Correlations between Weight Changes and Lipid Profile Changes in Schizophrenic Patients after Antipsychotics Therapy

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- **Background:** In our previous study, we had identified strong associations between dyslipidemia and acute-phase schizophrenia during the 3-week study period. In this study, we further investigated the correlations between weight changes and lipid changes during this short period in Taiwan.
- **Methods:** During a 1-year period, the data of age, body mass index, antipsychotic drugs and fasting blood samples for serum lipid profiles were collected at baseline and endpoint of 3 weeks. The antipsychotic drugs used include haloperidol, loxapine, sulpiride, olanzapine, risperidone, and clozapine.
- **Results:** A total of 97 schizophrenia patients were enrolled in this study. The authors found that most antipsychotic drugs showed increased weight changes in Taiwanese patients. Using linear regression, the authors also found that the weight changes in patients taking clozapine had significantly negative correlation with HDL changes during the 3-week study period. However, no significant correlations between weight changes and lipid changes were noted in patients using other antipsychotic drugs.
- **Conclusions:** The results of this study showed that most antipsychotic drugs showed increased weight changes and schizophrenia patients using clozapine might have negative correlations between weight changes and HDL changes during a very short period. However, due to the limitation of the sample size, larger samples are needed to prove the results after controlling confounding factors. (*Chang Gung Med J 2007;30:26-32*)

Key words: antipsychotics, cholesterol, lipid, obesity, schizophrenia, weight change.

Patients with schizophrenia are prone to obesity due to positive and negative symptoms and overall sedentary lifestyle.⁽¹⁾ Weight gain has also been noted in patients taking antipsychotic medication.^(2,3) Allison et al. found that treatment using lower-potency conventional antipsychotics was associated with greater weight gain than treatment with higherpotency agents.⁽⁴⁾ The greater propensity for histamine H1 antagonism is thought to be the primary reason that lower-potency drugs were associated with greater weight gain than higher-potency agents.^(5,6) However, the atypical drugs clozapine, risperidone and olanzapine (weaker dopamine D2 antagonists) appear to have induced significant weight gain when compared with the more powerful agent haloperidol.⁽⁴⁾ In addition to histamine H1

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antagonism, 5-HT2c receptor,^(7,8) leptin^(9,10) and cytokines⁽¹¹⁾ also had an impact on weight gain induced by atypical antipsychotics. These factors have contribution to the control system which was implicated in the link between peripheral tissue, neuronal systems, insulin resistance, inflammation/ immunity, obesity and diabetes mellitus.⁽¹²⁾

Although many researchers have discussed the impact of antipsychotics on weight gain, dyslipidemia and metabolic disorders in Western countries,⁽¹³⁻¹⁶⁾ only two reports of obesity and weight gain have been noted in Chinese schizophrenia patients.^(17,18) Hsiao et al., in a cross-sectional naturalistic study, found that the prevalence of obesity among Chinese schizophrenia patients in Taiwan was higher than in the general population, and atypical antipsychotics other than olanzapine did not seem to be more closely associated with obesity or severe obesity compared with atypical antipsychotics.⁽¹⁷⁾ Lee et al. found that treatment using olanzapine was associated with significantly greater weight gain than treatment using risperidone in Chinese schizophrenia patients in Hong Kong, and that lower baseline body weight and body mass index were associated with greater weight gain in both olanzapine- and risperidone-treated subjects, respectively.(18)

Weight gain is generally associated with increases in fasting glucose and lipids.(19,20) Henderson et al. showed a significant correlation between weight gain and increased fasting cholesterol and triglyceride levels when controlled for time of exposure.⁽²¹⁾ Osser et al. showed a relationship between increased fasting triglycerides and weight gain for a group of olanzapine-treated patients.⁽³⁾ However, Meyer, in a retrospective study during a 1year period, reported that olanzapine therapy was associated with significantly greater increases in triglyceride (TG) and total cholesterol (TC) levels for non-geriatric adult patients than risperidone, and the increases were not correlated with changes in weight parameters.⁽²²⁾ No reports have mentioned the correlations of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, or the ratios of TC/HDL and LDL/HDL (atherogenic index) with the changes in weight parameters in patients with schizophrenia.

In our previous study, we identified strong associations between dyslipidemia and acute-phase

METHODS

Subjects and design

This 1-year prospective study, which took place from December 2002 through November 2003, was performed at the Chang Gung Memorial Hospital in Kaohsiung, Taiwan.

Ninety seven subjects with schizophrenia were enrolled from the psychiatric inpatients in the acute ward. The diagnosis of schizophrenia was established by one psychiatrist (Dr. Huang) using the semi-structured clinical interview for DSM-IV criteria.⁽²⁴⁾

Disease severity was assessed at baseline and endpoint, after 3 weeks of therapy, by the same psychiatrist using the Positive and Negative Syndrome Scale (PANSS).⁽²⁵⁾ The antipsychotic drugs used in this study included conventional antipsychotic drugs (e.g., 10-15 mg/day haloperidol, 800-1200 mg/day sulpiride, and 100-150 mg/day loxapine) and atypical antipsychotic drugs (e.g., 3-5 mg/day risperidone, 10-20 mg/day olanzapine, and 100-300 mg/day clozapine).^(17,26) The use of these drugs is common in the hospital, thus, the data could be compared with results of reports from Western countries. Patients were chosen to take anyone of these drugs unless they had received the drug before.

Fasting blood samples for serum lipid profiles of all participants were collected at baseline and endpoint during a 3-week period in the same laboratory.

The routine biochemistry, hematology and urine analysis examinations were performed to exclude the subjects with heart disease, liver disease, renal disease and hypercholedemia. None of them took any medication for at least 1 week before they entered into the study. All participants gave written informed consent after receiving a full explanation of the study.

Laboratory data

Serum lipid profiles, including TC, TG, LDL, HDL,VLDL cholesterol levels, and the ratios of TC/HDL and LDL/HDL (atherogenic index) were measured in the hospital laboratory using enzymatic determination (Liquid selective detergent, Daiichi Pure Chemicals, Tokyo, Japan). Blood samples were taken between 7:30 a.m. and 8:30 a.m. after the patients had fasted for at least 10 hours.

Statistical analysis

The weight changes of participants who were taking antipsychotic drugs during the 3-week period showed weight changes. Linear regression was used to calculate the correlations between weight changes and lipid profile changes in patients taking different antipsychotics (with the kg/week as the dependent variable, and changes of TC, TG, HDL, LDL, VLDL, TC/HDL and LDL/HDL as independent variables). All tests were 2-tailed. All statistical calculations were performed using SPSS version 10.0.

RESULTS

A total of 97 patients were enrolled in this study. The demographic data of age, baseline BMI, duration of illness, baseline total PANSS score and the data of weight changes/week and serum lipid changes are shown in Table 1. Some data had been published.⁽²³⁾ Of the 44 patients taking conventional antipsychotic drugs, we found increases of 0.0 kg/week for patients taking haloperidol (n = 18), 0.4 kg/week for patients taking sulpiride (n = 13), and 0.9 kg/week for patients taking sulpiride (n = 13). Of the 53 patients taking atypical antipsychotic drugs, we found increases of 0.8 kg/week for patients taking antipsychotic drugs, we found increases of 0.8 kg/week for patients taking antipsychotic drugs, we found increases of 0.8 kg/week for patients taking risperidone (n = 24), and 0.50 kg/week for patients taking clozapine (n = 14).

Table 2 shows the correlations between weight changes and lipid profile changes using linear regression. We found that patients taking clozapine had a significantly negative correlation (r = -0.779, p = 0.033) in HDL changes, but not in other lipid profile changes. We did not find weight changes to have any significant correlation with any lipid profile changes in patients taking either conventional or atypical antipsychotics drugs. Furthermore, we also did not find weight changes to have any significant correlation with any lipid profile changes in patients taking haloperidol, sulpiride, loxapine, risperidone or olanzapine.

DISCUSSION

In the results of studies in Western countries, during 10 weeks of treatment using conventional agents, the mean gain was 1.1 kg using the highpotency agent haloperidol.⁽⁴⁾ Those results were higher than our findings (0.1 kg over 3 weeks of treatment; 0.0 kg/week) and were also higher than the results of another study (0.5 kg over 14 weeks of treatment) in Taiwan.⁽²⁷⁾ We found increases of 1.0 kg during a 3-week period (0.4 kg/week) for patients taking loxapine, which is not consistent with the earlier reports of weight loss.^(4,28) We also found increases of 2.8 kg during a 3-week period (0.9 kg/week) for patients taking sulpiride.

Among patients taking atypical antipsychotics, Allison et al.⁽⁴⁾ reported increases of 4.45 kg with clozapine, 4.15 kg with olanzapine and 2.1 kg with risperidone during a 10-week period in Western countries. Our results showed increases of 1.6 kg (0.5 kg/week) with clozapine, 2.3 kg with olanzapine (0.7 kg/week) and 0.4 kg with risperidone during a 3-week period.

These results suggest the antipsychotic drugs most likely to influence weight changes in this study were sulpiride, olanzapine, clozapine, loxapine,

	Age (years)*	Sex ratio (F/M)	Baseline BMI (kg/m ²)*	Duration of illness (months)	Baseline Total PANSS Score	Weight change/ week (kg/week)	TC change (mg/dl)	TG change (mg/dl)	HDL change (mg/dl)	VLDL change (mg/dl)	LDL change (mg/dl)	TC /HDL change	LDL /HDL change
Total (n = 97)	32.3 ±9.4	47/50	23.8 ±4.7	65.3 ± 69.6	107.9 ± 10.2	0.5 ± 1.0	$4.2\pm\!29.2$	14.0 <u>+</u> 82.5	2.4 ±11.4	3.6 ±12.2	-2.8 ± 25.3	-0.2 ± 0.9	-0.3±0.8
Conventional drug	36.5 ±7.3	22/22	$23.4 \pm \!$	57.0 ± 62.4	106.4 ± 10.9	0.4 ± 1.1	$-0.9\pm\!\!28.1$	$-0.3 \pm\! 102.9$	$0.8 \pm \!\! 13.4$	1.8 ± 12.5	-5.5 ± 25.7	$-0.2\pm\!\!0.7$	-0.2±0.5
(n = 44)													
Atypical drug	33.5 ±10.2	25/28	$24.0 \pm \!$	72.3 ± 74.9	109.3 ± 10.5	0.5 ± 1.0	$8.4\pm\!29.7$	$25.8\pm\!\!59.0$	3.7±9.4	5.2 ±11.8	-0.5 ± 24.9	$-0.2\pm\!1.0$	-0.3 ± 1.0
(n = 53)													

Table 1. Demographic Data and the Data of Weight and Serum Lipid Changes in Patients during a 3-week Period

Abbreviation: BMI: body mass index; PANSS score: positive and negative syndrome scale score; *: some data were noted in reference 23.

	TC change	TG change	HDL change	VLDL change	LDL change	TC/HDL	LDL/HDL
	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)	(mg/dl)	change	change
$\overline{\text{Total}(n=97)}$						0	
r value	0.498	0.498	0.498	0.498	0.498	0.498	0.498
<i>n</i> value	0.762	0.591	0.937	0.112	0.674	0.448	0.664
Conventional drug $(n = 44)$	0.702	0.071	0.707	0.112	0.07.1	01110	0.000
<i>r</i> value	0.355	0.355	0.355	0.355	0.355	0.355	0.355
<i>p</i> value	0.909	0.758	0.584	0.330	0.727	0.634	0.630
Haloperidol $(n = 18)$							
<i>r</i> value	0.751	0.751	0.751	0.751	0.751	0.751	0.751
<i>p</i> value	0.106	0.095	0.144	0.107	_	0.563	0.528
Sulpiride $(n = 13)$							
<i>r</i> value	0.558	0.558	0.558	0.558	0.558	0.558	0.558
<i>p</i> value	0.745	0.724	0.625	0.714	0.584	0.934	.839
Loxapine $(n = 13)$							
<i>r</i> value	0.684	0.684	0.684	0.684	0.684	0.684	0.684
<i>p</i> value	_	0.542	0.585	0.192	0.245	0.298	0.277
Atypical drug $(n = 53)$							
<i>r</i> value	0.632	0.632	0.632	0.632	0.632	0.632	0.632
<i>p</i> value	0.337	0.400	0.700	0.319	_	0.585	0.833
Risperidone $(n = 24)$							
<i>r</i> value	0.779	0.779	0.779	0.779	0.779	0.779	0.779
<i>p</i> value	0.195	0.491	0.229	0.421	_	0.561	0.792
Olanzapine $(n = 15)$							
<i>r</i> value	0.862	0.862	0.862	0.862	0.862	0.862	0.862
<i>p</i> value	0.448	0.171	0.150	0.156	_	0.725	0.959
Clozapine $(n = 14)$							
r value	0.779	0.779	0.779	0.779	0.779	0.779	0.779
p value	0.074	0.910	0.033*	0.767	_	0.854	0.351

Table 2. Correlations between Weight Changes and Lipid Profile Changes after Taking Antipsychotics during a 3-week Period

Abbreviations: *r* value: with the kg/week as the dependent variable, and changes of TC, TG, HDL, LDL, VLDL, TC/HDL and LDL/HDL as independent variables; *: p value < 0.05; some data were noted in reference 23.

risperidone and haloperidol. Thus, not only did olanzapine and clozapine induce severe weight changes in Taiwanese, but also sulpiride. In fact, the weight gain induced by sulpiride was noted in other reports,^(17,29) and the related mechanisms were also discussed.^(30,31)

The result of some studies have shown that weight gain is generally associated with increases in lipids,^(3,19-21) but other results have not supported this finding.^(22,32) Meyer found that olanzapine may have direct effects on serum lipids and fasting glucose independent of their effects on weight and BMI.⁽³²⁾ Our data showed that only patients taking clozapine had negative correlations between weight changes and HDL level changes, and not patients taking olanzapine, risperidone, sulpiride, loxapine or haloperidol. However, these results might be due to increased

Type I error. Finally, no correlation between weight changes and other lipid profile changes were found in any of the patients taking any kind of antipsychotics in our study.

In past studies, the authors showed that Taiwanese psychiatric patients have combined dyslipidemia in acute phases.^(23,33,34) They are at high risk of developing coronary heart disease.⁽³⁵⁻³⁸⁾ In this study, we found that both conventional and atypical antipsychotics had great effects on weight changes in Taiwanese schizophrenia patients during a 3-week period. This suggests that the baseline screening and follow-up monitoring in weight changes and lipid profile are essential to assess the likelihood of developing cardiovascular disease, diabetes, or other complications.

In conclusion, in this study we identified that

the weight changes and lipid profile changes appeared during a very short study period. Prospective long-term follow-up studies in weight changes should be done as soon as possible to prevent the development of metabolic disease and heart disease. However, this study had some limitations including sample size, diet and other confounding factors which might have influenced lipid profile levels. In the future, larger samples are needed to prove the results after controlling confounding factors.

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精神分裂症病人在使用抗精神病藥物後其體重變化 與脂質變化之相關性

黄條來1,2 盧俊源1

- **背 景**: 吾等先前的研究指出精神分裂症病人在3星期内即可發生脂質異常。而在此研究中 我們將進一步調查在這短期間內體重變化與脂質變化之相關性。
- **方法**: 在一年的期間內,研究個案的年龄、身體指數、使用的抗精神病藥物、治療 3 星期 前後的空腹的脂質濃度。使用的抗精神病藥物包括 haloperidol, loxapine, sulpiride, olanzapine, risperidone 與 clozapine。
- 結果:共有97個精神分裂症病人加入此研究。我們發現大部分的抗精神病藥物在3星期內 皆會引起體重增加。而線性迴歸的統計分析更指出使用 clozapine 的病人其體重變化 與高密度脂蛋白濃度的改變量有顯著的負相關。但服用其他抗精神藥物與其他脂質 成分之間並無顯著的相關性。
- 結論:這研究成果顯示大部分的抗精神病藥物在3星期內皆會引起體重增加,且使用 clozapine 的病人其體重變化與高密度脂蛋白濃度的改變量有顯著的負相關。然仍需加大 個案數以證實此結果。 (長康醫誌 2007;30:26-32)
- **關鍵詞**:精神分裂症,膽固醇,脂質。

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