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**Screening for diabetes using Japanese monitoring guidance in schizophrenia patients treated with second-generation antipsychotics: A cross-sectional study using baseline data**

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**Field:** psychopharmacology and neuropsychopharmacology

**Running title:** Screening for diabetes in schizophrenia

**Abstract**

**Aim:** The Japanese Blood Glucose Monitoring Guidance for patients receiving second-generation antipsychotics has been newly developed. We aimed to report a cross-sectional study using a baseline data of the Japanese monitoring guidance to find undiagnosed hyperglycemia systematically as a routine clinical practice and to quantify the frequency of glucose abnormalities in schizophrenia patients treated with second-generation antipsychotics.

**Method:** Data for 537 patients with schizophrenia who had not been diagnosed as diabetes prior to baseline screening and started the monitoring between June 2008 and January 2009, were collected from medical records in 25 hospitals. Blood glucose (fasting or casual), hemoglobin<sub>A1c</sub>, serum lipids, height/weight, clinical diabetic symptoms, and family history of diabetes were assessed. Patients were classified into normal, pre-diabetic or probable diabetic type based on their values of blood glucose or hemoglobin<sub>A1c</sub>, and various background characteristics and serum lipid values were compared among the three types.

**Results:** Out of 537 patients, 13 (2.4%) met criteria for probable diabetic type, 51 (9.5%) for pre-diabetic type, and 473 (88.1%) for normal type. Individuals categorized as probable diabetic type had a higher body mass index and higher frequency of family history of diabetes mellitus than those within normal type.

**Conclusion:** Glucose abnormalities were newly detected in 11.9% of schizophrenia patients treated with second-generation antipsychotics by the baseline monitoring. To assess the detective power and usefulness of the guidance, longitudinal investigations are necessary.

**Key words:** Diabetes mellitus; Glucose monitoring guidance; Metabolic abnormality; Schizophrenia; Second-generation antipsychotic

## Introduction

Second-generation antipsychotics (SGAs) have provided a clear benefit for many patients with schizophrenia in part due to their reduced propensity to cause extrapyramidal side effects often associated with first-generation antipsychotics (FGAs).<sup>1</sup> However, SGAs can induce substantial weight gain in vulnerable individuals,<sup>1,2</sup> and these agents have been associated with an increased risk for dyslipidemia and type 2 diabetes mellitus.<sup>3</sup> The development of diabetes mellitus within an individual schizophrenia patient can depend on the contribution of drug effects as well as the contribution of individual host factors such as family history, the disease itself, sedentary lifestyle and unhealthy dietary habits.<sup>3</sup> A meta-analysis comparing diabetes risk for different antipsychotics in people with schizophrenia indicated that SGAs are associated with increased risk for diabetes compared with FGAs.<sup>4</sup> The potential relationship between some SGAs and both obesity and diabetes is of considerable clinical concern because obesity and diabetes are important risk factors for cardiovascular disease (CVD), and the relative risk of CVD mortality is significantly greater in people with psychiatric disorders than in the general population.<sup>5</sup> Accordingly, the U.S. Food & Drug Administration (FDA) proposed the inclusion of following statement in the package insert of all atypical antipsychotic drugs: "Patients starting on these drugs who have diabetes risk factors, such as obesity or a family history of diabetes, should have fasting blood glucose testing at the start of treatment and periodically thereafter."<sup>6</sup> In Japan, olanzapine and quetiapine became contraindicated in patients with diabetes mellitus or past history of diabetes mellitus after the emergency safety information (dear doctor letter) was issued in 2002,<sup>7,8</sup> and it is instructed that other SGAs should be used with caution in diabetic patients as well as in those with diabetic risk factors.<sup>9</sup>

Therefore, patients treated with SGAs should receive appropriate baseline screening and ongoing monitoring to avoid cardiovascular risk factors including obesity and diabetes and to extend the longevity. There have been several international reviews and guidelines published to prevent metabolic adverse reactions to SGAs. In Japan, four experts on psychopharmacology and diabetes mellitus recently proposed a monitoring guidance for blood glucose in patients treated with SGAs based on the review of consensus guidelines<sup>5,10,11</sup> and articles,<sup>12-18</sup> the characteristics of Japanese patients, and

the healthcare environment in Japan.<sup>19</sup>

In this study, we conducted a cross-sectional study using a baseline data of the Japanese blood glucose monitoring guidance in order to find undiagnosed hyperglycemia systematically as a routine clinical practice in schizophrenia patients treated with SGAs and clarify the metabolic profiles of those patients.

## Methods

This cross-sectional study was achieved using the baseline data for patients who began to receive the Japanese monitoring guidance for blood glucose during June 2008 and January 2009. Subjects were primarily diagnosed with schizophrenia based on ICD-10 criteria, treated with at least one of the following SGAs at entry as clozapine (under clinical trial for approval), risperidone, perospirone, olanzapine, quetiapine, aripiprazole and blonanserin. Participants included both in- and outpatients who started to receive a new SGA or were receiving some SGAs at baseline monitoring. Individuals were excluded, who had been diagnosed with diabetes mellitus by internists or received diabetes treatments prior to baseline screening, and who had seclusion or physical restraint episodes during baseline monitoring. Selection of participants was conveniently, not consecutively achieved on each site. Data were collected from medical records that the collaborating investigators gained in usual clinical settings as far as possible. The study was conducted in the Department of Psychiatry, Hokkaido University Hospital, and at 24 associated hospitals (9 public general hospitals and 15 private psychiatric hospitals) in the Hokkaido district. The study was approved by the institutional review board of Hokkaido University Hospital.

Baseline measurements consisted of blood glucose (fasting or casual) or hemoglobin<sub>A1c</sub> (Hb<sub>A1c</sub>), serum lipids (total and HDL cholesterol, triglycerides), height/weight for body mass index (BMI), clinical diabetic symptoms, and past history/family history of diabetes. According to the Japanese monitoring guidance, patients were classified into normal type, pre-diabetic type or probable diabetic type (Fig. 1). If having two or three blood glucose measurements (e.g. fasting blood glucose and Hb<sub>A1c</sub>) at one visit, the patient was categorized as the type based on the worst one. We compared various background characteristics and serum lipid values among the three types based on blood glucose measurement. [Insert Figure 1 about here]

Values are expressed as means  $\pm$  standard deviation (SD). In this study, Hb<sub>A1c</sub> is expressed as National Glycohemoglobin Standardization Program (NGSP) value instead of Japan Diabetes Society (JDS) value. The relationship of both values is as follows; NGSP value = JDS value + 0.4.<sup>20</sup> Analysis of variance was used to compare the three classified types for the following variables: age, total or HDL-cholesterol, number of clinical signs for diabetes, and number of antipsychotics. Wilcoxon/Kruskal-Wallis' test was utilized for BMI and triglycerides. All post-hoc comparisons were Bonferroni corrected. Categorical demographic variables were compared among groups using Chi square test, and included sex and family history of diabetes. Significance was defined as  $P < 0.05/2 = 0.025$ .

## Results

Fig. 2 illustrates the process of subject selection. A total of 555 schizophrenia patients treated with SGAs were selected, who began to receive the Japanese blood glucose monitoring guidance during the study period. Eighteen patients were excluded because of being diagnosed as diabetes or receiving diabetes treatment. In total, 537 patients (249 male and 288 female) including 291 inpatients and 246 outpatients remained for analysis. The mean age of patients was 48.3 ( $\pm 16.0$ ) years, and they had been ill for a mean of 22.1 ( $\pm 15.0$ ) years. The frequency of patients with a family history of diabetes was 11.5%. Patients received a mean of 1.7 ( $\pm 0.9$ ) antipsychotics including FGAs. Number of patients receiving each SGA at baseline, including polypharmacy, is shown in Table 1. Coadministration of additional antipsychotics is not excluded. [Insert Figure 2 and Table 1 about here]

Only half of the patients had a normal BMI (51.0%), and 33.6% of the patients were overweight (BMI > 25). The mean BMI was 23.3 ( $\pm 4.4$ ). Lipid abnormalities were also prevalent: 19.0% of patients had elevated total cholesterol (>220 mg/dL), 22.0% had elevated triglycerides (>150 mg/dL), 17.8% had low HDL cholesterol (<40 mg/dL). Clinical diabetic symptoms such as dry mouth, polyposia, massive consumption of soft drinks, polyuria, and pollakiuria were present in 16.6% of patients.

In the total sample, 473 (88.1%) were classified into normal type, 51 (9.5%) into pre-diabetic type, and 13 (2.4%) into probable diabetic type (Fig. 2). Glucose abnormality (pre-diabetic and probable diabetic type) was newly detected in 64 patients

(11.9%). Demographic and clinical characteristics in the three classified types are shown in Table 2. Both BMI and the frequency of family history of diabetes were significantly higher in probable diabetic type than in normal type [ $\chi^2=8.64$ ,  $df=2$ ,  $P=0.013$  for BMI;  $\chi^2=12.7$ ,  $df=4$ ,  $P=0.013$  for the frequency of family history for diabetes]. Age was also significantly higher in pre-diabetic type than in normal type, but there was no significant difference between probable diabetic type and normal type [ $F(2,534)=6.09$ ,  $P=0.0024$ ]. Triglycerides were numerically higher in probable diabetic and pre-diabetic type than in normal type, but this was not statistically significant [ $\chi^2=5.49$ ,  $df=2$ ,  $P=0.064$ ]. There were no significant differences in total or HDL cholesterol, or the numbers of clinical diabetic symptoms or antipsychotics among the three types [ $F(2,524)=0.80$ ,  $P=0.92$  for total cholesterol;  $F(2,464)=0.70$ ,  $P=0.50$  for HDL cholesterol;  $F(2,527)=0.46$ ,  $P=0.63$  for the number of clinical diabetic symptoms;  $F(2,533)=1.35$ ,  $P=0.26$  for the number of antipsychotics]. [Insert Table 2 about here]

## Discussion

A cross-sectional study using a baseline data of the Japanese blood glucose monitoring guidance for 537 patients at multi-local sites showed that the probable diabetic type was present at 2.4% ( $N=13$ ) and the pre-diabetic type at 9.5% ( $N=51$ ) in schizophrenia patients receiving SGAs. One must take into account that all patients in this study had never been diagnosed with diabetes prior to baseline screening, so cases classified as probable diabetic type are newly detected. Strictly speaking, it is unclear whether patients classified as probable diabetic type actually have diabetes mellitus, but if these patients are assumed to have the disease, 2.4% met criteria for diabetes. This result is much lower than the data from another Japanese cross-sectional study of Okumura et al.<sup>21</sup> suggesting that the overall prevalence of diabetes was 8.6% in schizophrenia patients treated with SGAs (72%) and FGAs (28%). In their study, however, definition of diabetes was not based on clinical measurements such as plasma glucose and  $Hb_{A1c}$ , but on doctor diagnosis of diabetes. On the other hand, using an oral glucose tolerance test, van Winkel et al.<sup>22</sup> showed a mean annual incidence of diabetes of 3.15% in schizophrenia patients treated with antipsychotics (90% SGAs and 10% FGAs) although the test is probably not a realistic method for screening patients with schizophrenia in mental health care settings.

In the comparison of background characteristics such as age, family history of diabetes mellitus and BMI among the three types, the BMI values for the probable diabetic type were significantly higher than those for the normal type. Several studies on general populations indicate that obesity is a critical risk factor for glucose abnormality,<sup>3</sup> thus it is also important to monitor and manage obesity in patients treated with SGAs. The percentage of patients with a family history of diabetes mellitus was also significantly higher for the probable diabetic type than the normal type. Regarding serum lipid values among patients within the three classified types, there were no differences in total or HDL cholesterol. Although no statistically significance was found, serum triglyceride levels were numerically higher in pre-diabetic and probable diabetic types than in normal type. It has been suggested that elevated triglyceride levels appear to precipitate or exacerbate diabetes.<sup>23</sup> Our present findings suggest the same possibility as in general populations that increased triglyceride levels may be a warning for developing diabetes as well as other risk factors such as higher age, increased body weight, and family history of diabetes. Since lipid dysregulation during treatment of schizophrenia is not a class effect of all atypical antipsychotic drugs,<sup>24</sup> psychiatrists should appropriately integrate plans for regularly monitoring both lipid and glucose levels to avoid the morbidity and mortality associated with CVD. Recently, Sugawara et al.<sup>25</sup> reported that patients with schizophrenia or schizoaffective disorder in Japan had high prevalence of metabolic syndrome compared to the general population. Therefore, metabolic syndrome in schizophrenia patients should be carefully monitored to minimize the risks. On the other hand, number of clinical signs for diabetes did not differ among the three types, which suggests that subjective signs and symptoms for diabetes are frequently challenging to disentangle from adverse effects of antipsychotic medication.

This is the first cross-sectional study using a baseline data of the Japanese monitoring guidance for blood glucose in patients treated with SGAs. Clearly, schizophrenia patients treated with SGAs should be considered at very high risk of developing diabetes, therefore the use of a monitoring guidance for blood glucose should be encouraged in this high-risk population. Moreover, this kind of screening instrument should be routine clinical practice in all psychiatric settings. A retrospective cohort study using data from a large managed care database in U.S.A.<sup>26</sup> suggests that baseline

glucose monitoring in patients treated with SGAs remains low (21.8%) even after the American Diabetic Association guidelines<sup>5</sup> were issued. Twelve-week glucose testing was lower (17.9%) than baseline testing. Thus, further investigations are necessary to achieve the monitoring guidelines such as 6-month and 12-month follow-up after baseline measurement as outlined in the Japanese monitoring guidance for blood glucose. Upon one-year follow-up, it will be noteworthy to detect how many patients progress from normal type to pre-diabetic type or from pre-diabetic type to probable diabetic type.

This study has some limitations. First, the data were collected from medical records that the collaborating investigators obtained in routine clinical settings, which might impact the results. There were many missing data in this study, which should result in lower detection rate of diabetes in the schizophrenia patients treated with SGAs. Second, the data were not consecutively collected at multiple sites located in the Hokkaido district, thus we did not correctly determine the prevalence of diabetes in schizophrenia patients receiving SGAs in Japan. Third, originally baseline data of the Japanese monitoring guidance for blood glucose should be obtained when some SGA is newly started, but in this study all data were not necessarily so. Moreover, the duration of treatment with SGAs until blood examination and the dose of antipsychotics were not checked. Fourth, how many of patients refused to be monitored using this guidance was not known. Fifth, it is possible that other psychotropics such as valproate or antidepressants may affect the results. In this study, co-administrated drugs but antipsychotics were not checked. Sixth, this study failed to compare with the results in schizophrenia patients treated with FGAs. A meta-analysis of Leucht et al.<sup>1</sup> indicated that weight gains induced by SGAs and low-potency FGAs were not significantly different in schizophrenia patients. Thus, it should be necessary to use a monitoring guidance for blood glucose in schizophrenia patients treated with not only SGAs but also FGAs. Last, lack of other cardiovascular risk factors such as hypertension and smoking may be another limitation in order to avoid cardiovascular or cerebrovascular diseases and to extend the longevity in schizophrenia patients. Given these possible source of bias, the results need to be interpreted with caution.

In conclusion, the cross-sectional study using a baseline data of the Japanese monitoring guidance suggests that glucose abnormalities were newly detected in 11.9%

of schizophrenia patients treated with SGAs by the baseline monitoring. To assess the detective power and usefulness of the guidance, longitudinal investigations are necessary.

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### Figure legend

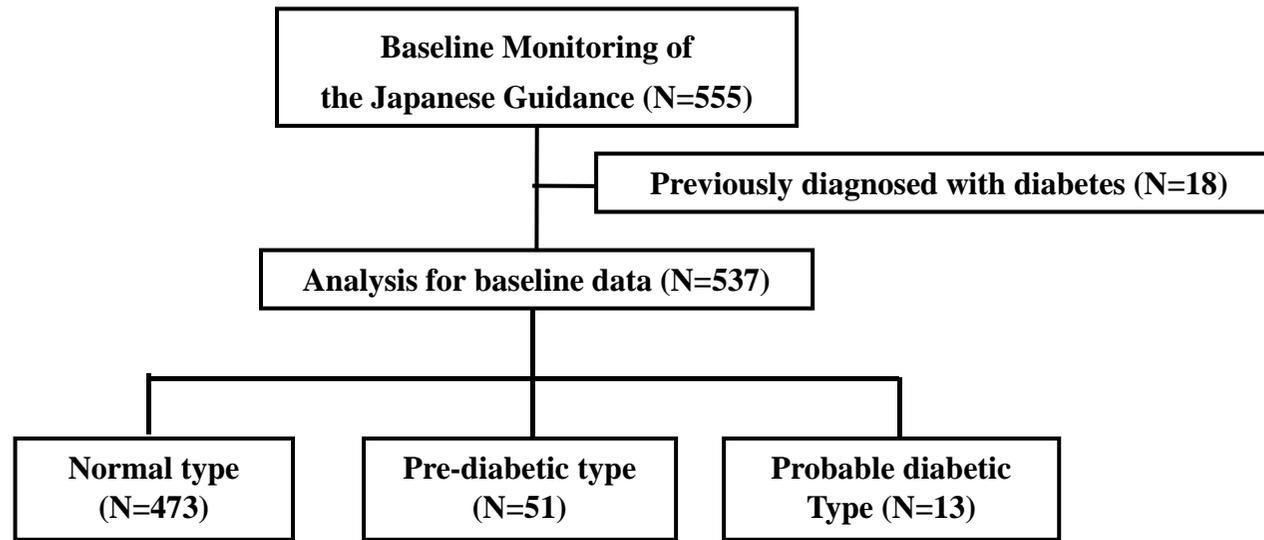
**Fig.1.** Flow Chart of Blood Glucose Monitoring Guidance based on the reference value  $Hb_{A1c}$  is expressed as National Glycohemoglobin Standardization Program (NGSP) value.

**Fig.2.** Flow diagram of patient selection and classification

**Fig.1**

	Normal type	Pre-diabetic type	Probable diabetic type
fasting blood glucose or casual blood glucose or HbA1C	less than 110mg/dl less than 140mg/dl less than 6.0%	110~125mg/dl 140~179mg/dl 6.0~6.4%	over 126mg/dl over 180mg/dl over 6.5%
	Method 1	Method 2	Method 3
	Perform the test at the interval of 3 months for the first half year and at the interval of 6 months subsequently.	Perform the test 1 month and 3 month after the commencement of antipsychotics and at the interval of 3 months subsequently. Serum lipid should be measured at the interval of 6 months.	Perform the test at the interval of 1 month. Serum lipid should be measured at the interval of 3 months.

**Fig. 2**



**Table 1. Antipsychotic Treatment**

Treatment	Number	%
Total		
Risperidone	245	45.6
Olanzapine	178	33.1
Quetiapine	112	20.8
Aripiprazole	75	14.0
Perospirone	57	10.6
Blonanserin	21	3.9
Clozapine	4	0.7
SGA monotherapy	281	52.3
Risperidone	106	
Olanzapine	87	
Quetiapine	25	
Aripiprazole	31	
Perospirone	23	
Blonanserin	5	
Clozapine	4	
combined SGA	97	18.1
SGA + FGA	159	29.6

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SGA: second generation antipsychotics

FGA: first generation antipsychotics

**Table 2. Patient Background Characteristics in the Classified Type**

<b>Variables</b>	<b>Normal type (N=473)</b>	<b>Pre-diabetic type (N=51)</b>	<b>Probable Diabetic type (N=13)</b>
<b>Sex[% male] (N)</b>	<b>45.0 (473)</b>	<b>58.8 (51)</b>	<b>23.1 (13)</b>
<b>Age (years) (N)</b>	<b>47.5 ± 16.1 (473)</b>	<b>55.3 ± 14.1** (51)</b>	<b>52.8 ± 9.8 (13)</b>
difference (95%CI)		7.80 (2.32, 13.28)	5.30 (-5.56, 16.16)
<b>Family history of DM (%)</b>	<b>10.8 (473)</b>	<b>11.8 (51)</b>	<b>38.5* (13)</b>
<b>BMI (N)</b>	<b>23.1 ± 4.1 (466)</b>	<b>23.8 ± 5.7 (50)</b>	<b>26.7 ± 4.9* (13)</b>
difference (95%CI)		0.67 (-0.84, 2.19)	3.55 (0.69, 6.42)
<b>Total-cholesterol (mg/dL) (N)</b>	<b>185.4 ± 40.9 (463)</b>	<b>186.8 ± 41.5 (51)</b>	<b>189.2 ± 41.4 (13)</b>
difference (95%CI)		1.44 (-12.77, 15.65)	3.81 (-23.3, 30.90)
<b>HDL-cholesterol (mg/dL) (N)</b>	<b>53.7 ± 15.7 (415)</b>	<b>54.3 ± 15.4 (43)</b>	<b>47.5 ± 11.6 (9)</b>
difference (95%CI)		0.01 (-5.87, 5.90)	6.22 (-6.15, 18.59)
<b>Triglyceride (mg/dL) (N)</b>	<b>116.6 ± 74.3 (453)</b>	<b>154.9 ± 153.5* (48)</b>	<b>160.3 ± 95.6 (13)</b>
difference (95%CI)		39.92 (9.44, 70.39)	43.66 (-12.81, 100.13)
<b>Number of signs for DM (N)</b>	<b>0.3 ± 0.8 (473)</b>	<b>0.2 ± 0.7 (51)</b>	<b>0.5 ± 0.8 (13)</b>
difference (95%CI)		0.05 (-0.23, 0.31)	0.18 (-0.33, 0.68)
<b>Number of antipsychotics (N)</b>	<b>1.7 ± 0.9 (473)</b>	<b>1.9 ± 1.1 (51)</b>	<b>1.5 ± 0.9 (13)</b>
difference (95%CI)		0.20 (-0.11, 0.52)	0.14 (-0.45, 0.74)

BMI: body mass index; CI: confidence interval; DM: diabetes mellitus

Case number obtained data in parenthesis

\*\* P<0.005, \* P<0.025 vs. Normal