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Original Article

# Dysregulation of glucose metabolism since young adulthood increases the risk of cardiovascular diseases in patients with bipolar disorder

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**Abstract** Aging patients with bipolar disorder (BD) are at a high risk of cardiovascular diseases (CVDs). However, few studies have directly examined the association between metabolic risks and CVDs in patients with BD across the lifespan. Therefore, the aim of this study was to determine lifetime metabolic risk factors for CVDs in patients with BD. We recruited BD-I patients who were more than 50 years old and had had at least one psychiatric hospitalization. Patients who had a cardiologist-confirmed CVD diagnosis (ICD-9 code 401–414) were assigned to the case group. Fifty-five cases were matched with 55 control patient without CVDs based on age and sex. Clinical data were obtained by retrospectively reviewing 30 years of hospital records. Compared to control subjects, a significantly higher proportion of cases had impaired fasting glucose between ages 31 and 40 (44.0% versus 17.4%, $p = 0.046$), diabetes mellitus between ages 41 and 50 (25.6% versus 8.6%, $p = 0.054$), and diabetes mellitus after age 51 (36.3% versus 12.7%, $p = 0.005$). No significant difference was found in overweight, obesity, or dyslipidemia. After adjusting for years of education, first episode as mania, and second generation antipsychotic use, lifetime diabetes mellitus remained a risk factor for CVDs (OR = 4.45, 95% CI = 1.89–10.66, $p = 0.001$). The findings suggest that glucose dysregulation across the adult age span is probably the major metabolic risk contributing to CVDs in patients with BD. Clinicians therefore have to notice the serum fasting glucose levels of BD patients since young

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adulthood.



## Introduction

Bipolar disorder (BD) is a chronic and recurrent mental illness which usually first manifest in younger adulthood. Evidence suggests that when the illness extends into later life, adults with BD are at an increased risk of several unfavorable outcomes, such as functional decline, cognitive impairment, and increased medical burdens [1—3]. Furthermore, studies have indicated that patients with BD actually had a reduction in life expectancy by up to 20 years [4—9]. Given the greater medical burden and shorter lifespan in BD patients as compared with those in the general population, the International Society for Bipolar Disorders Task Force recently proposed that an age of 50 years should be considered the demarcation line identifying patients with BD being of older age [10].

Studies from both Western and Eastern countries have revealed that the premature mortality of BD is attributable not only to suicides and accidents but also to various medical conditions [4—9]. Of the medical conditions that contribute to early death in patients with BD, cardiovascular diseases (CVDs) have been increasingly recognized as the principal contributor [4—9]. Similarly, studies have indicated that patients with BD are vulnerable to metabolic risk factors such as obesity, diabetes mellitus, and dyslipidemia, with the first onset of such conditions occurring in young adulthood [11—13]. The possible mechanisms underlying the high cardiometabolic burden in patients with BD include the pathophysiology of BD itself, unhealthy behaviors associated with BD psychopathology, and the adverse effects of psychotropic medications [3,14,15].

Findings from previous studies have shown that Eastern patients with BD have lower levels of blood cholesterol and lower rates of dyslipidemia when compared with Western patients with BD [3,16—20]. Similarly, obesity has been found to be less severe in Eastern adults with BD [3,16,21]. By contrast, evidence suggests that the prevalence of diabetes mellitus is comparably high worldwide in patients with BD throughout the adult age span [17,20,22]. These findings may first reflect a racial difference in the CVD risk profiles of patients with BD. Second, because both CVDs and diabetes mellitus are highly prevalent in patients with BD from both Eastern and Western countries, these results may also suggest that glucose dysregulation is the major metabolic risk factor for CVDs in patients with BD. However, only a few studies have directly examined the association between metabolic risk factors and CVDs in patients with BD across the patients' lifespan.

In the present study, the aim was to determine the metabolic risk factors of CVDs in patients with BD across the adult age span. We hypothesized that the glucose dysregulation (e.g. diabetes mellitus and impaired fasting glucose) was the major metabolic risk factor contributing to CVDs in patients with BD during the aging process.

## Methods

### Study sample

All data used in this study were obtained from hospital records of the Taipei City Psychiatric Center (TCPC), Taipei, Taiwan. TCPC is a mental health center established in 1969 and is currently a teaching hospital affiliated with the Taipei Medical University. It provides comprehensive psychiatric services with 383 and 133 acute and chronic beds, respectively, for the Northern Taiwan catchment region which has a population of 7 million people. Using computerized data files from TCPC between January 1, 2006 and December 31, 2015, we initially identified 328 potential subjects based on the following criteria: (1) age 50 or older; (2) at least one psychiatric admission to TCPC because of a manic episode; and (3) a final diagnosis of The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) bipolar I disorder (BD-I) confirmed by at least one board-certified psychiatrist.

In order to obtain comprehensive data throughout the course of illness in patients with BD, we utilized 30 years of hospital records in this retrospective case—control study. At the TCPC, a case-note form contains more than 95 items which provide comprehensive sociodemographic data as well as information regarding the clinical features of psychiatric illness, concurrent physical illnesses, family history, and results of physical examinations and laboratory tests. The CVD categories used in this study included ischemic heart disease and hypertension (International Statistical Classification of Diseases and Related Health Problems, Ninth Revision codes 401—414), which are the principle causes of cardiovascular morbidity in patients with BD [23]. For each subject, the diagnosis of CVD was determined after reviewing the medical charts. The criteria for CVD diagnosis were as follows: (1) a definitive diagnosis of CVDs on the discharge note; (2) standard treatment for the CVDs lasting at least 6 months, or (3) significant physical or laboratory findings that supporting the diagnosis of CVDs as determined by a board-certified cardiologist.

A total of 67 patients with BD-I and comorbid CVDs were identified as case subjects. Each case subject was then matched with one patient with BD-I but without CVD as a control subject on the basis of age and sex. Because no suitable control was available for 12 case subjects, a total of 55 case subjects and their 55 matched controls were ultimately included in this study. Thirty-nine of case subjects and 35 controls had at least one psychiatric admission between age 41 and 50, and 25 of cases and 23 of controls

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