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ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 32 (2008) 925–931
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Metformin for metabolic dysregulation in schizophrenic patients treated with olanzapine

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Received 10 August 2007; received in revised form 5 November 2007; accepted 7 November 2007
Available online 17 November 2007

Abstract

The second generation antipsychotic drugs, such as risperidone, olanzapine, and quetiapine, are effective in treating patients with schizophrenia and have been considered as the first line therapy. Recently, increasing attention has been drawn to the potential diabetogenic effect of these novel antipsychotics. The goal of this study was to evaluate the effect of metformin treatment on the olanzapine-induced metabolic disturbance in schizophrenic patients. Twenty-four schizophrenic subjects who had received olanzapine treatment at least 3 months were assigned to the therapy with metformin 1500 mg/day for 8 weeks. The metabolic parameters were quantitatively assessed at baseline, weeks 2, 4, and 8 by using the intravenous glucose tolerance test. After an 8-week treatment with metformin, the body weight, fasting levels of glucose, triglyceride, and insulin, insulin secretion, and insulin resistance significantly decreased. Half of study subjects with metabolic syndrome obtained improvement after the metformin trial. Subjects' psychopathological condition remained unchanged during the study period. The olanzapine-induced metabolic disturbance could be reversed after 8-week metformin treatment. Based on the results of this study, we hypothesize that metformin could modulate the effect of olanzapine-induced metabolic disturbance.

Keywords: Insulin resistance; Metabolic syndrome; Metformin; Olanzapine; Schizophrenia

1. Introduction

The second generation antipsychotic drugs (SGAs), such as olanzapine, risperidone, quetiapine, and ziprasidone, are effective in treating both the positive and negative symptoms of schizophrenia (Kelleher et al., 2002). These advantages have led to an increasing use of SGA as the first line therapy for schizophrenia. However, SGAs have been linked to several forms of morbidity, including obesity, hyperlipidemia, and type 2 diabetes mellitus (Bergman and Ader, 2005; Jin et al., 2004; Melkersson and Dahl, 2004). Compared with the general population, the life expectancy of schizophrenic patients is shorter by as much as 20%, due to higher rates of suicide, accidental deaths, and natural causes such as cardiovascular disease and diabetes (Harris and Barraclough, 1998). Several studies have suggested that these metabolic abnormalities may lead to a greater vulnerability to cardiovascular disease and thus may contribute to the excessive mortality among schizophrenic patients (Casey et al., 2004; Goff et al., 2005; Simpson and Tsuang, 1996).

Abbreviations: SGA, second generation antipsychotics; IVGTT, intravenous glucose tolerance tests; CGI, Clinical Global Impression-Severity of Illness scale; GAF, Global Assessment of Functioning Scale; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA, homeostasis model assessment.

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doi:10.1016/j.pnpbp.2007.11.013

Olanzapine, along with clozapine, has the greatest propensity of all available SGAs to induce weight gain and metabolic dysregulation (Allison et al., 1999; Baptista et al., 2002; Ciudad et al., 2005; Jin et al., 2004; Lambert et al., 2006). The underlying pathophysiological mechanisms of these metabolic disturbances associated with SGA treatment have not been clarified. The mechanisms of SGA induced metabolic disturbance are likely to be multi-factorial and to involve both peripheral and central factors. Among peripheral factors, glucoregulatory abnormalities probably play an important role (Elman et al., 2006; Newcomer, 2004). Deterioration of insulin effects on target tissues (insulin resistance) is often a key pathogenic factor underlying the metabolic dysfunction.

Lifestyle modifications have been applied successfully for the control of weight and metabolic dysregulation in several population-based studies in which predominantly self-referred, highly motivated, non-psychotic subjects were included (Knowler et al., 2002). Recent studies suggest that behavioral interventions in schizophrenic patients may prevent future weight gain, and in some instances promote weight loss (Bushe et al., 2005; Loh et al., 2006; McKibbin et al., 2006). However, patients with schizophrenia are difficult to successfully institute behavioral and dietary modifications. Hence, effective pharmacological strategies are urgently needed to assist an optimal control of metabolic disturbance during olanzapine treatment.

Metformin, which is prescribed for patients with non-insulin-dependent diabetes to control blood glucose levels, has been reported to achieve weight loss in several groups of patients with insulin resistance (Glueck et al., 2001; Velazquez et al., 1994). Several studies evaluated the effects of metformin on antipsychotics-induced weight gain. In the first, a crossover, placebo-controlled study, metformin was ineffective in reversing weight gain induced by antipsychotics in five adult schizophrenic patients (Baptista et al., 2001). In the second, an open-label study, metformin significantly decreased body weight in 19 pediatric patients taking psychotropic drugs (Morrison et al., 2002). In the third, a double-blind, placebo-controlled study, metformin did not prevent the olanzapine-induced weight gain after 14-week trial (Baptista et al., 2006, 2007b). In the fourth, a 16-week double-blind placebo-controlled trial revealed that metformin is safe and effective in treating the weight gain and insulin resistance associated with the antipsychotic use in children and adolescents (Klein et al., 2006). Recently, a double-blind, placebo-controlled study, metformin safely helped the olanzapine-treated patients in body weight and carbohydrate metabolism after 12-week trial (Baptista et al., 2007a). Inconsistencies in the effect of metformin on the changes of metabolic variables are noted.

The present study was aimed to assess the reversal effect of metformin on metabolic disturbance induced by olanzapine among schizophrenic patients. The intravenous glucose tolerance test (IVGTT) is a well-established method for assessing glucose metabolism and has been widely used in the medical fields of diabetes and obesity research. A prospective design was chosen to allow clarify the time course of metabolic changes during metformin treatment.

2. Methods

2.1. Study subjects

This open-label, prospective, multi-center study was conducted in four hospitals in Taipei, Taiwan. The facility's institutional review board approved this study. After providing a description of the study to the patients, written informed consent was obtained. Those male or female inpatient subjects were 18–60 years. They had fasting glucose level of 126 mg/dL or less and did not have personal or family history of diabetes. Clinical interview, screening studies, physical and neurological examinations, and laboratory tests were administered, and medical record review for history and recent laboratory values were conducted to determine eligibility for study enrollment. The Structured Clinical Interview for DSM-IV was conducted for the diagnosis. All enrolled patients fulfilled the DSM-IV diagnosis of schizophrenia and received olanzapine treatment for at least 3 months. Subjects were excluded for axis I disorder except schizophrenia; current substance abuse; medical conditions that could confound glucoregulatory assessment, including diabetes mellitus and other endocrine diseases; severe cardiovascular, hepatic, or renal diseases; malignancy; epilepsy; or pregnancy. A urine pregnancy test was performed before the study for female subjects of childbearing potential. Medications (e.g., lithium, carbamazepine, valproic acid, propranolol, tricyclic antidepressant, or SSRI) that may influence body weight, glucose/lipid metabolism, or drug disposition were not allowed.

2.2. Study design

The olanzapine dosage was maintained unchanged during the study period. Subjects received metformin 1500 mg/day for 8 weeks. Glucose metabolism was studied using intravenous glucose tolerance tests (IVGTT). Before the baseline IVGTT, subjects were admitted to an inpatient facility for diet stabilization with an isocaloric diet (25–35 kcal/kg) before and during the active treatment period. Subjects' activities provided by the hospitals did not change during the study process.

2.3. Clinical assessment

The study was carried out in an inpatients setting. Drug safety was rigorously evaluated by the investigators at baseline and during the period of the metformin administration. Daily vital signs were measured. Subjects were weighted with a digital electronic scale, and weight was recorded to the nearest 0.1 kg. Physical and neurological examinations were repeated weekly. The subjects were assessed for general psychopathology every 2 weeks using Clinical Global Impression-Severity of Illness scale (CGI-S) (Guy, 1976) and the Global Assessment of Functioning Scale (GAF; DSM-IV, axis V) (American Psychiatric Association, 1994). The Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987) was used biweekly for monitoring both extrapyramidal symptoms and other side-effect profiles. The clinical assessment and the UKU Side Effect Rating Scale were performed by a research psychiatrist throughout.

Electrocardiogram (ECG), urinalysis, and biochemistry were checked at baseline and weeks 2, 4, and 8.

The laboratory tests were performed in the morning after an overnight fast both before and 2, 4, and 8 weeks after the start of metformin. Glucose (0.5 g/kg body weight) was administered intravenously. Blood samples for measurement of glucose and insulin were taken from the opposite arm at $t=-15$, 0, 5, 10, 15, 20, 30, 40, 50, and 60 min (Duijnhoven et al., 2001; Lehtovirta et al., 2005). Insulin secretion, the secretion response to a glucose load, was calculated as area under the curve using a linear trapezoidal technique from the serum value at each time point after subtraction of the $t=0$ value (increment).(Duijnhoven et al., 2001) The glucose disappearance rate (k_G) was calculated by linear regression from the log-transformed glucose values of $t=10$ to 30 min (Bergman and Ader, 1985). Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR: fasting glucose [mmol/L]*fasting insulin [mU/L]/22.5) (Matthews et al., 1985). The HOMA beta cell function (HOMA-B index) was calculated with the following formula: HOMA-B=(20*fasting insulin [mU/L])/(fasting glucose [mmol/L]−3.5) (Matthews et al., 1985).

In this study, we used the modified ATP III criteria for Asians to evaluate subjects for a diagnosis of metabolic syndrome (Tan et al., 2004). Three of the following 5 criteria were required: 1) abdominal obesity (waist circumference >90 cm, in men and >80 cm, in women); 2) fasting hypertriglyceridemia, (≥150 mg/dL); 3) low fasting high-density lipoprotein (HDL) levels (<40 mg/dL in men and <50 mg/dL in women); 4) high blood pressure (≥130/≥85 mm Hg or current treatment with antihypertensive medication); and 5) high fasting plasma glucose levels (≥110 mg/dL) or current treatment with antidiabetic medication. And we define diabetes mellitus as the fasting plasma glucose levels ≥126 mg/dL.

2.4. Laboratory assays

Laboratory assays were performed by the chemistry laboratory of Taipei Institute of Pathology. The serum levels of glucose, triglyceride, cholesterol, low-density lipoprotein (LDL), HDL were measured by using the Olympus AU400 chemistry analyzer. The plasma glucose level was measured with a hexokinase method. The plasma levels of triglyceride and cholesterol were measured with enzymatic colormetric method. Plasma HDL level was determined by homogeneous liquid selective detergent. Plasma low-density lipoprotein-cholesterol was calculated from the Friedewald equation (Friedewald et al., 1972). Plasma insulin and leptin were determined using the radioimmunoassay kit and quantified using a Packard Cobra Quantum Gamma Counter.

2.5. Statistical analyses

Descriptive statistics were represented as mean±SD. The Kolmogorov–Smirnov testing revealed the normality of distribution for the variables. Subgroups were compared using *t*-test for continuous variables and chi-square test for categorical variables. For all outcome measures, including body weight, BMI, and laboratory assessments, we analyzed the change from baseline by using a repeated-measures analysis of covariance, controlling for baseline. Bonferroni tests were used for post hoc comparisons. A *p*-value of less than 0.05 was considered to have statistical significance.

3. Results

3.1. Overall sample description

Thirty patients were screened for eligibility in this study. Six patients were excluded for refusal to participate ($N=3$), not meeting inclusion criteria ($N=2$), and uncooperativeness ($N=1$). Twenty-four patients (16 men, 8 women) were included in the study.

For the entire sample, the mean±SD age was 40.3±9.7 years. All subjects were Taiwanese and 16 (67%) were men. The mean durations of illness and receiving medication were 11.7±6.3 and 9.1±5.9 years, respectively. The mean duration of olanzapine treatment was 5.7±2.6 months. The mean dose of olanzapine was 11.5±3.0 mg/day.

3.2. Safety assessment

Most subjects were moderately symptomatic at baseline. After 8-week metformin comedication, the CGI-S and GAF scores remained steady (Table 1). No subjects experienced psychotic exacerbation during the study period.

Overall, the study procedure was well-tolerated, and subjects were able to complete all aspects of the study. The most prevalent treatment-emergent adverse events included nausea ($N=9$), asthenia ($N=6$), and diarrhea ($N=4$). These events were all mild and tolerable, and most of them disappeared spontaneously.

3.3. Metabolic assessment

The mean changes in body weight were −0.6±0.8, −1.4±1.3, and −2.2±1.8 kg at weeks 2, 4, and 8, respectively. The decrease in mean body weight and BMI over time reached statistical significance after 8 weeks of metformin treatment (Table 1). At week 8, changes in weight and BMI were −3.1% and −3.5%, respectively. The percentage of subjects that achieved a weight loss of 5% was 29.1% ($N=7$). The fasting glucose and triglycerides also significantly decreased at 8 weeks after metformin trial. No significant changes in the levels of total cholesterol, high-density lipoprotein, low-density lipoprotein, and leptin were detected during the treatment period.

Intravenous glucose tolerance test was performed at baseline and weeks 2, 4, and 8 of metformin treatment. The fasting insulin level significantly decreased at week 8. Compared with the baseline, the insulin secretion, beta cell function (HOMA-B index), and insulin resistance (HOMA-IR index) significantly decreased after 8 weeks of metformin trial. The glucose disappearance rate remained the same after 8-week metformin treatment.

There were 12, 10, 10, and 6 subjects met the criteria of metabolic syndrome at baseline, and weeks 2, 4, and 8, respectively. Prevalence of the individual metabolic syndrome criteria

Table 1
Demographic and biochemical parameters in schizophrenic patients treated with olanzapine and metformin

	Baseline	2-week	4-week	8-week
CGI-S	3.1±0.5	3.0±0.6	3.1±0.7	3.0±0.7
GAF	60.8±4.7	60.8±4.2	60.7±5.2	61.2±5.1
Body weight (kg)	71.6±9.5	71.0±9.6	70.2±9.2	69.4±8.9[a]
BMI	25.8±4.0	25.4±4.2	25.1±4.1	24.9±4.2[a]
Fasting glucose (mg/dL)	97.8±10.4	95.3±9.9	94.9±10.1	93.8±8.9[a]
Fasting insulin (mU/L)	17.8±9.5	17.3±8.8	16.5±10.5	14.1±11.0[a]
Triglyceride (mg/dL)	177.7±79.5	159.7±105.2[b]	151.7±78.5[b]	139.6±67.6[a]
Total cholesterol (mg/dL)	168.0±24.7	160.7±25.3	158.4±23.9	151.5±21.7
HDL	40.7±13.8	41.1±13.9	41.3±12.6	41.6±12.3
LDL	96.0±19.4	95.8±22.7	95.5±19.5	94.8±19.0
Leptin	11.0±6.5	10.9±7.3	10.8±8.3	10.5±7.4
Insulin secretion (mU*min/L)	5187±2096	4973±2177	4374±2134	3864±1963[a]
HOMA-IR (mmol*mU/L)	5.24±2.19	4.95±2.01	4.59±2.06	3.67±1.93[a]
HOMA-B	241.1±159.7	237.2±163.1	219.5±181.2	187.5±177.9[a]
Glucose disappearance rate (K_G) (mmol/L per min)	1.56±0.31	1.50±0.37	1.51±0.34	1.50±0.33

Abbreviations: CGI-S = Clinical Global Impression-Severity of Illness scale, GAF = Global Assessment of Functioning Scale, BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, HOMA = homeostasis model assessment, HOMA-IR = HOMA insulin resistance index, HOMA-B = HOMA beta cell function index.
All values are shown as mean±SD.
[a] Different from baseline, $p<0.01$.
[b] Different from baseline, $p<0.05$.

is displayed in Table 2. No statistical difference in the prevalence of metabolic syndrome or individual metabolic syndrome criteria was found. No subject met the criteria of diabetes mellitus during the study period.

3.4. Effects of gender

An additional analysis was performed to discriminate the effects of gender on the metabolic variables. At baseline, we did not detect any significant differences in the levels of fasting glucose, insulin, total cholesterol, high-density lipoprotein, and leptin between genders. But the levels of triglycerides and low-density lipoprotein were higher in women than in men at baseline. After 8-week metformin trial, the changes in body weight, BMI, and the levels of fasting glucose, insulin, triglyceride, total cholesterol, high-density lipoprotein, low-density lipoprotein, and leptin did not differ between the genders.

Table 2
Prevalence of metabolic disturbance in schizophrenic patients treated with olanzapine and metformin

	Baseline	2-week	4-week	8-week
Metabolic syndrome[a]	12 (50.0)	10 (41.7)	10 (41.7)	6 (25.0)
Abdominal obesity	7 (29.2)	7 (29.2)	7 (29.2)	6 (25.0)
Fasting hypertriglyceridemia	12 (50.0)	11 (45.9)	10 (41.7)	7 (29.2)
Low fasting HDL	8 (33.3)	7 (29.2)	7 (29.2)	5 (20.8)
High blood pressure	6 (25.0)	4 (16.7)	4 (16.7)	3 (12.5)
High fasting glucose	6 (25.0)	5 (20.8)	3 (12.5)	3 (12.5)

All values are expressed as N (%).
[a] Definitions of components of metabolic syndrome: 1. abdominal obesity (waist circumference >90 cm, in men and >80 cm, in women); 2. fasting hypertriglyceridemia, (≥150 mg/dL); 3. low fasting HDL levels (<40 mg/dL in men and <50 mg/dL in women); 4. high blood pressure (≥130/≥85 mm Hg or current treatment with antihypertensive medication); and 5. high fasting plasma glucose levels (≥110 mg/dL) or current treatment with antidiabetic medication.

4. Discussion

Olanzapine, along with clozapine, has the greatest propensity of all antipsychotics to induce weight gain and metabolic abnormality (Allison et al., 1999; Newcomer, 2005). Weight gain has been a barrier for patients' medication adherence and can increase their risk for future cardiovascular and other medical complications. Prevention and treatment of olanzapine-induced weight gain and metabolic dysfunction are a priority in clinical practice. In this open-trial study with comprehensive assessment of metabolic parameters, we found that metformin could attenuate olanzapine-induced weight gain, hyperlipidemia, and metabolic disturbance in schizophrenic patients.

The effects of metformin on the antipsychotics-induced metabolic disturbance in psychiatric patients were reported in limited numbers of studies (Baptista et al., 2001, 2006, 2007a,b; Klein et al., 2006; Morrison et al., 2002). The methodological difference makes the comparison between those studies difficult. In some studies, the investigators recruited adolescent sample or included subjects receiving different kinds of antipsychotic drugs for various diagnoses (Baptista et al., 2001; Klein et al., 2006; Morrison et al., 2002). Only in three studies, the effects of metformin in olanzapine-treated schizophrenic patients were assessed (Baptista et al., 2006, 2007a,b). However, those studies had discordant results in the changes of body weight, insulin sensitivity, and lipid profiles. The reason of inconsistent results warrants further investigation.

Out of the psychiatric field, metformin has been used in controlling weight and metabolic dysregulation for several decades. Most metformin studies have been conducted in subjects with type II diabetes, glucose intolerance, insulin resistance, polycystic ovary syndrome, or obesity (Hundal and Inzucchi, 2003). The mechanism of action of metformin involves inhibiting hepatic glucose production, improving peripheral glucose

disposal, reducing intestinal glucose absorption, and possibly ameliorating the effect of glucotoxicity and/or lipotoxicity on insulin action and insulin secretion by pancreatic beta cells (Hundal and Inzucchi, 2003). In several studies, metformin was found to decrease body weight, BMI, fasting levels of insulin, glucose, and total cholesterol, and to increase insulin sensitivity in obese but non-diabetic adults (Charles et al., 2000; Glueck et al., 2001; Kay et al., 2001). The clinical benefits and good safety record have made metformin a progressively used drug in insulin resistant states. The relevance of metformin therapy as a treatment for metabolic dysregulation induced by olanzapine was evident from the significantly high incidence of insulin resistance and its consequences identified in study subjects.

Consistent with previous study (Baptista et al., 2007a), the results of this study revealed that metformin treatment decreased body weight and BMI in non-diabetic schizophrenic subjects. A weight loss of 5% to 10% can bring considerable health benefits by improving or reversing obesity-related comorbidities and preventing the new diseases related to obesity (Pasanisi et al., 2001). Nearly one third of participated subjects achieved more than 5% weight loss in our study. Besides, metformin medication decreased insulin resistance, as indicated by HOMA-IR, and consequently decreased the insulin secretion in our subjects. The fasting insulin levels and fasting glucose also decreased significantly after metformin trial. These results showed that metformin therapy reversed olanzapine-induced abnormalities in glucose metabolism by decreasing insulin resistance.

The term "metabolic syndrome" refers to a clustering of specific cardiovascular disease and type 2 diabetes risk factors whose underlying pathophysiology is thought to be related to insulin resistance. Many studies have shown that subjects diagnosed with metabolic syndrome are at greater risk of developing cardiovascular disease. At baseline screening, the prevalence of metabolic syndrome in our sample (50%) was higher than the Taiwan population-based rate of 15.7% (Hwang et al., 2006). The finding of our study is consistent with previous studies of schizophrenic patients treated with antipsychotic drugs (Heiskanen et al., 2003; McEvoy et al., 2005). It is noteworthy that the prevalence of metabolic syndrome in our patients decreased from 50% to 25% after 8 weeks of metformin treatment. In Diabetes Prevention Program study, subjects' preexisting metabolic syndrome was resolved, though not statistically significant, after metformin treatment, and metformin also found to reduce the incidence of metabolic syndrome among subjects with impaired glucose tolerance (Orchard et al., 2005). Based on those evidences, we suggest that the effect of metformin to resolve metabolic syndrome in psychiatric patients is worth further exploration.

Sex dimorphism in leptin concentrations has been clearly shown in previous studies and its concentrations were found to be lower in men than in women (Sivitz et al., 2003; Gómez, 2007). The results of several studies showed that the gender-related differences in leptin regulation also exist in schizophrenic subjects (Arranz et al., 2004; Baptista et al., 2007b,c). Our results did not confirm this gender differences probably owing to our small sample size. Baptista et al. (2007a) reported that metformin administration could produce significant body weight loss and tend to decrease leptin levels among olanzapine-treated schizophrenic patients. But the results of our study showed the lack of leptin decrease in spite of significant weight loss. The relationships between antipsychotic medication, metformin, weight, leptin, and gender must be further clarified in larger sample and longer duration.

This study showed that metformin treatment was well-tolerated in schizophrenic patients. No severe adverse reactions could be attributed to the study drug in this 8-week trial. The clinical condition of subjects also remained stable during the study period. No outcome variables differed significantly during the trial period.

Some limitations of the current study warrant specific comment. First, it was an open-label study, and this study design is subject to the placebo effect. But the pattern of sustained changes in weight and metabolic parameters suggest that these changes were not solely due to the placebo effect. Second, in absence of placebo-controlled group in our study, we could not exclude that recruited patients had strong motivation to reduce body weight and change their lifestyle during the study period. But we have tried to minimize the influence through keeping their diet and activity unchanged. Third, the duration of metformin exposure employed in the study was relatively short. Most trials using metformin to reduce body weight in non-psychiatric fields lasted more than 8 weeks and some studies were extended up to 4 years to get more robust effect (Glueck et al., 2006). Fourth, data with the small sample size may limit the generalization of our findings. Fifth, the exclusion of other antipsychotic-treated subjects may also limit the generalization of this study. Sixth, different doses of metformin were not evaluated. Therefore, studies that include larger samples, subjects receiving different antipsychotics, and longer duration and different dose of metformin exposure will help to address these limitations in this study.

5. Conclusions

The current study demonstrates that metformin is safe and effective in reversing olanzapine-induced metabolic disturbance. Based on these results, we speculate that metformin may attenuate the olanzapine-induced metabolic dysregulation through improving insulin resistance. Further research should be conducted to establish the long-term efficacy of metformin as a preventive agent in psychiatric patients predisposed to medication-induced metabolic dysregulation.

Acknowledgments

This study was supported by grants from Taipei City Hospital, Taipei Institute of Pathology, Taipei Medical University (TMU94-AE1-B07), Taipei Medical University-Wan Fang Hospital (95TMU-WFH-10 and 96TMU-WFH-15), National Science Council (NSC-93-2314-B-532-007 and NSC-95-2314-B-038-065), and Department of Health, Executive Yuan (DOH96-TD-D-113-033), Taipei, Taiwan. Professor Winston W. Shen gave editing comments on this manuscript.

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