Introduction

Schizophrenia is a multifactorial disorder that involves many pathways. Brain-derived neurotrophic factor (BDNF) is involved in the growth, survival, differentiation, and repair of neurons [1] and is found to be associated with neuropsychiatric disorders, such as schizophrenia and mood disorder [2]. S100A10, also known as p11, is a member of the S100 family of calcium effector proteins [3]. Antidepressant effect of BDNF has been shown to be closely related to S100A10 in primary neuronal cultures and transgenic mice [4]. In the peripheral blood mononuclear cell of patients with schizophrenia, S100A10 mRNA levels are higher than the controls [5].

Patients with schizophrenia tend to have higher mortality and shorter lifespan [6, 7]. Cardiovascular disease is found to be a major contributing factor to the increased mortality of patients with schizophrenia [8, 9]. The diagnosis of metabolic syndrome can be used to help identify individuals at risk of cardiovascular disease [10]. The prevalence of metabolic syndrome in patients with schizophrenia is about 35% in males and 50% in females, both far greater than general population [11]. Many factors such as the use of antipsychotic medications, lifestyle, social economic status, and genetics, contribute to the increased prevalence of metabolic syndrome among patients with schizophrenia [12].

Several members of S100 proteins are associated with metabolic syndromes. In the rat model of metabolic syndrome, S100A3 gene expression is upregulated through microarray [13]. Increased expression of S100A8 is found in the whole blood of Latinos with metabolic syndrome as compared to those without [14]. Peripheral serum S100A8, S100A10, and S100B levels are also found to be increased in metabolic syndrome patients [15].
A9, and A12 mRNA levels are closely associated with insulin resistance and inflammation [15]. Lower serum S100A1 levels and higher serum S100B levels have been found in patients with metabolic syndrome than those in healthy controls [16, 17]. S100A10 protein has close interactions with serotonin receptors and annexin A2. S100A10 increases localization of serotonin 1B (5-HT_{1B}) receptors at the cell surface [18]. While CNS serotonin inhibits appetite, peripheral serotonin synthesis is associated with obesity, and inhibition of peripheral serotonin can reduce obesity [19]. In adipose tissues, annexin A2 contributes to glucose and fatty acid transport [20]. Those data suggest that S100 proteins play a rôle in the energy metabolism.

In this study, we intended to investigate the relationship between serum BDNF levels, serum S100A10 levels, and metabolic syndrome in patients with schizophrenia.

Methods

Participants

From July 2016 to June 2018, we recruited patients with schizophrenia at the Chang Gung Memorial Hospital. Schizophrenia was diagnosed by a psychiatrist using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [21]. Clinical symptoms were evaluated using Positive and Negative Syndrome Scale (PANSS). We also collected demographic data, blood pressure (BP), and waist circumference. Written informed consent was provided by all participants after the content of the study was fully explained. The institutional review board of Chang Gung Memorial Hospital approved the study designs (protocol number = IRB 201600266A3, and date of approval = May 11, 2016; IRB 201600266A3C101, and date of approval June 29, 2017).

Laboratory data

Venous blood was drawn from each participant in the morning following a six-hour fast. Serum levels of fasting blood sugar, triglyceride (TG), and high-density lipoprotein cholesterol (HDL) were measured in the hospital laboratory. Serum BDNF protein levels were measured using a commercially available ELISA kit of the sandwich type, i.e., CircuLex S100A10 ELISA Kit (CycLex Company, Ltd., Taipei), which employs the quantitative sandwich enzyme immunoassay technique. All samples were assayed or duplicated by the same senior laboratory assistant according to the manufacturers’ manuals.

Criteria of metabolic syndrome

Health Promotion Administration of Ministry of Health and Welfare of Taiwan used the following five criteria of metabolic syndrome in 2004:

- iWaist circumference $\geq 90$ cm in males or $\geq 80$ cm in females, or body mass index (BMI) $\geq 27$ kg/m²
- Systolic BP $\geq 130$ mgHg or diastolic BP $\geq 85$ mmHg
- Fasting blood sugar $\geq 110$ mg/dL
- LTG $\geq 150$ mg/dL
- LHDL < 40 mg/dL in males or < 50 mg/dL in females.

Patients were considered to have metabolic syndrome if they met three or more of those five criteria.

The above criteria were modified from the U.S. National Cholesterol Education Program Adult Treatment Panel III (2001). The most notable difference is in the definition of central obesity (waist circumference $\geq 100$ cm or 40 inches in male or $\geq 88$ cm or 35 inches in female).

Statistical analysis

We described results as mean $\pm$ standard deviation. Chi-square was used to analyze the distribution of metabolic syndrome among male and female samples. Independent $t$-test and analysis of variance (ANOVA) were used to compare serum BDNF and S100A10 levels between patients with and without metabolic syndrome, as well as demographic data between the two groups. We used Pearson correlation to assess the relationship with the associated parameters.

Data analysis was done using Statistical Package of Social Science software version 19 (Chicago, Illinois, U.S.A.). The differences were considered significant if $p$-values were smaller than 0.05.

Results

A total of 93 patients with schizophrenia were recruited, including 41 males and 52 females. Their ages were ranged from 20.8 to 78.1 years, with the mean of 45.8 $\pm$ 11.3 years. Illness duration was ranged from 0.9 to 48.2 years, with the mean of 20.4 $\pm$ 9.4 years. PANSS scores were ranged from 32 to 131, with the mean of 81.7 $\pm$ 27.5.

Six (6.5%) patients met zero criteria of metabolic syndrome, 25 (26.9%) met one criteria; 26 (28.0%) met two criteria, 26 (28.0%) met three criteria, 7 (7.5%) met four criteria, and three (3.2%) met all criteria. Overall, 36 (38.7%) patients had metabolic syndrome. Among them, 19 of 41 (46.3%) male and 17 of 52 (32.7%) female patients had metabolic syndrome. The male and female distribution of metabolic syndrome was not significant. Using ATP III criteria, 15 (16.1%) patients met zero criteria of metabolic syndrome, 23 (24.7%) met one criteria, 22 (23.7%) met two criteria, 23 (24.7%) met three criteria, 7 (7.5%) met four criteria, and three (3.2%) met all criteria. Overall, 33 (35.5%) patients had metabolic syndrome.

Using independent $t$-test, no statistical significance was found in BDNF levels between patients with and without metabolic syndrome ($18.7 \pm 6.5$ ng/mL vs. $18.4 \pm 8.2$ ng/mL, no significant difference). Using independent $t$-test, patients with metabolic syndrome had significantly lower S100A10 levels compared to those without metabolic syndrome ($0.2 \pm 0.4$ ng/mL vs. $0.7 \pm 1.5$ ng/mL, $p < 0.05$). Those results are summarized in Table 1. Among all patients, no significant correlation was found between serum S100A10 levels, serum
BDNF levels, age, BMI, and PANSS scores (Pearson’s r values are 0.125, 0.102, −0.074, and 0.144, respectively). Among all patients, serum BDNF protein levels showed significant correlation with body weight (p < 0.01) and BMI (p < 0.001). In male patients (n = 41) only, using independent t-test, no statistical significance was found in BDNF levels between patients with and without metabolic syndrome (18.2 ± 7.2 ng/mL vs. 18.0 ± 8.5 ng/mL, no significant significance). In males, serum BDNF protein levels showed significant correlation with BMI (p < 0.05) but not body weight. Using independent t-test, patients with metabolic syndrome had significantly lower S100A10 levels compared to those without metabolic syndrome (0.1 ± 0.1 ng/mL vs. 1.0 ± 2.0 ng/mL, p < 0.05).

In female patients (n = 52) only, using independent t-test, no significance was found in BDNF levels between patients with and without metabolic syndrome (19.3 ± 5.7 ng/mL vs. 18.6 ± 8.2 ng/mL, no significant significance). In females, serum BDNF protein levels showed significant correlation with body weight (p < 0.01) and BMI (p < 0.01). Using independent t-test, patients with metabolic syndrome had no significantly different S100A10 levels compared to those without metabolic syndrome (0.3 ± 0.5 ng/mL vs. 0.5 ± 1.1 ng/mL, no significant difference).

Using two-way ANOVA adjusted with sex and metabolic syndrome, no significance was found in S100A10 levels. In patients without metabolic syndrome, serum BDNF protein levels showed significant correlation with body BMI (p < 0.01). Among patients without metabolic syndrome, S100A10 levels were not significantly different between males and females. In patients with metabolic syndrome, serum BDNF protein levels showed significant correlation with body BMI (p < 0.01). Among patients without metabolic syndrome, males had significantly lower S100A10 levels (p < 0.05). The distributions of S100A10 of males and females with and without metabolic syndrome (Figure 1).

**Discussion**

As shown in Table 1, the major finding of this study was significantly decreased (p < 0.05) serum S100A10 levels in schizophrenic patients with metabolic syndrome (0.2 ± 0.4 ng/mL) compared to schizophrenic patients without (0.7 ± 1.5 ng/mL). A few studies existed to investigate S100A10 in the past, and their findings are not easily comparable due to methodology differences. In patients with schizophrenia, major depressive disorder, and bipolar disorder, higher S100A10 mRNA levels are found compared to those of healthy controls [5]. Comparison of whole-genome gene expression profiles using microarrays on LCLs from 413 patients with schizophrenia and 446 controls has shown decreased expression of S100A10 in the patients [22]. In a study investigating SNPs and abnormal eye movements in patients with schizophrenia, 16 SNPs are found relevant to the horizontal position gain during the fast Lissajous paradigm of the smooth pursuit test; 10 SNPs at 1q21.3 are located in intron or intergenic regions of the THEM4 or S100A10 genes, and further analysis suggests that those are in the enhancer or promoter regions [23]. The underlying mechanism of S100A10 in schizophrenia is unclear, but several possibilities exist. S100A10 can increase the localization of serotonin receptors at the cell surface [18] and serotonin dysfunction has also been associated with schizophrenia. Another theory involves the increased phospholipase A2 (PLA2) in schizophrenia [24, 25]. S100A10 has been found to inhibit the activity of PLA2, so a decreased level of S100A10 may contribute to the increased PLA2 levels in schizophrenia [26].

In S100A10 and metabolic syndrome, we found no direct reference. Several S100 family proteins, such as S100A1, A3, A8, A9, A12, and B, are associated with metabolic syndrome [13-17]. In the male Zucker Diabetic Fatty rat model of metabolic syndrome, microarray for 14921 genes have revealed 36 genes with up-regulation and 49 genes with down-regulation, as compared to those of lean controls, and S100A3 gene is among the up-regulated genes [13]. Whole blood gene microarray of 74 Latinos with metabolic syndrome, and 110 counterparts without has shown increased expression of S100A8 in those with metabolic syndrome [14]. Peripheral blood S100A8, A9, and A12 mRNA

| Table 1. Serum brain-derived neurotrophic factor and S100A10 levels in patients with schizophrenia, with and without metabolic syndrome |
|---|---|---|
| With metabolic syndrome (n=36) | Without metabolic syndrome (n=57) |
| Age (years) | 45.3 ± 10.1 | 46.2 ± 12.3 |
| Onset (years) | 24.6 ± 6.4 | 26.5 ± 9.2 |
| Duration (years) | 21.3 ± 9.4 | 19.8 ± 9.4 |
| BMI (kg/m²) | 28.1 ± 4.4 | 24.7 ± 6.2** |
| PANSS score | 85.9 ± 28.0 | 79.1 ± 27.1 |
| BDNF (ng/mL) | 18.7 ± 6.5 | 18.4 ± 8.2 |
| S100A10 (ng/mL) | 0.2 ± 0.4 | 0.7 ± 1.5* |

*p < 0.05; **p < 0.01, using independent t-test (n = 94). BDNF, brain-derived neurotrophic factor; BMI, body mass index; PANSS, Positive and Negative Syndrome Scale

Figure 1. S100A10 distribution of males and females with and without metabolic syndrome.
levels are closely associated with insulin resistance and inflammation [15]. A study has shown lower serum S100A1 levels in the metabolic syndrome group than the controls [16]. Another study has shown higher S100B protein levels in the metabolic syndrome group than the controls [17]. While no direct reports of S100A10 have been found, S100A10 have been known to interact closely with serotonin and annexin A2, two molecules closely related to obesity. Global activation of central serotonin system suppresses feeding [27] but peripheral serotonin acts as a factor that enhances nutrient absorption and storage [28]. In mice, the inhibition of peripheral serotonin synthesis can promote brown adipose tissue thermogenesis, leading to reduction of obesity [19]. Annexin A2, responsible for endosomal regulations, contributes to glucose and fatty acid transport [20]. Silencing of annexin A2 improves insulin sensitivity and glucose uptake [29]. S100A10 can influence metabolic syndrome through the interactions of those molecules.

We found no significant difference in serum BDNF levels between schizophrenic patients with and without metabolic syndrome (Table 1). But we found that BDNF levels were significantly correlated with BMI ($p < 0.001$) and body weight ($p < 0.01$). This discrepancy of findings can be caused by the fact that some criteria of metabolic syndrome are not influenced by BDNF pathway. Previously, we also have not noticed a difference until male and female patients were analyzed separately [30]. Another study reports no differences in serum BDNF levels between patients with schizophrenia and BMI matched controls [31]. Many studies report that BDNF can function differently in different genders. Zhang et al. found that BDNF levels are correlated negatively with BMI gain only in female patients with schizophrenia, but not in males [31]. Another study showed that female patients with schizophrenia have higher BDNF levels than male patients, but this gender difference cannot be found in healthy controls [32]. However, in this study, we did further analysis separating the genders found nothing significant. This finding is different from those earlier findings. We also found that in male patients, those with metabolic syndrome had significantly lower S100A10 levels than those without, but the phenomenon could not be found in females. Whether S100A10 behaves differently according to gender requires further investigation to confirm.

The prevalence of metabolic syndrome of the study sample was 38.7%, being similar to earlier published reports in Taiwan [30, 33-35].

### Study limitations

The readers are warned against over-interpreting our study results because this study has three limitations:

- The sample size was relatively small.
- We did not control many confounding factors, such as dosage and duration of antipsychotic medications as well as additional medications such as mood stabilizers and antidepressants. The lifestyles of the patients were not investigated, as exercises and healthy diet could have direct effect on metabolic syndrome.
- The study had a cross sectional design, without longitudinal follow-up, limiting the data interpretation.

### Summary

Decreased serum S100A10 levels were found in patients with schizophrenia with metabolic syndrome compared to those without. Those data suggest that S100A10 could play a role in metabolic syndrome among patients with schizophrenia.

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### Conflicts of interest

None.

### References


