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Original Article

Elevated Lipoprotein (a) and 10-Year Risk of Cardiovascular Disease among Iranian Patients with Bipolar Disorder

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ABSTRACT

Background: Bipolar disorder is associated with a high risk of cardiovascular disease. The aim of this study was to determine the elevated lipoprotein (a) level and 10-year risk of cardiovascular disease among patients with bipolar disorder.

Methods: This cross-sectional study was conducted on 100 patients with bipolar disorder in Yazd province, Iran. Elevated lipoprotein (a) concentration was defined as the lipoprotein (a) level of greater than 30 Mg/dL. The Framingham risk equation was used to estimate the 10-year risk of cardiovascular disease. The data were analyzed using Chi-square or Fisher's exact test, and independent sample-t or Mann-Whitney test. Statistical significance level was set at $p \leq 0.05$.

Results: In this study, 75 male (75%) and 25 female (25%) patients with bipolar disorder were investigated. Based on the findings, smoking was significantly more prevalent among men than women ($p<0.001$). No statistically significant difference was observed between males and females with regard to the total cholesterol, high- and low-density lipoprotein cholesterol, systolic blood pressure, body mass index, and lipoprotein (a) ($p>0.05$). High levels of lipoprotein (a) were observed in 41% of the participants. Most individuals (77.3%) were at low risk for developing cardiovascular disease in the next 10 years.

Conclusion: The findings suggest a high level of lipoprotein (a) among patients with bipolar disorder. Most participants were at a low risk for developing cardiovascular disease in the next 10 years. Psychiatrists and health professionals should be informed about cardiovascular risk factors in bipolar patients and monitor them regularly for early detection.

Keywords: Lipoprotein (a), Cardiovascular disease, Bipolar disorder

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Introduction

Evidences suggest that bipolar disorder (BD) is associated with an elevated risk of cardiovascular disease (CVD) (1, 2). Cardiovascular risk in patients with BD is related to several factors such as metabolic syndrome, unhealthy lifestyle (i.e., smoking, low physical inactivity, unbalanced diet), psychosocial functioning, and adverse side effects of the psychotropic medications (2, 3).

A 10-year cardiovascular risk assessment is a way to diagnose individuals at high risk of CVD (4). Garcia-Portilla et al. reported a high 10-year CVD risk of 23.4% among bipolar patients (5). Slomka et al. also found that 19% of the patients with BD were at high risk of developing CVD in the next 10 years (6).

The traditional cardiovascular risk factors have been used to assess CVD risk in a long time. These risk factors are applied for early detection and targeted therapies. In meeting therapeutic targets, other factors should be considered. For example, lipoprotein (a) (Lp(a)) is a new marker used as an independent risk factor for myocardial infarction and stroke (7, 8). It consists of a low-density lipoprotein (LDL) particle and apolipoprotein(a) (9).

A paucity of information exists regarding Lp(a) concentrations among psychiatric patients, especially in patients with BD. In a study by Emanuele et al, Lp(a) > 25 mg/dl was observed in 61.5% of the patients with BD (10).

Although some studies investigated the traditional cardiovascular risk factors in patients with BD, emerging risk factors such as high levels of Lp(a) have been less studied in BD patients. Moreover, no epidemiological study has ever investigated the level of Lp(a) in Iranian bipolar patients. The status of CVD risk in the future is also not clear for these patients. Considering the above-mentioned ideas, we conducted the first study on patients with diagnosed BD in Iran. The aim was to estimate the 10-year risk of CVD and assess the serum Lp(a) concentration. Findings of the present study can provide other researchers and physicians with a cardiovascular risk profile for the bipolar patients. As a result, they can consider the physical health of these patients and improve their quality of life.

Materials and Methods

Study design

This cross-sectional study was carried out over 100 patients with diagnosed bipolar mood disorder in 2016. The study participants were selected from the patients admitted to Yazd psychiatric center and Fatemeh Al-Zahra charity institute using the convenience sampling method. This research was approved by the Ethics Committee of Yazd Shahid Sadoughi University of Medical Sciences with the Ethics Code of IR.SSU.RSI.REC.1395.15. Furthermore, a parent or close family member of the patient was required to sign the informed consent form.

Study population

All patients were diagnosed after being visited by a psychiatrist according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders. All patients were in the manic, depressive, or partially treated phases of the disease. They were also using antipsychotic medications. Exclusion criteria included co-morbidity with other psychiatric disorders, diagnosis of substance abuse, epilepsy, pregnancy, mental retardation, inherited disorders of lipoprotein metabolism, as well as disagreement to participate in the study.

Measurement of the study variables

Patients' age was determined using their birth dates available from medical records. Cigarette smoking status (yes/no) was determined by asking the patients' nurses or family members. The patients' weight was measured using a calibrated digital scale (Omron, Japan) in light clothes and no shoes. In addition, height was measured at standing position without shoes by a tape fixed on the wall. Consequently, the participants' body mass index (BMI) was calculated after dividing weight (in Kilogram) by height square (in meter). In addition, the patients' blood pressure was measured once using a mercury sphygmomanometer (ALPK2, Japan) in sitting position from the right arm.

To assess the participants' total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and Lp(a), five milliliters of venous blood sample was taken from each patient after 8-12 hours of fasting. Later, the serum samples were separated and immediately transmitted to the laboratory. Finally, serum samples were analyzed by an auto-analyzer (Alpha Classic

analyzer, Pars Azmoon kit, Iran for TC and HDL-C, and Selectra E analyzer, USA, Pars Azmoon kit, Iran for Lpa). The patients' LDL-C was calculated according to Friedewald's formula (11).

Elevated levels of Lp(a) was considered as Lp(a) of greater than 30 Mg/dL according to the reference value of our laboratory.

10-year risk of CVD

In the current study, the Framingham risk equation was used to predict the 10-year risk of CVD. The Framingham Risk Score (FRS) is a common function frequently applied by physicians and researchers to estimate the 10-year risk of fatal or non-fatal cardiovascular events (4). In FRS, the risk level is calculated for men and women separately based on several risk factors including age, TC, smoking, HDL-C, systolic blood pressure (SBP), and antihypertensive drug consumption.

Patients were classified into three categories based on their FRSs: FRS ≤ 10% showed a low risk level, FRS within 10-20% indicated an intermediate risk level, and FRS ≥ 20% represented high risk (12).

Statistical analysis

Statistical analyses were performed by $SPSS_{24}$ software. The results were reported in frequency (percentage) and mean ± standard deviation for describing qualitative and quantitative variables, respectively. The Chi-square or Fisher's exact test was run to compare the qualitative variables. Normality of the quantitative data was checked using Kolmogorov-Smirnov test. Independent sample t- or Mann-Whitney U-test was also applied to compare the quantitative variables. The level of statistical significance was defined as p-values of less than 0.05.

Results

Based on the findings, 75 male (75%) and 25 female (25%) patients with BD participated in this study. The mean age of men was higher than that of women, but no statistically significant difference was observed between the participants in terms of age (p=0.19) (Table 1).

Table 1. Baseline characteristics of the participants

Variable	Male (n=75)	Female (n=25)	All patients (n=100)	P-value
Age (years)	43.15 ± 11.69	39.48 ± 13.45	42.23 ± 12.18	0.19 *
Current smoking				
Yes	52 (69.3)	1 (4.0)	53 (53.0)	<0.001 ‡
No	23 (30.7)	24 (96.0)	47 (47.0)	
TC (mg/dl)	168.63 ± 38.20	179.33 ± 42.66	171.30 ± 39.42	0.24 *
HDL-C (mg/dl)	37.74 ±9.55	41.88 ± 10.30	38.78 ± 9.85	0.08 †
LDL-C (mg/dl)	95.76 ± 32.78	100.25 ± 34.72	96.89 ± 33.16	0.56 *
SBP (mg/dl)	114.27 ± 17.22	109.40 ± 20.02	113.05 ± 17.98	0.34 †
BMI (kg/m^2)	25.67 ± 4.25	28.33 ± 7.00	26.34 ± 5.17	0.08 †
Lp (a) (mg/dl)	28.10 ± 24.73	36.69 ± 26.67	30.25 ± 25.37	0.10 †

Data are expressed as mean± standard deviation or frequency (percentage), TC: total cholesterol, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SBP: systolic blood pressure, BMI: body mass index, Lp(a): lipoprotein(a). *Independent sample t test. † Mann-Whitney U test. ‡ Chi-square test.

Although smoking was significantly more prevalent among men than women (p<0.001), no statistically significant difference was found between male and female patients in the case of TC, HDL-C, LDL-C, SBP, BMI, and Lp(a) (p>0.05) (Table1).

As presented in Table 2, 41 (41%) patients had an elevated level of Lp(a). Moreover, increased concentration of Lp(a) was significantly more common in female patients than men (p=0.007). Most participants (77.3%) were at the low risk level for developing CVD in the next 10 years. In addition, a borderline significant difference was observed between the level of risk among males and females (p=0.05).

No statistically significant difference was found in terms of CVD risk between patients with and without elevated level of Lp(a) (Table 3).

Table 2. Frequency of elevated Lp(a) level and 10-year risk of CVD in male and female patients with BD

	Male (n=75)	Female (n=25)	All patients (n=100)	P-value
Elevated Lp(a)	25 (33.3)	16 (64.0)	41 (41.0)	0.007 ‡
10-year risk of CVD				
Low risk	53 (71.6)	22 (95.7)	75 (77.3)	
Intermediate risk	16 (21.6)	1 (4.3)	17 (17.5)	0.05 †
High risk	5 (6.8)	0 (0)	5 (5.2)	

Data are expressed as frequency (percentage), Lp(a): lipoprotein(a), BD: bipolar disorder, CVD: cardiovascular disease. ‡ Chi-square test. † Fisher's exact test.

Table 3. Frequency distribution of 10-year risk of CVD based on elevated level of Lp(a)

	Elevated Lp(a) (n= 41)	None-elevated Lp(a) (n= 59)	All patients (n=100)	P-value
10-year risk of CVD				
Low risk	30 (75.0)	45 (78.9)	75 (77.3)	
Intermediate risk	8 (20.0)	9 (15.8)	17 (17.5)	0.86 †
High risk	2 (5.0)	3 (5.3)	5 (5.2)	

Data are expressed as frequency (percentage), Lp(a): lipoprotein(a). CVD: cardiovascular disease, † Fisher's exact test

Discussion

The findings showed a high frequency of elevated Lp(a) among patients with BD. The results of our study are in the same line with a previous study reporting that increased Lp(a) level was more prevalent among patients with BD than healthy individuals (10). However, a prospective cohort study on healthy volunteers showed that the mean and standard deviation of Lp(a) was 19 ± 23 mg/dL (13). Another study showed that the mean and standard deviation of Lp(a) among general population was 13.3 ± 13 mg/dL (14). Lp(a) levels in these two studies were much less than the mean and standard deviation in our study (30.25 ± 25.37).

The exact reasons for the elevated level of Lp(a) among patients with BD are still uncertain. However, this finding can be justified by high levels of LDL-C and low level of HDL-C in these patients. In other words, Lp(a) is structurally similar to LDL-C (15) and a tradeoff exists between LDL-C and HDL-C (16). In addition, bipolar patients have unhealthy lifestyle, such as high rates of smoking and obesity, low level of physical inactivity, and inappropriate diet (high consumption of saturated fat and low intake of fresh fruits and vegetables) (3, 17, 18). All these factors are associated with increased LDL and decreased HDL cholesterol levels (16). Consequently, a high level of Lp(a) is expected.

High concentration of Lp(a) may also be justified by genetic factors determined through differences in apolipoprotein(a) gene (19).

In contrary to other studies, we found that only 5.2% of the patients were at high-risk of developing CVD in the next 10 years. However, Grover et al. demonstrated that 10.7% of the participants were at a very high/high CVD risk (20). Garcia-Portilla et al. also reported that 23.4% of the participants with BD had very high/high CVD risk (5). Moreover, Slomka et al. revealed that 18.6% of bipolar patients were at high Framingham risk category (6). A sophisticated mechanism exists behind the increased risk of CVD in people with BD including metabolic abnormalities, smoking, depressive symptoms and lack of access to health care services (5, 6, 21). Increased Lp(a) level, as an emerging risk factor, is also associated with CVD, independent from other conventional risk factors (8, 10). So, in spite of the fact that our participants were at the low risk level of traditional cardiovascular risk factors, they may still be considered as the high-risk group for developing CVD due to the very high prevalence of elevated Lp(a).

We observed that the mean of Lp(a) was higher among women than men, but the difference was not statistically significant, which may be due to our small sample size and high dispersion in the observed data.

In confirmation of our findings, Framingham study introduced Lp(a) as a strong risk factor of myocardial infarction in women (22). Similarly, Costello et al. reported a high frequency of elevated Lp(a) among women, which made Lp(a) as an important risk factor (7).

High serum Lp(a) level is related to premature CVD (19). Considering that our participants were fairly young and the level of Lp(a) was high among them, they may be more prone to develop premature CVD.

This study has some limitations that should be considered in interpreting the results. Initially, we could not establish a causal relationship between Lp(a) and elevated risk of CVD due to the cross-sectional nature of our research. Second, given the lack of an appropriate sampling frame, we did not have the opportunity to perform random sampling. Furthermore, we could not utilize a larger sample size considering the low number of available patients. Third, the use of surrogates may overestimated or underestimated the prevalence of smoking. Ultimately, this study was conducted on hospitalized patients, which limits generalizability of the results to non-hospitalized patients.

Conclusion

This study confirmed elevated Lp(a) among the patients with BD and showed that most participants were at a low risk of developing CVD in the next 10 years. We suggest psychiatrists and healthcare staff to be cautious more about developing CVD in patients with BD and to perform sufficient physical monitoring in this regard. Moreover, we recommend regular screening for both traditional and emerging cardiovascular risk factors in these individuals, especially in women.

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Conflicts of interest

There are no conflicts of interests.

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