainly by the use of antipsychotics.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), ezetimibe (Zetia, Vytorin, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paliperidone (Invega), quetiapine (Seroquel), risperidone (Risperdal and others).

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