Adiponectin as a Potential Biomarker for the Metabolic Syndrome in Chinese Patients Taking Clozapine for Schizophrenia

Ya Mei Bai, M.D., Ph.D.; Jen-Yeu Chen, M.D.; Wei-Shiung Yang, M.D., Ph.D.; Yu-Chiao Chi, M.S.; Ying-Jay Liou, M.D.; Chao-Cheng Lin, M.D.; Ying-Chieh Wang, M.D.; Chih-Yuan Lin, M.D.; Tung-Pine Su, M.D.; and Pesus Chou, D.P.H.

Objective: As the metabolic syndrome is an important side effect of some antipsychotics, use of a biomarker will enable clinicians to identify metabolic changes more effectively than anthropometry and biochemistry. Adiponectin, an adipocyte-derived hormone, serves as a central regulatory protein in many of the physiologic pathways controlling lipid and carbohydrate metabolism. The aim of this study is to determine the possible relationship between adiponectin and the metabolic syndrome among Chinese patients taking clozapine for schizophrenia.

Method: The study sample consisted of 188 hospitalized Chinese patients with schizophrenia (DSM-IV criteria) who had been receiving clozapine for at least 3 months. Cross-sectional anthropometric measurements, biochemical analysis, and serum adiponectin levels were assessed to determine the prevalence of metabolic syndrome. Retrospective chart reviews were conducted to obtain demographic data, age at which clozapine treatment was initiated, and weight change after the initiation of clozapine treatment. The study was conducted from March to September of 2005.

Results: The prevalence of the metabolic syndrome was 28.4%. Adiponectin levels were negatively associated with weight change after the initiation of clozapine treatment, systolic blood pressure, diastolic blood pressure, body weight, body mass index (BMI), waist circumference, serum triglycerides, and insulin and were positively associated with high-density lipoprotein cholesterol. Multiple logistic regression analysis showed that age (OR = 1.083, p = .009), BMI (OR = 1.423, p < .001), and serum adiponectin (OR = 0.847, p = .01) each correlated significantly with the presence of the metabolic syndrome.

Conclusion: Independent of age and BMI, hypoadiponectinemia is a potential biomarker of the metabolic syndrome in patients taking clozapine for schizophrenia.

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Received Oct. 24, 2006; accepted April 3, 2007. *From the Department of Psychiatry, Taipei Veterans General Hospital and the Department of Psychiatry, College of Medicine, National Yang-Ming University (Drs. Bai and Su); the Department of Psychiatry, Yu-Li Veterans Hospital (Drs. Chen, Liou, C-C Lin, Wang, and C-Y Lin); the Graduate Institute of Clinical Medicine & Department of Internal Medicine, National Taiwan University and Hospital (Dr. Yang and Ms. Chi); the Institute of Biomedical Sciences, Academia Sinica (Dr. Yang); and the Community Medicine Research Center and Institute of Public Health, National Yang-Ming University (Dr. Chou), Taipei, Taiwan. Dr. C-C Lin is now with the Department of Psychiatry, National Taiwan University Hospital and the Graduate Institute of Medical Informatics, Taipei Medical University, Taipei.*

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Corresponding author and reprints: Ya Mei Bai, M.D., Ph.D., Department of Psychiatry, Taipei Veterans General Hospital, Taiwan, No. 201, Sec. 2, Shih-Pai Rd., Taipei 112, Taiwan (e-mail: ymbi@mail2000.com.tw).

There is increasing concern about the metabolic syndrome associated with the administration of antipsychotics, but reports on the prevalence of metabolic syndrome among psychiatric patients are still limited. Cohn et al.[1] found an overall prevalence of 42.6% for men and 48.5% for women among 240 subjects with schizophrenia or schizoaffective disorder,[1] more than twice the prevalence of the age-matched U.S. cohort.[2] In the Northern Finland 1966 Birth Cohort study, the prevalence of metabolic syndrome was higher in subjects with schizophrenia in comparison to the control group (19% vs. 6%, p = .010).[3] De Hert et al.[4] reported a prevalence of metabolic syndrome of 36% among 430 schizophrenia patients and concluded that this prevalence is at least twice as high as an age-adjusted community sample in Belgium. Using baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial, McEvoy et al.[5] reported that the prevalence of metabolic syndrome was 40.9% among 689 patients, showing that CATIE males were 138% and females 251% more likely to have metabolic syndrome than the Third National Health and Nutrition Examination Survey (NHANES III) matched sample.[5] Overall, the prevalence of metabolic

syndrome among psychiatric patients varied from 11% to 49% in different countries, but is at least twice as high among psychiatric patients as in the general population. However, all previous reports are from Caucasian sources; there have been no Asian reports so far.

Adiponectin, an adipocyte-derived hormone, serves as a central regulatory protein in many of the physiologic pathways controlling lipid and carbohydrate metabolism.[6] It also displays anti-inflammatory, antiatherogenic, and insulin-sensitizing properties and mediates other vascular processes.[7] Plasma concentrations of adiponectin are inversely related to body weight, especially visceral adiposity, and other traditional cardiovascular risk factors, such as blood pressure and low-density lipoprotein cholesterol and triglyceride levels, and is positively related to high-density lipoprotein (HDL) cholesterol levels. The ability of adiponectin to reduce insulin resistance, in conjunction with its anti-inflammatory and antiatherogenic properties, makes this novel adipocytokine a promising therapeutic target, and agents that enhance adiponectin secretion or action have the potential to ameliorate metabolic and vascular disease.[8–10] Clinical studies have confirmed that treatment with thiazolidinediones may increase adiponectin concentrations in patients with type 2 diabetes, independent of improvements in blood glucose control or parallel treatment with insulinotropic drugs. Therefore, adiponectin levels hold great promise for clinical use as a potent indicator of underlying metabolic complications.[11]

However, although metabolic syndrome is currently an item of widespread concern in psychiatry, a limited number of researchers have investigated the role of adiponectin in the development of metabolic syndrome associated with the administration of atypical antipsychotics. Clozapine, the first atypical antipsychotic, remains the most effective agent against treatment-resistant schizophrenia,[12] but its side effects—weight gain and metabolic changes—were significant. A 5-year naturalistic study of 82 patients taking clozapine showed that weight gain persisted until 46 months after initiation of treatment, and patients appear to be at increased risk for developing diabetes and lipid abnormalities.[13] The same group's 10-year study confirmed that clozapine-treated patients are at risk for death from cardiovascular disease secondary to clozapine-associated obesity, diabetes, hypertension, and hyperlipidemia.[14] Furthermore, our own 8-year study showed that patients with good initial clinical responses will have higher risks of long-term weight gain than poor responders.[15] Patients taking clozapine are usually maintained on this medication for years, because switching from clozapine to other antipsychotics frequently causes psychiatric instability.[16] Considering these long-term health risks, close monitoring for the development of metabolic syndrome seems indicated. But monitoring of the metabolic syndrome consists of multiple anthropometric and biochemical assessments; use of a convenient biomarker will enable clinicians to identify metabolic changes more effectively than anthropometry and biochemistry. In this study, with long-term cohort data for weight change associated with clozapine treatment and a cross-sectional survey for metabolic syndrome, we investigated the prevalence of metabolic syndrome among Chinese patients taking clozapine and examined the possible relationship between adiponectin and metabolic syndrome to determine the possibility of using serum adiponectin level as a metabolic syndrome marker.

METHOD

The study sample consisted of hospitalized Chinese patients with schizophrenia (DSM-IV criteria) with a mean ± SD age of 43.3 ± 8.67 years) who had received clozapine treatment for at least 3 months. Over the course of their hospitalization, the body weight of all patients was monitored monthly and recorded. Alcohol consumption was prohibited on all wards, and smoking was only allowed in the male ward. Retrospective chart reviews provided demographic data and established the age at initiation of clozapine treatment and the weight change after the initiation of clozapine treatment. Anthropometric and biochemical assessments were performed to investigate the prevalence of metabolic syndrome according to the 2005 International Diabetes Federation (IDF) Asia criteria: waist circumference greater than 90 cm in men or greater than 80 cm in women as the essential criteria of central obesity, plus 2 of the following 4 criteria: (1) fasting serum triglyceride levels of 150 mg/dL or above; (2) fasting HDL cholesterol level less than 40 mg/dL in men or less than 50 mg/dL in women; (3) blood pressure 130/85 mm Hg or above; and (4) fasting glucose level of 100 mg/dL or above. Overnight fasting blood samples were drawn between 7:00 a.m. and 8:00 a.m. from all patients. Serum glucose, triglyceride, and cholesterol levels were measured using a glucose oxidase autoanalyzer, a triglyceride enzyme autoanalyzer, and a cholesterol oxidase autoanalyzer, respectively (Dimension RxL, DADE Behring Company, Inc., Newark, Del.). Serum adiponectin was measured using a quantitative Human Adiponectin ELISA Kit (B-Bridge International, Inc., Tokyo, Japan).

The study, conducted from March to September of 2005, was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of Yu-Li Veterans Hospital. It was completely described to all patients, who provided written informed consent before participating.

RESULTS

A total of 188 patients completed the study. Table 1 shows their characteristics. All patients were of the Han

Table 1. Characteristics of Patients With Schizophrenia Treated With Clozapine (N = 188)[a]

Variable	Result
Age at initiation of clozapine treatment, y	38.06 ± 8.52
Age at survey, y	43.3 ± 8.67
Gender, male, N (%)	120 (63.8)
Baseline BMI before clozapine treatment	24.2 ± 4.5
BMI at survey	25.5 ± 4.6
Body weight gain, kg	3.13 ± 9.10
Clozapine dose, mg/d	330.5 ± 106.6
Duration of clozapine treatment, mo	57.6 ± 27.4
Concomitant use of mood stabilizers, N (%)	49 (26.1)
Concomitant use of other antipsychotics, N (%)	68 (36.2)
Waist circumference, cm	85.4 ± 12.8
Systolic blood pressure, mm Hg	116.9 ± 14.1
Diastolic blood pressure, mm Hg	73.6 ± 9.9
HDL cholesterol level, mg/dL	38.5 ± 12.6
LDL cholesterol level, mg/dL	87.7 ± 27.1
Fasting glucose level, mg/dL	95.0 ± 36.9
Insulin level, μg/mL	10.1 ± 12.5
HOMA	2.6 ± 3.8
Adiponectin level, μg/mL	7.83 ± 5.26

[a]Values are expressed as mean ± SD except where noted.
Abbreviations: BMI = body mass index, HDL = high-density lipoprotein, HOMA = homeostasis model assessment, LDL = low-density lipoprotein.

nationality. Smoking was only allowed in the male patient ward, and 81 male patients (68%) were smokers. Male patients received higher mean doses of clozapine than female patients (mean ± SD = 349.0 ± 108.7 mg/day vs. 298.2 ± 94.6 mg/day), but there were nevertheless no significant gender differences in plasma clozapine concentrations (mean ± SD = 234.5 ± 198.2 ng/dL vs. 269.8 ± 140.5 ng/dL). The following prevalences were found: central obesity, 45.5%; hypertriglyceridemia, 28.1%; low HDL cholesterol, 73.4%; hypertension, 24.0%; hyperglycemia, 16.9%; and metabolic syndrome, 28.4%. Serum adiponectin was negatively associated with weight changes after the initiation of clozapine treatment, systolic blood pressure, diastolic blood pressure, body weight, body mass index (BMI), waist circumference, hip circumference, serum triglycerides, serum uric acid (not shown), and serum insulin, and positively associated with HDL cholesterol (Figure 1). Multiple logistic regression analysis showed that age (OR = 1.083, p = .009), BMI (OR = 1.434, p < .001), and serum adiponectin (OR = 0.847, p = .01) were significant independent factors for the presence of metabolic syndrome when controlling for the variables of gender, clozapine dose, duration of clozapine treatment, and concomitant use of mood stabilizers and other antipsychotics (Table 2). The area under the receiver operating characteristic (ROC) curve ± SD for adiponectin to predict metabolic syndrome was 0.747 ± 0.026 (p < .001) and the cutoff value was 7.6 μg/mL, with 0.76 sensitivity and 0.63 specificity. Serum adiponectin normally ranges between 2.0 and 20.0 μg/mL in the general population, as measured with the same enzyme-linked immunosorbent assay (ELISA) kits noted above.[17]

In this study, the adiponectin level was only assessed in the cross-sectional survey, and no pre–clozapine treatment adiponectin levels are available. To adjust for the possible pre–clozapine treatment characteristics that may be associated with the development of metabolic syndrome and adiponectin level, a second logistic regression model integrated 2 additional factors: age at initiation of clozapine treatment and baseline BMI. Results showed age at initiation of clozapine treatment (OR = 1.056, p = .049), baseline BMI (OR = 1.226, p < .001), concomitant use of mood stabilizers (OR = 2.642, p = .041), and adiponectin level (OR = 0.783, p < .001) were significant independent factors for presence of metabolic syndrome (Table 3).

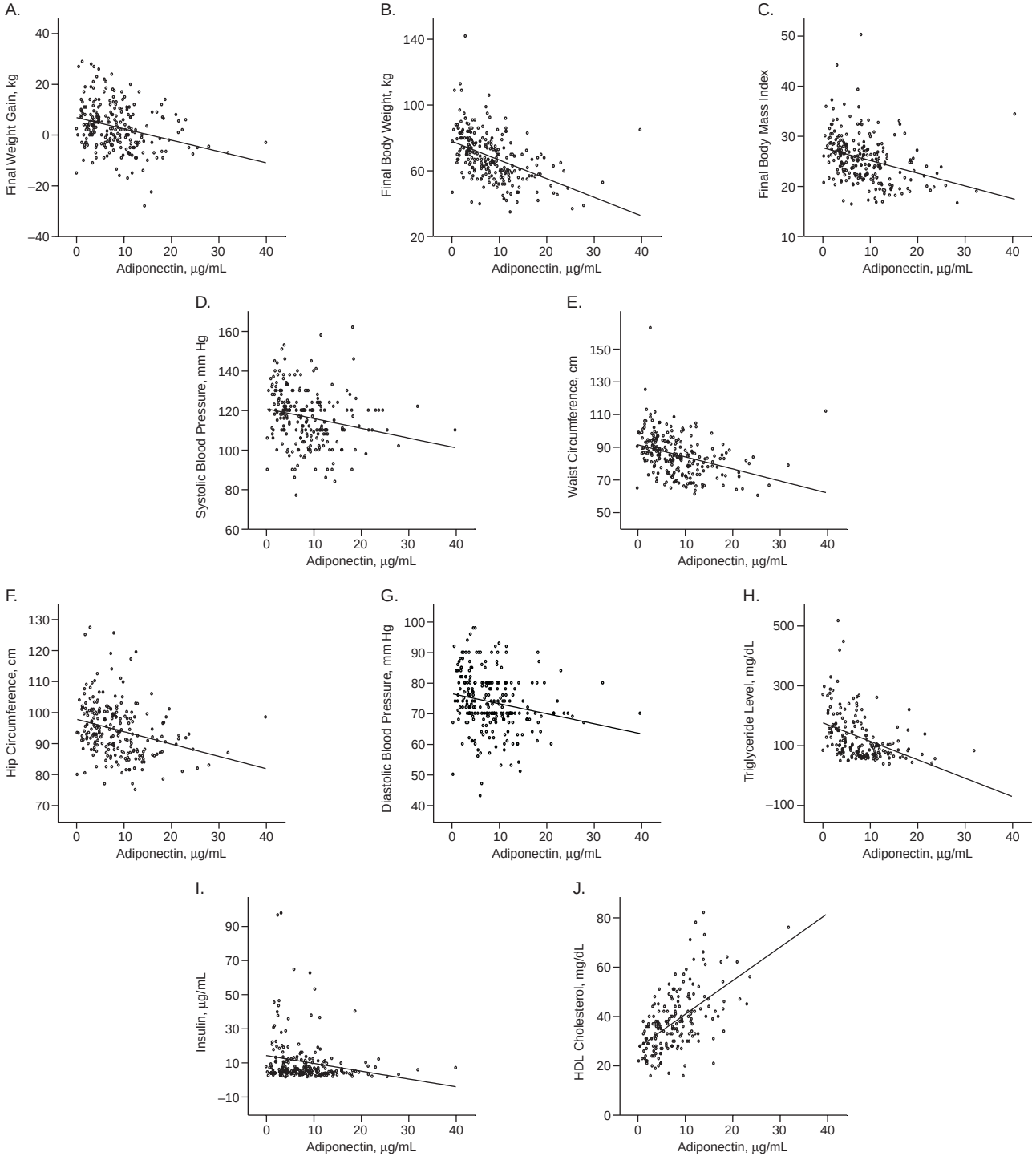
DISCUSSION

Our results showed the prevalence of metabolic syndrome among 188 Chinese patients taking clozapine was 28.4%. The prevalence of metabolic syndrome in the general Taiwanese population, according to Chuang et al.,[18] was 12.9% (15.5% in men and 10.5% in women) of 24,329 subjects who had received health checkups at health screening centers. In a report based on the 2006 nationally representative survey data from Hong Kong, Taiwan, Thailand, and the United States, the age-standardized prevalence of metabolic syndrome for the general population was lowest in Taiwan (11% in men, 12% in women) and highest in the United States (31% in men, 35% in women).[19] In conclusion, our results are consistent with those of previous Caucasian reports in that the prevalence of the metabolic syndrome among patients taking clozapine for schizophrenia is at least twice that of the general population.

The primary mechanism by which adiponectin enhances insulin sensitivity appears to be through increasing fatty acid oxidation and inhibiting hepatic glucose production.[20] Adiponectin helps prevent vascular disease by inhibiting local proinflammatory signals, preventing preatherogenic plaque formation, and impeding arterial wall thickening. Proinflammatory state and endothelial dysfunction are nominators of metabolic syndrome, a complex set of risk factors for cardiovascular disease and diabetes that includes vascular and metabolic insulin resistance, hyperglycemia, hypertension, and dyslipidemia. Over the past few years, thiazolidinediones, such as rosiglitazone or pioglitazone, have become known as therapeutic options for patients with metabolic syndrome.[21] Insulin sensitizers appear to exert their benefits through indirect induction of adiponectin expression.

A limited number of reports concerning the association of adiponectin and antipsychotics have previously been noted. Togo et al.[22] found that adiponectin concentrations decreased with increasing BMI in patients taking olanzapine for 4 weeks or more (N = 18), while elevated

Figure 1. Correlation of Adiponectin Levels and Metabolic Syndrome Components in Patients Treated With Clozapine[a]



A. Weight gain and adiponectin, r = –0.291, p < .001.
B. Body weight and adiponectin, r = –0.455, p < .001.
C. Body mass index and adiponectin, r = –0.321, p < .001.
D. Systolic blood pressure and adiponectin, r = –0.209, p = .001.
E. Waist circumference and adiponectin, r = –0.395, p < .001.
F. Hip circumference and adiponectin, r = –0.307, p < .001.
G. Diastolic blood pressure and adiponectin, r = –0.202, p = .002.
H. Triglyceride level and adiponectin, r = –0.407, p < .001.
I. Insulin and adiponectin, r = –0.219, p = .005.
J. High-density lipoprotein cholesterol and adiponectin, r = 0.565, p < .001.

Table 2. Multiple Logistic Regression for Cross-Sectional Predictors of Metabolic Syndrome Among Patients Treated With Clozapine

Variable	Patients With Metabolic Syndrome (N = 50)	Patients Without Metabolic Syndrome (N = 126)	OR	95% CI	p Value
Age at survey, mean ± SD, y	43.42 ± 8.58	43.19 ± 8.77	1.083	1.020 to 1.149	.009**
Gender, N (%)					
Male	31 (62.0)	79 (62.7)	1.193	0.408 to 3.486	.747
Female	19 (38.0)	47 (37.3)		…[a]	
Body mass index at survey, mean ± SD	29.5 ± 4.3	24.0 ± 3.9	1.434	1.236 to 1.664	< .001**
Clozapine dose, mean ± SD, mg/d	318.5 ± 106.8	335.0 ± 108.5	0.998	0.993 to 1.002	.333
Duration of clozapine treatment, mean ± SD, mo	59.3 ± 25.2	56.9 ± 28.6	1.002	0.985 to 1.019	.823
Concomitant use of mood stabilizers, N (%)					
Yes	3 (6.0)	2 (1.6)	2.238	0.903 to 6.286	.079
No	47 (94.0)	124 (98.4)		…[a]	
Concomitant use of other antipsychotics, N (%)					
Yes	6 (12.0)	15 (11.9)	1.937	0.454 to 8.259	.372
No	44 (88.0)	111 (88.1)		…[a]	
Adiponectin level, mean ± SD, µg/mL	5.13 ± 3.91	9.14 ± 5.36	0.847	0.746 to 0.961	.010**

[a]Reference group.
**p < .01.

Table 3. Multiple Logistic Regression for Cohort Predictors of Metabolic Syndrome Among Patients Treated With Clozapine

Variable	Patients With Metabolic Syndrome (N = 50)	Patients Without Metabolic Syndrome (N = 126)	OR	95% CI	p Value
Age at initiation of clozapine treatment, mean ± SD, y	38.14 ± 8.38	37.96 ± 8.61	1.056*	1.000 to 1.115	.049*
Gender, N (%)					
Male	31 (62.0)	79 (62.7)	0.803	0.290 to 2.222	.673
Female	19 (38.0)	47 (37.3)		…[a]	
Baseline body mass index, mean ± SD	26.8 ± 4.9	23.1 ± 3.9	1.226**	1.105 to 1.360	< .001**
Clozapine dose, mean ± SD, mg/d	318.5 ± 106.8	335.0 ± 108.5	0.998	0.993 to 1.002	.390
Duration of clozapine treatment, mean ± SD, mo	59.3 ± 25.2	56.9 ± 28.6	1.011	0.995 to 1.027	.178
Concomitant use of mood stabilizers, N (%)					
Yes	3 (6.0)	2 (1.6)	2.642*	1.041 to 6.704	.041*
No	47 (94.0)	124 (98.4)		…[a]	
Concomitant use of other antipsychotics, N (%)					
Yes	6 (12.0)	15 (11.9)	0.966	0.223 to 4.184	.963
No	44 (88.0)	111 (88.1)		…[a]	
Adiponectin level, mean ± SD, µg/mL	5.13 ± 3.91	9.14 ± 5.36	0.783**	0.690 to 0.888	< .001**

[a]Reference group.
*p < .05.
**p < .01.

levels were observed in patients taking risperidone, regardless of adiposity (N = 15). They concluded that adiponectin is involved in the regulation of glucose metabolism and weight during treatment with olanzapine or risperidone for schizophrenia, presumably having a normalizing effect on metabolic abnormalities.[22] Hosojima et al.[23] reported that among 13 patients with schizophrenia who received 4-week treatment of olanzapine at a mean dose of 14.5 mg/day, adiponectin and insulin levels had not significantly changed,[23] but a limited case number and a short duration of treatment were drawbacks of the study.

In the present study, with a large number of patients taking clozapine and long-term weight change data, decreased levels of plasma adiponectin (*hypoadiponectinemia*) were associated with most metabolic parameters (blood pressure, pulse rate, body weight, BMI, waist circumference, hip circumference, triglycerides, and insulin) but positively correlated with HDL cholesterol levels. The first multiple logistic regression analysis showed that hypoadiponectinemia is a significantly predictive factor for metabolic syndrome, independent of age and BMI and controlling for the variables of gender, clozapine dose, duration of clozapine treatment, and concomitant use of mood stabilizers and other antipsychotics. However, the study was a cross-sectional survey, the subjects were first assessed for adiponectin level, and we don't have pre–clozapine treatment adiponectin level data. The patients received clozapine treatment for a mean ± SD of 57.6 ± 27.6 months. Five years ago, adiponectin was not yet well investigated. To adjust for the possible pre–clozapine treatment characteristics associated with the development of metabolic syndrome and adiponectin level, a second

logistic regression model controlled for 2 pre–clozapine treatment predictive factors: age at initiation of clozapine treatment and baseline BMI. The result showed that after controlling for pre–clozapine treatment characteristics, hypoadiponectinemia still remained as a significant factor for the presence of metabolic syndrome. Importantly, levels of plasma adiponectin were negatively associated with weight gain after initiation of clozapine treatment. Therefore, serum adiponectin holds great promise for use as a potential clinical biomarker of the metabolic syndrome among patients taking clozapine.

The area under the ROC curve ± SD for adiponectin was 0.747 ± 0.026 ($p < .001$), and the cutoff value was 7.6 μg/mL, with 0.76 sensitivity and 0.63 specificity. Ogawa et al.[24] have also suggested that adiponectin be evaluated for use as a biomarker for early therapeutic intervention in obese children with the metabolic syndrome. They suggested a cutoff value of adiponectin at 6.65 μg/mL, with the area under the ROC curve ± SD of 0.672 ± 0.055. More studies for the association of adiponectin and other antipsychotics are required to determine the appropriate cutoff value of adiponectin as a biomarker for monitoring metabolic syndrome among our psychiatric patients.

The main limitation of this study inheres in its cross-sectional nature, without pretreatment adiponectin levels. Prospective studies with adiponectin levels taken both before and after clozapine treatment will be necessary to validate our conclusion.

Drug names: clozapine (FazaClo, Clozaril, and others), olanzapine (Zyprexa), pioglitazone (Actos), rosiglitazone (Avandia).

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