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RESEARCH ARTICLE

Is abnormal non-high-density lipoprotein cholesterol a gender-specific predictor for metabolic syndrome in patients with schizophrenia taking second-generation antipsychotics?

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Abstract Evidence supports an association between metabolic syndrome (MetS) and schizophrenia. However, specific risk factors for MetS and gender differences in patients with schizophrenia taking second-generation antipsychotics (SGAs) have not been well explored. A cross-sectional cohort of 329 Han Chinese patients was recruited in a psychiatric hospital in central Taiwan. Using the definitions of the International Diabetes Federation for Chinese, the prevalence of MetS was 23.7 % (men: 25.7 %; women: 21.2 %). Logistic regression analyses showed that patients with a BMI≥24 and an abnormal non-high-density lipoprotein cholesterol (non-HDL-C) were significantly ($p<0.001$) more likely to develop MetS. A BMI≥24 was a significant risk factor in men (OR: 6.092, $p<0.001$) and women (OR: 5.886, $p<0.001$). An abnormal non-HDL-C was a significant specific risk factor for men with MetS (OR: 4.127, $p<0.001$), but not for women. This study supports a greater prevalence of MetS in patients with schizophrenia taking SGAs than in the general population. Abnormal BMI and non-HDL-C were significantly associated with developing MetS, and an abnormal non-HDL-C was a specific risk factor for men. Future development of specific interventions and regular monitoring for MetS is imperative for early identification and prevention.

Keywords Schizophrenia · Second-generation antipsychotics · Metabolic syndrome · Prevalence

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Accumulating evidence supports an association between metabolic changes and schizophrenia (Papanastasiou 2013; Kraemer et al. 2011). It is estimated that nearly two-thirds of patients with schizophrenia are obese (Keltner 2006; Rummel-Kluge et al. 2010) and up to one-third have metabolic syndrome (MetS) (De Hert et al. 2009; Saddichha et al. 2007). The prevalence of MetS in these patients is nearly 3 or 4 times higher than in the general population (American Diabetes Association et al. 2004; Saari et al. 2005).

Genetic predisposition, exposure to antipsychotics, and lifestyle characteristics have been identified as important factors in patients with schizophrenia for developing MetS (Papanastasiou 2013; De Hert et al. 2008). Some studies report that antipsychotic-naïve patients have abnormalities in glucose tolerance and insulin resistance (Venkatasubramanian et al. 2007; Fernandez-Egea et al. 2009), and suggest that diabetes and schizophrenia may share a common genetic predisposition. In addition, patients taking second-generation antipsychotics (SGAs) had three times the risk of developing MetS than did those taking first-generation antipsychotics (De Hert et al. 2008). The weight-gain risks of SGAs increase the probabilities of hyperglycemia and dyslipidemia, which in

turn increase the risk of diabetes and cardiovascular disease (CVD). SGAs have been increasingly used because of the disadvantages of the side effects of parkinsonism, tardive dyskinesia, and prolactin elevation from treatments with first-generation antipsychotics (Crossley et al. 2010). Currently, clozapine, olanzapine, risperidone, quetiapine, zotepine, amisulpride, ziprasidone, and aripiprazole are commonly used worldwide. The receptor profiles of different SGAs diversely affect weight gain and other metabolic changes (Newcomer 2005). A growing number of randomized trials have shown that the SGA clozapine (Clozaril; Novartis Pharmaceutics, Basel, Switzerland) and olanzapine (Zypyrexa; Eli Lilly, Indianapolis, IN, USA) are associated with the highest prevalence of metabolic abnormalities, and that risperidone (Risperdal; Janssen Pharmaceuticals, Titusville, NJ, USA) poses a moderate risk (McEvoy et al. 2005; Newcomer 2007; Hosojima et al. 2006).

Probably because of the variety of societies with divergent ethnic groups and lifestyles, the reported prevalence of MetS in patients taking SGAs ranges from 14.7 % to 69.3 % (Rummel-Kluge et al. 2010; De Hert et al. 2009; Huang et al. 2009; Bou Khalil 2012). In two non-Euro-American studies (Bou Khalil 2012; Rampal et al. 2012), the lowest prevalence was in the Chinese. Moreover, gender differences for developing MetS in people with schizophrenia have been found in many studies. However, the evidence is inconsistent. Some studies (Bou Khalil 2012; Aichhorn et al. 2006; Lee and Leung 2008; Seeman 2010) report that women have a greater prevalence, but others report a greater prevalence for men (Bai et al. 2009; Brunero et al. 2009; Tirupati and Chua 2007).

While several risk factors for developing MetS have been identified, including an association between SGA and MetS, specific risk factors and gender differences have not been well explored. Therefore, this study investigated the prevalence of MetS and the risk factors for patients with schizophrenia who are using SGAs in Taiwan.

Methods

Research design and ethical considerations

A cross-sectional cohort of 329 Han Chinese patients with schizophrenia was recruited from eight chronic psychiatric wards of a 1,400-bed psychiatric hospital in central Taiwan in 2011. The Institutional Review Board of the hospital approved the study protocol. All procedures related to human participants were conducted in accordance with the Declaration of Helsinki, and all patients provided signed written consents.

Subjects

Patients who met the following criteria were recruited: [1] Han Chinese and over 20 years old, [2] a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, [3] hospitalized for at least 3 months, and [4] using at least one SGA (clozapine, risperidone, ziprasidone, quetiapine, aripiprazole, zotepine, amisulpride, or olanzapine). Patients ready for discharge or who had their antipsychotic medications adjusted for less than 3 months were excluded. All participants had completed metabolic assessment profiles, and their compliance with the prescribed medication regimen and laboratory fasting requirements was supervised.

Measurement

Demographic and clinical data—gender, age, age at onset of schizophrenia or schizoaffective disorder, number of years of illness, number of hospitalized years, antipsychotic use, and assessments of anthropometric profiles—were obtained from the patients' medical records. For those patients who were taking more than one SGAs, patients were assigned to the corresponding SGA subgroup while they had received a particular type of SGA for at least 50 % of their antipsychotic treatment and the other SGAs were being taken for<50 %.

The prevalence of MetS was defined according to the criteria of the International Diabetes Federation for Chinese (MetS-IDF[C]) (Alberti et al. 2006). A waist circumference≥ 90 cm in men or≥80 cm in women, and any 2 of the following factors were considered to indicate MetS: [1] triglycerides (TG)≥150 mg/dl, [2] high-density lipoprotein cholesterol (HDL-C)<40 mg/dl in men or<50 mg/dl in women (or specific treatment for these lipid abnormalities), [3] systolic blood pressure≥130 or diastolic BP≥85 mmHg (or treatment of previously diagnosed hypertension), and [4] fasting glucose level≥100 mg/dl (or previously diagnosed type 2 diabetes). Body mass index (BMI) was calculated based on height and weight that applies to adult men and women.

The protocol for metabolic assessments requires that blood be drawn after an 8-h fast. All laboratory tests were done in a central laboratory at the hospital. Serum glucose, TG, and cholesterol levels were measured using auto analyzers of glucose oxidase, TG enzyme, and cholesterol oxidase (Synchron CX9 ALX Clinical System; Beckman Coulter, Brea, CA, USA).

Statistical analysis

Descriptive statistics of demographic variables, as well as anthropometric and metabolic assessments, are presented. Based on categorical or continuous variables, differences in demographic variables and anthropometric assessments between patients with and without MetS were examined using χ^2 or t tests. Gender differences were also analyzed. Univariate

logistic regression analyses were done to examine the associations between the presence of MetS (dependent variable) and the significant demographic and anthropometric variables (independent variables) from the previous analysis. Because of their correlation, indicators of metabolic assessment were not included for regression analysis. These procedures were also done separately by gender. If an independent variable showed a significant association with the dependent variable, it was then entered into a multivariate logistic regression analysis. Significance was set at $p<0.05$, and 95 % confidence intervals (CIs) of odds ratios (ORs) were calculated. Pearson's product–moment or Spearman's rank order correlation coefficient (r) was used to evaluate independent variables for multicollinearity. If r was>0.4, the variables were entered separately in the models to determine differences in their associations with the dependent variable. SPSS 18.0 for Windows was used to analyze all data (SPSS Inc., Chicago, IL, USA).

Results

Table 1 lists the clinical characteristics and medications of 329 patients. There were no significant differences between men and women in mean age, age at onset, duration of illness, or length of current hospitalization.

Anthropometric and metabolic assessments

Based on the MetS-IDF(C) criteria, the prevalence of MetS in this study was 23.7 % (78/329). The prevalence of MetS was greater in men (25.7 %, 47/183) than in women (21.2 %, 31/146) (Table 2). Significant differences between patients with and without MetS were found for all metabolic indicators ($p\leq0.016$).

Anthropometric data showed significant gender-based differences for some metabolic assessments. In men with or without MetS, there were significant differences in weight ($t=6.22$, $p<0.001$), waist circumference ($t=10.21$, $p<0.001$), BMI ($t=7.167$, $p<0.001$), TG ($t=8.15$, $p<0.001$), non-HDL-C ($t=5.66$, $p<0.001$), cholesterol ($t=3.48$, $p=0.001$), HDL-C ($t=-10.06$, $p<0.001$), and systolic and diastolic blood pressure ($t=2.41$, 2.75, $p=0.017$, 0.007). In women with or without MetS, there were significant differences in weight ($t=3.44$, $p=0.001$), waist circumference ($t=5.10$, $p<0.001$), BMI ($t=3.38$, $p=0.001$), TG ($t=6.23$, $p<0.001$), fasting glucose ($t=5.05$, $p<0.001$), HDL-C ($t=-6.15$, $p<0.001$), and diastolic blood pressure ($t=3.65$, $p=0.001$).

Risk factors associated with the presence of MetS

Table 3 presents the logistic regression analysis of risk factors for metabolic syndrome in all patients. The non-HDL-C was

Table 1 Demographic characteristics of patients

Variables (years)	Total ($n=329$)	Males ($n=183$)	Females ($n=146$)
Age	47.48 (9.08)	46.64 (9.25)	48.54 (8.77)
Age at Onset	30.32 (9.07)	29.93 (9.02)	30.80 (9.13)
Duration of Illness	17.16 (4.97)	16.71 (5.06)	17.74 (4.82)
Length of Current Hospitalization	4.98 (2.91)	4.95 (2.91)	5.04 (2.94)
Number of SGAs taken			
One	131 (39.82)	69 (37.70)	62 (42.47)
Two	110 (33.43)	70 (38.25)	40 (27.40)
Three	54 (16.41)	29 (15.85)	25 (17.12)
≥ 4	34 (10.34)	15 (8.20)	19 (13.01)
SGA types			
Clozapine	146 (44.38)	75 (40.98)	71 (48.63)
Others			
Risperidone	82 (24.92)	51 (27.87)	31 (21.23)
Olanzapine	24 (7.29)	15 (8.20)	9 (6.16)
Zotepine	43 (13.07)	24 (13.11)	19 (13.01)
Amisulpride	18 (5.47)	8 (4.37)	10 (6.85)
Aripiprazole	8 (2.43)	5 (2.73)	3 (2.05)
Quetiapine	6 (1.82)	4 (2.19)	2 (1.37)
Ziprasidone	2 (0.61)	1 (0.55)	1 (0.68)
Total Others	183 (55.62)	108 (59.02)	75 (51.37)

Data are means (standard deviation) unless otherwise indicated

SGA second-generation antipsychotic

Table 2 Gender-based differences in anthropometric and metabolic assessments, and metabolic abnormalities

Variables (units)	Total (n=329)	Males (n=183)	Females (n=146)	t	χ^2	p-value
BMI (kg/m^2)	23.67±3.56	23.52±3.67	23.86±3.43	0.87	-	< 0.386
Height (cm)	161.56±9.28	167.41±6.86	154.22±6.21	18.08	-	< 0.001*
Weight (kg)	61.91±11.45	65.98±11.43	56.82±9.35	7.82	-	< 0.001*
Waist Circumference (cm)	86.58±9.95	86.95±10.45	86.11±9.32	0.76	-	0.450
TG (mg/dL)	107.16±61.60	111.31±62.03	101.96±60.87	1.37	-	0.172
Fasting Glucose (mg/dL)	92.00±19.50	93.59±21.76	90.0±16.08	1.66	-	0.097
Cholesterol (mg/dL)	167.23±35.22	164.27±33.80	170.95±36.70	−1.71	-	0.088
HDL-C (mg/dL)	46.05±12.85	41.69±11.06	51.51±12.89	−7.44	-	< 0.001*
Non-HDL-C (mg/dL)	121.19±35.52	122.59±35.23	119.43±35.91	0.80	-	0.425
Blood pressure (mmHg)						
Systolic	111.92±12.97	113.13±13.17	110.40±12.59	1.90	-	0.059
Diastolic	74.14±10.32	74.51±10.43	73.67±10.19	0.74	-	0.463
Metabolic Abnormalities (n (%))						
Central Obesity	183 (55.62)	74 (40.44)	109 (74.66)	-	38.53	< 0.001*
HDL-C	168 (51.06)	96 (52.46)	72 (49.32)	-	0.32	0.571
Fasting Glucose	74 (22.49)	44 (24.04)	30 (20.55)	-	0.57	0.451
TG	68 (20.67)	46 (25.14)	22 (15.07)	-	5.02	0.025*
Blood Pressure	60 (18.24)	37 (20.22)	23 (15.75)	-	1.09	0.297
MetS†	78 (23.71)	47 (25.68)	31 (21.23)	-	0.89	0.346

Data are means±standard deviation unless otherwise indicated

BMI body mass index, *TG* triglyceride level, *HDL-C* high-density lipoprotein-cholesterol, Non-HDL-C=total cholesterol (TC)-HDL-C; MetS: metabolic syndrome; † based on the IDF for Chinese criteria for metabolic syndrome

* p<0.05

calculated by subtracting HDL-C from total cholesterol because it is predictive for MetS (Huang et al. 2008). Patients with a BMI≥24 and an abnormal non-HDL-C were significantly more likely to develop MetS (p<0.001). Table 4 shows the model of risk factors for developing MetS by gender. A BMI≥24 was a significant risk factor for both sexes (men- OR: 6.092, p<0.001; women- OR: 5.886, p<0.001). An abnormal non-HDL-C was a significant risk factor for men with MetS (OR: 4.127, p<0.001).

Table 3 Logistic regression analysis of risk factors for metabolic syndrome in patients with schizophrenia and taking second-generation antipsychotics in Taiwan (n=329)

Variables	B	Odds Ratio	95 % CI	p-value
Gender	0.257	1.293	0.722–2.316	0.387
Duration of Illness (years)	0.037	1.038	0.980–1.100	0.207
Overweight BMI	1.806	6.084	3.207–11.540	< 0.001*
Abnormal non-HDL-C	1.098	2.999	1.682–5.347	< 0.001*

B beta coefficient, *CI* confidence interval *BMI* body mass index, *HDL-C* high-density lipoprotein-cholesterol

* p<0.05; Categorical reference indicators: Gender (1: male, 0: female); Overweight BMI (1 to≥24 kg/m^2, 0 to<24 kg/m^2); Abnormal non-HDL-C (1 to abnormal non-HDL-C: ≥ 130 mg/dL, 0 to normal non-HDL-C: < 130 mg/dL)

Discussion

In the present study, the prevalence of MetS in Han Chinese patients with schizophrenia and using SGAs in Taiwan was higher than in the general population (25.7 % vs. 15.5 % for men, 21.2 % vs. 10.5 % for women) (Chuang et al. 2004). This finding is consistent with the data from Bai et al. (2009), who reported that the prevalence of MetS was 23.8 % in a cohort of Han Chinese patients in Taiwan with schizophrenia and taking SGAs. However, a higher prevalence (34.9 %) was reported by Huang et al. (2009), who studied patients using a variety of antipsychotics in non-institutional settings in urban areas in Taiwan.

There was a gender difference in the association between non-HDL-C and the prevalence of MetS in the present study. Tirupati and Chua (2007) identified a BMI of 28.7 as a significant criterion with the highest predictive accuracy of MetS in patients with schizophrenia in Australia, but we found that a BMI≥24 concomitant with an abnormal non-HDL-C were strong risk

Table 4 Factors associated with metabolic syndrome in patients with schizophrenia taking second-generation antipsychotics in Taiwan (by gender)

Variables	Males				Females			
	B	OR	95 % CI	*p*-value	B	OR	95 % CI	*p*-value
Overweight BMI	1.807	6.092	2.594–14.306	< 0.001*	1.773	5.886	2.195–15.787	< 0.001*
Abnormal non-HDL-C	1.417	4.127	1.879–9.062	< 0.001*	0.652	1.920	0.798–4.620	0.145
Duration of Illness (years)	0.021	1.021	0.945–1.103	0.598	0.066	1.068	0.975–1.170	0.157

B beta coefficient, *OR*: odds ratio, *CI* confidence interval, *HDL-C* high-density lipoprotein-cholesterol

* $p<0.05$; Categorical reference indicators: Overweight BMI (1 to≥24 kg/m^2 , 0 to<24 kg/m^2); Abnormal non-HDL-C (1 to abnormal non-HDL-C: ≥ 130 mg/dL; 0 to normal non-HDL-C: < 130 mg/dL)

factors in the Han Chinese sample. When divided by gender, a BMI≥24 was significantly associated with the presence of MetS in both men and women; however, an abnormal non-HDL-C was the most significant factor associated with having MetS in men, but not in women. This might indicate that having an abnormal non-HDL-C is a specific risk factor for developing MetS in men taking SGAs, but not in women. In a large epidemiological cohort study with a non-obese Japanese population (Noda et al. 2010), similar evidence showed that elevated non-HDL-C was associated with a higher risk of mortality from CVD in men, but not in women. Because the Japanese population is ethnically similar to our sample, their results may be comparable.

The non-HDL-C level has been supported as a surrogate predictive marker for atherosclerosis (Sniderman and Kwiterovich 2013), ischemic stroke (Wu et al. 2013), and MetS (Huang et al. 2008; Stroup et al. 2011). The non-HDL-C level is superior to the LDL-C level as a risk assessment tool because of its predictive accuracy and ease of measurement. Estimating the non-HDL-C level requires only measurements of total cholesterol (TC) and HDL-C. We therefore propose that the relatively easy-to-measure non-HDL-C level should be monitored for developing MetS in men with schizophrenia. However, the relationship of very-low-density lipoprotein (VLDL)-C to TG needs to be considered, in particular because of the high day-to-day variability of TG and the non-Gaussian distribution of TG concentrations.

We also found a higher but nonsignificant prevalence of MetS in men than in women. The possible mechanisms of the gender difference are as follows. First, men generally have more risk factors for developing atherosclerosis and metabolic abnormalities than do women (Hata and Kiyohara 2013). They are liable to have more unhealthy lifestyles, such as smoking, that contribute to developing MetS (Hata and Kiyohara 2013; Higashiyama et al. 2009). Second, there may be a gender difference in the cumulative effects of the progression of atherosclerosis because of the lag time in the advancement of dyslipidemia over a lifespan, and, in turn, its contribution to metabolic abnormalities. For example, non-HDL-C levels are lower in premenopausal women than in men of the same age group, which may delay the cumulative effects of developing atherosclerosis more in women than in men. Menopause may contribute a gender difference in metabolic risk (Hwang et al. 2006); however, there was no significant age interaction in women with and without MetS ($t=0.670$, $p=0.862$) in this study. Additional hormonal studies may be needed to clarify the reason for the gender difference in the association between increased non-HDL-C and MetS. In addition, although treatments with clozapine and olanzapine are associated with the greatest risk of clinically significant weight gain, diabetes mellitus, and dyslipidemia (Newcomer 2005), the risk of taking clozapine and subsequently developing MetS in this study was not higher than with other SGAs.

Our study has some limitations. First, the heterogeneous sample and its characteristics of the current study limit the generalizability of the findings because most patients were under 50 years old with long-term hospitalization, had late-onset schizophrenia without significant difference between two sexes, and were taking clozapine. In general, men have an earlier onset for schizophrenia. Second, the gender differences are not fully convincing because menopausal status, hormone levels, the distributions of concomitant physical diseases, and specific psychosocial factors were not comprehensively examined. Third, medication doses and familial risk factors or current treatments for MetS require additional investigations. Last, the cross-sectional design limited our ability to examine the temporal associations and causal relationships between the risk factors and the prevalence of MetS.

Conclusion

This cross-sectional study supported a greater prevalence of MetS in patients with schizophrenia taking SGAs than in the general population in Taiwan. A BMI≥24 and an abnormal non-HDL-C level were significantly associated with

developing MetS. Moreover, having an abnormal non-HDL-C level was a specific risk factor in men for developing MetS, but not in women. The development of specific interventions, such as monitoring BMI in both genders and the non-HDL-C level in men, is needed to identify and treat MetS early, and more attention should be paid to gender differences.

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