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**SERUM LIPIDS, METABOLIC SYNDROME AND LIFETIME SUICIDE ATTEMPTS IN PATIENTS WITH
BIPOLAR DISORDER**

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Abstract

Objective: Bipolar disorder is at high risk of suicide. Many clinical characteristics and, recently, biomarkers have been studied with the aim to find useful predictors of suicidality. The role of serum lipids has also been explored albeit with conflicting results; however, few studies have been focused on patients with bipolar disorder.

Aim of our study is to investigate whether serum cholesterol, triglycerides, HDL-c and metabolic syndrome are associated with lifetime suicide attempts in a large naturalistic sample of patients with bipolar disorder.

Methods: 220 patients with bipolar disorder were included. History of lifetime suicide attempts was systematically and retrospectively assessed for each patient. Blood exams testing total cholesterol, triglycerides, and HDL-c levels were performed, and metabolic syndrome was diagnosed according to NCEP ATP-III modified criteria. Serum lipid levels and metabolic syndrome were compared in patients with or without history of suicide attempt. According to a theory that links impulsivity and violence with low cholesterol, the association between lipid levels and violent suicidal behavior was also assessed.

Results: Lifetime suicide attempts rate was 32.3%. There were no statistically significant differences between patients with and without lifetime suicide attempts in cholesterol, triglycerides, HDL-c levels, and the prevalence of metabolic syndrome. No differences in the same variables were found in violent suicide attempters compared with nonviolent ones. Clinical characteristics such as gender, low education, higher number of manic and depressive episodes, and taking more medications for bipolar disorder were associated with lifetime suicide attempts.

Conclusions: Our results do not support the hypothesis of a strong association between serum lipid levels and suicide in patients with bipolar disorder.

Key words

Bipolar disorder; cholesterol; lipids; suicide attempts; metabolic syndrome

Introduction

Patients with Bipolar Disorder (BD) have an increased risk of suicide compared with patients with other Axis I disorders [1]. Individuals suffering from BD make at least one suicide attempt in their lifetime with a frequency ranging from 25% to 56% [2-4] and the death by suicide is an event occurring in 6-20% of cases [5-7].

There is extensive literature aiming at identifying possible markers of suicidality, especially biological ones. Recently, the role of serum lipids as biological markers of suicidality has been explored, focusing in particular on cholesterol levels, yet results are mixed and conflicting. Several studies have shown an association between low cholesterol levels and increased suicide risk [8,9]. Low cholesterol levels have been linked to suicide attempts [10-14] and suicidal ideation [15,16]. However, some studies have found no association between cholesterol and suicidal behavior [17-21] and few studies have found that suicidal patients had significantly higher cholesterol levels than non-suicidal patients [22,23]. This heterogeneity of results is most probably due to the disomogeneity of samples included in different studies. Indeed, some studies have been conducted on mixed samples of psychiatric patients, others on patients who committed suicide, while only a few studies have been performed on patients with specific diagnoses such as schizophrenia, mood disorders, alcohol dependence [12,24,25]. Finally, the definition of suicidal behavior is not straightforward and varies considerably among the studies, further complicating the comparability of the results.

Apart from cholesterol levels, the role of other serum lipids such as triglycerides and HDL as biomarkers for suicidality is also controversial, again due to the enrollment of mixed samples [18,25-29].

To date, only two studies have analyzed the association between suicidality and cholesterol and lipid levels specifically among patients with BD. One study [30] found a significant association between suicide attempts and lower cholesterol and triglyceride levels in a sample of 20 drug-free men with BD, while the other did not find any significant association between cholesterol levels and completed suicide in 43 patients with BD [31].

In order to further clarify the relationship existing between suicidal behavior and serum lipids in patients with BD, we compared total cholesterol, triglycerides, HDL-c levels and the prevalence of metabolic syndrome in a large naturalistic sample of patients with BD with or without lifetime history of suicide attempts.

Methods

Subjects

Subjects for this study were recruited from all patients with a principal diagnosis of Bipolar Disorder type I, II or NOS (DSM-IV) consecutively admitted to the Psychiatric Inpatient Unit and to the Mood and Anxiety Disorders Outpatient

Unit of the University of Turin (Italy) from January 2006 to March 2011. Potential participants were thoroughly explained aims and study procedures and had to give their consent before participation.

All subjects were of Caucasian Italian origin. Exclusion criteria included age < 18, pregnancy or postpartum and refusal to consent participating in the study.

Assessment and procedures

All diagnoses were confirmed by means of the Structured Clinical Interview for DSM Axis I Disorders (SCID-I) [32]. At study entry, socio-demographic information were collected for each subject. Clinical characteristics such as age at onset, duration of illness, number of previous manic/depressive episodes, psychiatric comorbidity, psychiatric family history and current medical and psychopharmacological treatments were ascertained either from clinical charts and by direct questioning the study participants.

History of suicidal behavior was retrospectively and systematically assessed for each patient. As recommended by the US National Institute of Mental Health a suicide attempt was defined as a self-destructive behavior with the intention of ending one's life, independently of the resulting damage [33]. According to the criteria of Traskman et al. [34], the suicide attempt method was defined as violent (e.g. firearm, hanging, jumping, car exhaust, drowning) or non violent (drug overdose or superficial phlebotomy).

A blood sample was drawn at approximately 07:00 am after an overnight fast. Blood exams included total cholesterol, glucose, triglycerides and HDL-c. Serum concentrations were examined in the "Baldi e Riberi" laboratory of analysis, San Giovanni Battista Hospital, Turin, Italy.

At index visit weight, height, BMI, waist circumference, and blood pressure were measured. Weight was measured undressed and fasting, height was measured barefoot. Waist circumference, measuring central adiposity, was taken at midway between the inferior margin of the ribs and the superior border of the iliac crest, at minimal respiration. Two blood pressure measurements were obtained by using a mercury sphygmomanometer: the first with the subject in a lying position, the second with the subject in a seated position at least two minutes after the first measurement. The mean blood pressure of the two measurements was used. The attending physician in hospital setting performed all procedures.

Metabolic syndrome was diagnosed according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III-modified criteria [35]:

- Abdominal obesity: waist circumference ≥ 102 cm in men and ≥ 88 cm in women
- Hypertriglyceridemia: ≥ 150 mg/dl or on lipid-lowering medication
- Low HDL-C: < 40 mg/dl in men and < 50 mg/dl in women

- High blood pressure: systolic pressure ≥ 130 mmHg and/or diastolic pressure ≥ 85 mmHg or on antihypertensive medication
- High fasting glucose: ≥ 100 mg/dl or on glucose-lowering medication

Statistical analysis

Subjects characteristics were summarized as mean and SD for continuous variables and frequency and percentage for categorical variables.

Patients were grouped according to whether they had a lifetime history of suicide attempts or they had never attempted suicide in their life. We excluded from the analysis those patients with current or previous cholesterol-lowering treatment.

Univariate analyses compared mean total serum lipid levels and frequency of subjects with metabolic syndrome among patients with history of suicide attempts compared with those without. Further, patients who had used a violent suicide method were compared with those who had attempted suicide with a non-violent method for the same characteristics. Between-group comparison of categorical variables were made with Pearson's Chi-square test. Continuous variables were compared by using Student's t test for two-class comparisons. We decided to use a 2-tailed significance level of $p < .05$.

Statistical analyses were conducted using the computer software Statistical Package for the Social Science, version 18.0 (SPSS Inc., Chicago).

Results

Two-hundred thirty-two patients with BD were asked to participate. Seven were <18 years of age, 5 refused their consent. Thus, 220 patients were enrolled in the study.

The mean age of the total sample was 49.0 ± 15.7 years (47.0 ± 15.8 in males and 50.5 ± 15.6 in females), 60.5% of the patients were females. The majority of the sample (58.6%) had bipolar II disorder; the mean age at onset of BD was 29.0 ± 12.8 years, the mean duration of illness was 20.0 ± 13.8 years. Patients were on a mean of 2.9 ± 1.2 medications for BD, 92.7% was on mood stabilizers medications, 46.8% on atypical antipsychotics and 53.6% was taking antidepressant treatment. In the total sample 71 patients (32.3%) reported a history of attempted suicide and twenty-six (11.8%) attempted suicide with a violent method. Violent suicidal attempts were jumping from heights ($n=9$), hanging ($n=5$), abdominal knife wounds ($n=4$), gunshot wounds ($n=3$), gas poisoning ($n=2$), car accident ($n=1$), others ($n=2$). In our sample, non violent method was drug overdose ($n=45$).

Nine patients had previously taken cholesterol-lowering medications and were therefore excluded from the subsequent analyses. Socio-demographic and clinical characteristics were not different between patients with or without lifetime suicide attempts, except for a higher number of previous manic (4.8 ± 5.8 vs 3.2 ± 3.0 , $p=0.032$) and depressive episodes (6.9 ± 6.7 vs 4.7 ± 4.7 , $p=0.016$) and a higher number of psychotropic medications (3.3 ± 1.3 vs 2.8 ± 1.3 , $p=0.013$) in attempters (Table 1).

There were no significant differences between attempters and non attempters in total serum cholesterol (192.5 ± 43.4 vs 190.1 ± 41.0 , $p=0.704$), triglycerides (138.6 ± 93.0 vs 126.3 ± 70.4 , $p=0.290$) and HDL cholesterol levels (52.9 ± 14.7 vs 51.8 ± 14.8 , $p=0.631$). Also, the prevalence of metabolic syndrome (20.9% vs 25.9%, $p=0.433$) and mean BMI (26.6 ± 5.0 vs 25.7 ± 4.8 , $p=0.220$) did not differ between attempters and non attempters. These results are shown in Table 2.

The suicide attempters' group was further analyzed according to whether they had employed a violent or a nonviolent suicide attempt. Table 3 shows differences in socio-demographic and clinical characteristics: there was a statistically significant difference between the two groups in sex distribution, with more women in the group of nonviolent suicide attempters than in the group of violent suicide attempters (81.4% vs 18.6%; $p<0.001$); on the contrary, men more frequently employed violent than nonviolent suicide attempts (64% vs 18.6%, $p<0.001$). Nonviolent attempt is also significantly associated to poorer education (11.3 ± 4.0 vs 13.3 ± 3.4 years, $p=0.037$). There were no significant differences within serum cholesterol (186.5 ± 45.0 vs 195.9 ± 42.5 , $p=0.392$), triglycerides (159.0 ± 116.7 vs 126.7 ± 74.9 , $p=0.168$), HDL cholesterol levels (52.1 ± 14.2 vs 53.3 ± 15.0 , $p=0.746$), prevalence of metabolic syndrome (20.8% vs 20.9%, $p=0.993$) and mean BMI (27.4 ± 5.2 vs 26.1 ± 4.8 , $p=0.283$) between violent and nonviolent suicide attempters (Table 4).

Discussion

This is the first study to evaluate the relationship between serum lipid levels, metabolic syndrome and suicide in a large sample of patients with BD. No differences were found in total serum lipid levels in BD patients with a history of suicide attempts compared to those without. This is in contrast to several previous studies illustrating that low cholesterol levels are associated to suicidal behavior. However, it is difficult to compare our results with others from the literature focusing on this hypothesis. Previous studies conducted to explain the potential association between lipid levels and suicidal behavior have produced conflicting results and to date it has been not clearly demonstrated a predictive role for cholesterol and lipid levels in suicide risk. This occurs for many reasons. First, suicidal behavior has been differently assessed among different studies: some have considered lifetime suicide attempts, other only recent suicide attempts, while others included just the presence of suicidal ideation. Second, most studies have employed

mixed samples of suicidal patients belonging to different diagnostic categories, without analyzing the effect of a specific diagnosis on the association.

Only two studies investigated the relationship between serum lipid levels and suicide in patients with BD. In the most recent one, Vuksan-Ćusa et al. [30] recruited 20 patients with BD and history of lifetime suicide attempt and compared them with 20 patients with BD without such a history. Authors found that cholesterol and triglycerides levels were lower in BD patients with a history of suicide attempts. This study included a little but extremely selected population of patients who were drug-naive for at least three months compared with an age-matched control group. In another study, cholesterol levels of 43 patients with BD who had committed suicide were compared with those of living individuals with BD (matched for age, gender and date of admission): the authors found no association between cholesterol levels and completed suicide [31]. This finding is in line with our results suggesting that cholesterol levels do not strongly correlate with suicide in BD.

Several studies suggest that serum cholesterol levels might be more likely linked to the violence of suicide attempt rather than to suicidality itself [36-38]. The mechanism that may link serum cholesterol with violent behavior and suicide is unclear, although the most credited theory states that low cholesterol levels may result in a reduction of central serotonergic activity [8,39], resulting in a poorer suppression of impulsive behaviors eventually leading to aggressive behavior and suicide [40,41]. The association between cholesterol levels and violent suicide attempts has been confirmed in studies including both individuals who attempted suicide from mixed diagnostic groups [36], and samples of psychiatric patients with schizophrenia [24,42] and depression [12]. To date, no study has investigated the association between cholesterol levels and violent suicidal behavior in patients with BD. In our study we did not find a significant difference in cholesterol and other serum lipid levels between violent and nonviolent suicide attempters.

There are possible explanations for the lack of correspondence between our results and literature data on the association of low cholesterol levels with suicidal behavior: since most suicide attempts occur during a depressive episode, it has been suggested that attempters may have less appetite and weight loss as a consequence of depressive symptoms which in turn results in a lower production of cholesterol [28]. Since in our sample patients with a history of suicide attempts have a higher number of depressive episodes than patients without a history of suicide attempts, we would expect similarly lower levels of serum cholesterol. However, depressive episodes in patients with BD more often present with atypical features such as hyperphagia and/or hypersomnia, that may eventually lead to excessive caloric intake and reduced energy expenditure, thus increasing lipid levels [43,44]. Furthermore, lipid levels in patients with BD could be also increased by the use of psychotropic medications, such as atypical antipsychotics and mood stabilizers [45,46]. The

increase in serum lipid levels in patients with BD due to such factors, may have masked the finding of low cholesterol levels in patients with lifetime suicide attempts.

Bipolar disorder is often associated with weight gain and other metabolic abnormalities leading to the occurrence of metabolic syndrome [47-50]. Regarding the possible relationship between metabolic syndrome and history of suicide attempts, one study by Fagiolini et al. [47] had found a higher prevalence of lifetime suicide attempts in the group of BD patients with metabolic syndrome compared with those without. However, we did not find any significant difference in the prevalence of metabolic syndrome, neither between attempters and non attempters, nor between violent and non violent suicide attempters. This finding is consistent with that from Vuksan-Ćusa et al. study [30], who found that the prevalence of metabolic syndrome in the sample was not different between suicide attempters and non attempters.

In our study, some markers of illness severity, such as the number of previous manic and depressive episodes and the number of psychotropic medications for BD were found associated with lifetime suicide attempts, according with the extant literature [3,51]. We have also confirmed that gender play an important role in violent suicide attempt for patients with BD. Women were far more likely than men to use nonviolent methods and men were more likely to use violent methods to attempt suicide. Our result is consistent with previous studies that have demonstrate that there are no other gender differences in suicidal behavior between men and women, apart from the method chosen to attempt suicide [52-54].

In conclusion, the results of our study do not demonstrate a primary role for cholesterol, lipid levels and metabolic syndrome in increasing suicide risk in patients treated for BD. The stress-diathesis model for suicidal behavior [55] states that patients who attempted suicide generally have both a diathesis (lower threshold) for suicidal behavior, and a trigger factor precipitating the suicide attempt (stressor). According to this model, low lipid levels might increase suicide risk either by lowering the threshold or acting as a stressor to trigger the aggressive/suicidal behavior. Since we found that cholesterol and other lipids are not associated with lifetime suicidal behavior, we cannot confirm cholesterol as a trait marker of suicidality in patients treated for bipolar disorder. Further research is awaited to clarify the role of cholesterol and other lipids as state markers that may precipitate suicidal behaviors, by measuring them in samples of patients immediately following a suicide attempt.

Considering that suicide is regrettably frequent in patients with BD future studies on this issues could help detecting individuals at risk of suicide attempt and take appropriate actions as early as possible.

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