Changes in High-density Lipoprotein and Homeostasis Model Assessment of Insulin Resistance in Medicated Schizophrenic Patients and Healthy Controls

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Background: This study intended to simultaneously investigate the relationships between high-density lipoprotein (HDL) and homeostasis model assessment of insulin resistance (HOMA-IR) in medicated schizophrenic patients vs healthy controls.

Methods: During a 1-year period, we recruited 37 medicated schizophrenic patients and 30 healthy controls. Metabolic syndrome-related biomarkers including insulin and lipid profiles were enzymatically determined.

Results: An analysis of covariance (ANCOVA) with BMI adjustment revealed that the patients had significantly lower HDL levels than the healthy controls (p = 0.017). ANCOVA with age adjustment revealed that the patients had significantly higher fasting insulin levels than the healthy controls (p = 0.034). In addition, in comparison with the healthy controls, the patients had higher mean serum levels of triglycerides, low-density lipoprotein, and total cholesterol as well as higher HOMA-IR values. However, there were no significant differences in any marker in the ANCOVA analysis after adjustment for age or BMI.

Conclusion: We found lower HDL and higher insulin levels in medicated schizophrenic patients than in healthy controls.

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Key words: high-density lipoprotein (HDL), HOMA-IR, insulin, schizophrenia

Schizophrenic patients receiving antipsychotic treatment may be highly prone to metabolic disorders such as weight gain, dyslipidemia and insulin resistance.[1] The roles of metabolic syndrome-related biomarkers including leptin, ghrelin, C-reactive protein, interleukin-6, tumor necrosis factor-α, resistin and adiponectin have been previously reported.[2-6]

It has been reported that high-potency conventional antipsychotic drugs (e.g., haloperidol) and atypical antipsychotic drugs (e.g., ziprasidone, risperidone and aripiprazole) are associated with a lower risk of hyperlipidemia. In addition, low-potency conventional antipsychotic drugs (e.g., chlorpromazine and thioridazine) and atypical antipsychotic drugs (e.g., quetiapine, olanzapine and clozapine) are also associated with a higher risk of hyperlipidemia.[7] In schizophrenic patients taking atypical antipsychotic drugs, strong associations have been

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reported between dyslipidemia and acute-phase schizophrenia and between dyslipidemia and responders. Both associations might increase the risk of diabetes and coronary heart disease in these patients.[8]

Second generation antipsychotics (olanzapine and clozapine) have been highly associated with metabolic dysregulation, including significant weight gain, with concomitant increases in homeostasis model assessment of insulin resistance (HOMA-IR) values, and levels of insulin, total cholesterol and triglycerides.[9] Normal-weight patients with schizophrenia treated with atypical antipsychotics had higher peak glucose levels, peak insulin levels, and HOMA-IR values than schizophrenic patients treated with conventional antipsychotic drugs.[10] Cytochrome P450 CYP1A2 (variants 1C and 1D) may be associated with higher serum clozapine levels and an increased risk of developing insulin and lipid elevations and insulin resistance in clozapine-treated patients.[11]

In the present study, we aimed to simultaneously evaluate the differences in serum insulin, lipid, and lipoprotein concentrations in healthy controls and in schizophrenic patients who continued therapy with the same antipsychotic drugs for at least 3 months in Taiwan.

METHODS

Patients and design

This study was performed at Chang Gung Memorial Hospital in Taiwan from January 2008 to December 2008. Institutional Review Board (IRB) approval was obtained from the Ethics Committee of the Chang Gung Memorial Hospital in Taiwan. All participants gave their written informed consent after receiving a full explanation of the study.

A total of 37 patients with schizophrenia (21 women and 16 men) with a mean age of 40.2 ± 12.5 years and a mean body mass index (BMI) of 24.3 ± 3.7 kg/m^2 were treated at Chang Gung Memorial Hospital. All patients were diagnosed with schizophrenia according to DSM-IV criteria and the patients included in the study did not have other psychiatric disorders. Physical examinations were performed to rule out significant physical illnesses including acute or chronic infections and inflammatory or immune disorders. Patients with comorbid axis I disorders, including substance abuse, were excluded from the study. All patients (n = 37) continued therapy with the same antipsychotic drugs for at least 3 months (n = 1: haloperidol, sulpiride, ziprasidone, amisulpride, and aripiprazole; n = 2: flupenthixol and quetiapine; n = 8: clozapine; n = 10: olanzapine and risperidone).

The control group included 30 healthy subjects (17 women and 13 men) with a mean age of 27.7 ± 5.0 years and a BMI of 21.9 ± 2.8 kg/m^2 who were recruited from the staff at Chang Gung Memorial Hospital. Those who had any personal or family history (first degree relative) of mental disorders were excluded from this study. All subjects in the control group were free of psychotropic medication and anti-inflammatory medication.

Laboratory data

For biochemical analyses, blood samples were collected between 6:00 A.M and 8:00 A.M after overnight fasting. Serum insulin (Bi-insulin IRMA, Schering Cis-Bio International, France) and lipid and lipoprotein concentrations, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), were enzymatically determined in the laboratory of the authors' hospital using enzymatic determination (Liquid Selective Detergent, Daiichi Pure Chemicals, Tokyo, Japan). The HOMA-IR was calculated as the fasting insulin concentration (mU/mL) x fasting glucose concentration (mg/dL) x 0.0555 /22.5.

Statistical analysis

Data analysis was performed using analysis of covariance (ANCOVA) with age or BMI adjustment to evaluate the differences between groups for all markers. An α value of $p < 0.05$ was considered to be statistically significant.

RESULTS

The patient data, serum lipid levels, and HOMA-IR of 67 participants (37 patients with schizophrenia and 30 subjects in the healthy control group) are shown in Table 1.

The schizophrenic patients had lower mean serum HDL levels than the healthy controls (53.4 ± 13.8 vs. 66.1 ± 14.4 mg/dL). Using ANCOVA with BMI adjustment, significant differences were

Table 1. Biomarker Levels of Participants (mean ± standard deviation)

	Control (n = 30)	Schizophrenia (n = 37)
BMI (kg/m^2)	21.9 ± 2.8	24.3 ± 3.7
Fasting insulin (mU/L)	7.4 ± 3.6	8.4 ± 6.4
Fasting glucose (mg/dL)	82.7 ± 9.5	101.2 ± 31.7
HDL (mg/dL)	66.1 ± 14.4	53.4 ± 13.8
LDL (mg/dL)	99.2 ± 21.0	111.4 ± 43.3
TG (mg/dL)	76.9 ± 39.0	127.1 ± 62.4
TC (mg/dL)	180.7 ± 23.6	185.0 ± 50.5
HOMA-IR index	1.5 ± 0.8	2.1 ± 1.6

Abbreviation: BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglycerides; TC: total cholesterol; HOMA-IR: homeostasis model assessment of insulin resistance. HOMA-IR was calculated as the fasting insulin concentration (mU/mL) × fasting glucose concentration (mgl/dL) × 0.0555 /22.5.

observed in serum HDL concentrations between the patients and healthy controls (F = 6.055; df = 1, 65; p = 0.017). On the basis of the ANCOVA after age or BMI adjustment, no significant differences were found in the lipid concentrations of LDL, TG, and TC between the patients and healthy controls (data not shown).

In addition, the schizophrenic patients had higher mean serum insulin levels than the healthy controls (8.4 ± 6.4 vs. 7.4 ± 3.6 mU/L). The age-adjusted ANCOVA also revealed significant differences in mean serum fasting insulin levels between the patients and healthy controls (F = 4.694; df = 1, 65; p = 0.034) but revealed no significant differences in the 2 groups after BMI adjustment.

Compared with the healthy controls, the schizophrenic patients had a higher mean HOMA-IR value (2.1± 1.6 vs. 1.5 ± 0.8). ANCOVA with adjustment for age (F = 3.355; df = 1, 65; p = 0.072) and BMI (F = 3.077; df = 1, 65; p = 0.084) revealed marginally significant differences between the patients and the healthy controls.

DISCUSSION

The first major finding of this study was that the HDL levels of the patients and healthy controls were significantly different in ANCOVA after BMI adjustment. This result is consistent with a previous study.[12] However, there were no significant differences in the serum concentrations of TG, LDL, and TC between these two groups using ANCOVA with BMI adjustment. These results are inconsistent with a previous study.[7] One study showed a greater risk of new HDL abnormality in olanzapine-treated patients than in risperidone-treated patients.[13] In some previous reports, atypical antipsychotics were associated with decreased HDL concentrations without changes in LDL, TC, or TG.[14-18] It has been reported that a lower prevalence of obesity and dyslipidemia in drug-naïve first-episode psychosis patients than in healthy controls suggests that obesity and dyslipidemia are effects of antipsychotic drugs.[19] Low serum HDL concentration may be related to lipase concentration. In some reports, antipsychotics were thought to affect serum lipase concentrations.[20-22] The pharmacological mechanism of action of antipsychotics on dyslipidemia has not yet been determined.[23] Because of the small sample size and heterogeneous medications of the patients in this study, the effects of dyslipidemia related to antipsychotics need further investigation.

The second major finding of this study was that insulin levels were significantly different between patients and healthy controls using age-adjusted ANCOVA. In addition, schizophrenic patients had higher mean serum insulin levels than healthy controls. Serum insulin levels in schizophrenic patients have been found to be markedly increased compared with those in a control population.[24] One report showed that drug-naïve first-episode psychosis patients with schizophrenia did not show a higher prevalence of diabetes precursors (impaired fasting glucose, impaired glucose tolerance, and insulin resistance) than healthy controls.[25] However, another report showed that antipsychotic-naïve schizophrenic patients have significantly higher mean plasma insulin levels than healthy controls.[26] In addition, this study revealed marginally significant differences in HOMA-IR between patients and healthy controls using ANCOVA with BMI adjustment. In previous reports, high HOMA-IR values were associated with antipsychotic drugs.[27-30] However, the mechanism of action of antipsychotic drug-associated insulin resistance remains unknown.

There were several unexplained factors and unsatisfactory results in this study because of the small sample size and heterogeneous medication of the patients; therefore, a larger sample of patients with homogenous medication, along with adequate statistical methods, is required to confirm these preliminary results.

Conclusion

Our data revealed significant changes in serum HDL in schizophrenic patients who received antipsychotic drug therapy. Significantly lower levels of HDL in medicated schizophrenic patients might be related to an antipsychotic-induced metabolic effect. The mechanisms underlying the effect of antipsychotic drugs on the production of metabolic-related biomarkers are still unknown. Further research is needed to investigate the relationships between HDL, lipase, and antipsychotic drugs.

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比較 HDL 和 HOMA-IR 在使用抗精神病藥物的精神分裂症病人和健康控制組之間的變化

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背 景： 在此研究中，測量高密度脂蛋白 (HDL) 和 HOMA-IR 的血清濃度在使用抗精神病藥物的精神分裂症病人和健康控制組之間的比較。

方 法： 研究對象有 37 位使用藥物治療的精神分裂症個案和 30 位健康個案。在精神分裂症個案和健康個案，同時使用酵素分析法測量高密度脂蛋白和 HOMA-IR 的血清濃度。

結 果： 使用 ANCOVA 合併 BMI 校正下，高密度脂蛋白的血清濃度在精神分裂症的個案和健康個案組的比較呈現較低濃度且有統計上的意義 ($p = 0.017$)。使用 ANCOVA 合併年齡校正下，空腹胰島素的血清濃度在精神分裂症的個案和健康個案的比較呈現較高濃度且有統計上的意義 ($p = 0.034$)。此外，精神分裂症個案的三酸甘油脂、低密度脂蛋白和總膽固醇血清濃度平均值比健康個案組高。然而，三酸甘油脂、低密度脂蛋白和總膽固醇在 ANCOVA 合併 BMI 校正或年齡校正，在精神分裂症的個案組和健康個案組並無統計上的意義 ($p > 0.05$)。

結 論： 低高密度脂蛋白血清濃度和高胰島素血清濃度在使用藥物治療的精神分裂症個案和健康個案的比較有統計上的意義。

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關鍵詞： 高密度脂蛋白，HOMA-IR，胰島素，精神分裂症

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