Chitinase-3-like protein 1 levels in bipolar disorder

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ABSTRACT

Objectives: To evaluate the relationship between the expression level and biologic role of YKL-40 in bipolar disorder (BD).

Methods: This case-control study was conducted in the Faculty of Medicine, Canakkale Onsekiz Mart University, Canakkale, Turkey in 2015. One hundred and four patients diagnosed as having bipolar disorder (DSM5 criteria), and 96 participants were included as healthy controls in this study. A human YKL-40 enzyme-linked immunosorbent assay (ELISA) kit was used to measure the serum YKL-40 levels. As independent variables, we collected data on C-reactive protein (CRP), demographic variables, and medications.

Results: The mean YKL-40 levels for the BD was 2723.5±543.8 pg/ml and control groups was 2132.5±576.3 pg/ml (t=7.42, p<0.001). The mean CRP levels for the BD was 0.4±0.6 mg/dl and control groups was 0.4±0.7 mg/dl (t=0.02, p=0.985). The receiver operating characteristics (ROC) analysis revealed an area under the curve (AUC) of YKL-40 in the diagnosis of BD as 0.79 (95% confidence interval [CI]: 0.72-0.85) with a sensitivity of 82.7% and specificity of 68.1% at a cutoff level of 2307.1 pg/ml. The use of antidepressants, antipsychotics, mood modifiers, and the presence of any comorbidity was not related to the YKL-40 levels (p>0.05).

Conclusion: With acceptable sensitivity and specificity levels, the YKL-40 can be utilized as a marker in the diagnosis and follow-up of BD.
Human cartilage glycoprotein 39 (HC-gp39) also known as YKL-40 is a 40 kDa heparin- and chitin-binding glycoprotein, 38 kDa heparin-binding glycoprotein, or chitinase-3-like protein 1 (CHI3L1). Human cartilage glycoprotein 39 (HC-gp39) is produced by activated microglia and reflects inflammatory processes, but its function is not completely known; it is hypothesized to be an agent of the innate immune system, involved in tissue remodeling during inflammation. In some disorders of the central nervous system, the serum YKL-40 level is altered. While YKL-40 expression from astrocytes is seen in neuroinflammatory disorders, an increase of serum and tissue YKL-40 levels were identified in brain tumors, in traumatic brain injury, and in Alzheimer’s disease. The diagnosis of BD endures in brain tumors, in traumatic brain injury, and in Alzheimer’s disease. The diagnosis of BD endures patient’s history and clinical process. Previous study has long explored biological indicators for mental disorders, specially for affective disorders. Frye et al, found significant difference in 6 proteins associated with bipolar depression, mood disorders, and including unipolar, hemopexin (HPX), growth differentiation factor 15 (GDF-15), matrix metalloproteinase-7 (MMP-7), hepsin (HPN), transthyretin (TTR), and retinol-binding protein 4 (RBP-4). In mood disorders, MMP-7 was significantly different. In bipolar cases (both of BP-I/II) HPX, GDF-15, MMP-7 were significantly different. In BO-1 HPX, GDF-15, RBP-4, TTR, and HPN proteins were all significantly different. These findings inspire that proteomic panels may be useful in defining and distinguishing mood disorders.

This study aimed to investigate the relationship between the expression level and biologic role of YKL-40 in BD.

**Methods.** This case-control study was conducted in the Medical Faculty, Çanakkale Onsekiz Mart University, Çanakkale, Turkey in 2015. The study reporting was carried out in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. The Local Ethics Committee of Çanakkale Onsekiz Mart University, Turkey approved the study protocol. All participants signed the informed consent and complies with the Declaration of Helsinki.

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severity, presence of additional disease; use of mood modifier, dual mood modifier, depot antipsychotic, or antidepressants; polypharmacy, HDRS, and YMRS.

The YMRS has 11 items and is based on the subjective report of patient’s clinical condition over the last 48 hours. During the clinical interview, clinical observations based on additional information was noted. Four items graded scale ranging from 0-8 points (including factors as speech, irritability, thought content, disruptive/aggressive behavior) was used in the interview. The other items are graded on a scale ranging from 0-4. The first 4 items have twice the weight of the other items to compensate for low cooperation by severely ill patients. The Turkish version of the scale was used in the research.

The HDRS is a tool used to measure the severity of depression among adults by asking questions about suicide ideation, mood, insomnia, feelings of guilt, agitation or retardation, weight loss, somatic symptoms and anxiety. The questionnaire has 17 items, scored on a 3- or 5-point scale, used to compare the relevant descriptor.

Global assessment of functioning is used to evaluate the overall functioning of a person during a specific period of time. The scale ranges in a continuum from psychological/psychiatric ailments to complete health. Global assessment of functioning is scored from 1 (lowest) to 100 (highest) and 0 (inadequate information).

The clinical global impression (CGI) was constructed for a brief clinician’s view of the patient’s global functioning before and after starting a study medication. The CGI has 2 one-item measures assessing the a) severity of psychopathology from 1-7 and b) change from the implementation of the treatment on a 7-point scale.

In the questionnaire, there was a brief information about the research to ensure that the research data was obtained correctly, and participants were asked not to put their identities on the questionnaire form. The study and control groups were matched based on age and gender.

Post-hoc sample size calculation demonstrated that to compare YKL-40 between 2 independent groups using the t-test, 96 participants in each group provides a power of 80% with a sigma of 570 pg/ml and true difference of means of 234 pg/ml.

Height, weight, and waist circumferences were measured by ordinary instruments used in the hospital. The BMI was calculated by the formula of weight (kg)/height (m²). The waist circumference was measured at the midpoint between the lower margin of the lowest palpable rib and the top of the iliac crest with standard measuring tape wrapped nearly around the patient. Measurement was made with the patient in upright position and the tape parallel to the floor.

Peripheral venous blood samples centrifuged at 4000 rpm for 10 minutes and were stored at -80°C until the serum analyzed and collected after a 12-hour fasting period. All samples were resolved only once before analyses. A human YKL-40 ELISA kit (Adipobiotech, Santa Clara, USA) did measurements of the YKL-40 levels. The levels of CRP were measured by immunoturbidimetry method.

**Statistical analysis.** Data was entered into the computer and analyzed using the Statistical Package for Social Science (SPSS) Version 20.0 software (IBM Corp., Armonk, NY, USA). The results were presented as frequencies, percentages, means, and standard deviations (SD). The YKL-40 was set as the dependent variable; its normal distribution was examined by the Kolmogorov Smirnov test. In the comparison of the clinical data and demographics, the independent samples t-test was used for quantitative variables and the Chi-square test for categorical variables. Some associated parameters were investigated by correlation analysis of Pearson’s or Spearman’s. The diagnostic accuracy of YKL-40 was evaluated with ROC analysis to evaluate diagnostic accuracy of YKL-40. A p-value of <0.05 was considered significant.

**Results.** In this study, 104 bipolar patients and 96 controls were included. There were no any significant differences in gender, age, occupation, residence, smoking status, and waist circumference among the patient and the control groups. The percentage of widow or divorced was higher in the BD group 14 (12.7%) than in the control group 3 (3.1%), (χ²=6.6, p<0.04). The percentage of family history of psychiatric illness was higher in the BD group 41 (41%) than in the control group 17 (17.7%), (χ²=33.5, p<0.001). The percentage of family history of psychiatric illness was higher in the BD group 41 (41%) than in the control group 17 (17.7%), (χ²=33.5, p<0.001). Measures of obesity such as body weight, BMI, and waist circumference were higher in the BD group than in the control group (p<0.05). Comparison of sociodemographic variables of controls and patients with BD are given in Table 1. The mean±SD GAF scores were 76.5±12.6. Distributions of other features of BD patients are summarize in Table 2.

The mean levels of YLK-40 for the BD group was 2723.5±543.8 pg/ml and control group was 2132.5±576.3 pg/ml, (t= 7.42, p<0.001). The mean
CRP levels for the BD group was 0.4±0.6 mg/dl and control group was 0.4±0.7 mg/dl, (t=0.02, p=0.985).

The use of antidepressants, antipsychotics, mood modifier, and the presence of any additional disease in patients with BD was not related to the plasma levels of YKL-40 (p>0.05). The mean levels of YKL-40 of patients not using polypharmacy was 3072.3±319.5 pg/ml, while those in polypharmacy had levels of 2682.3±551.1 pg/ml (t=2.30, p=0.02) (Table 3).

No any correlations was found between other numerical variables and YKL-40 plasma levels (p>0.05) except for YMRS (r=-0.198; p=0.043). The ROC analysis showed that the AUC of YKL-40 in the diagnosis of BD was 0.79 (95% CI: 0.72-0.85) (Figure 1).When we used 2307.1 as the cutoff level, 82.7% of all BD-positive samples would be correctly identified using YKL-40 (sensitivity), while 68.1% of all BD-negative samples would be correctly categorized (specificity). A logistic regression model was built with group (BD versus control) as the dependent variable. YKL-40 (cutoff 2307.1), marital status, and educational level were added to the model as categorical variables, while waist circumference and BMI were included as numerical variables. All variables entered had significant effects on the outcome: YKL-40 (p<0.001), marital status (p=0.04), education (p=0.03), waist circumference (p<0.001), and BMI (p=0.009). The odds ratio (OR) for YKL-40 was calculated as OR=7.4, 95% CI: 3.1-17.5.

### Table 1 - Comparison of sociodemographic parameters of patients with bipolar disorder and controls.

| Parameters               | Groups | P-value | t/χ² |
|--------------------------|--------|---------|------|
|                          | BD     | Control |      |
| Age (year)               | 40.5±13.2 | 37.6±13.8 | 0.124 | 1.54 |
| Gender                   |        |         |      |
| Female                   | 52±50.0 | 59±61.5 | 0.103 | 2.65 |
| Male                     | 52±50.0 | 37±38.5 |      |      |
| Occupation               |        |         |      |
| No regular work          | 23±22.3 | 28±29.8 | 0.006 | 10.24 |
| Employee                 | 20±19.4 | 21±22.3 |      |      |
| Officer                  | 12±11.7 | 17±18.1 | 0.161 | 6.56 |
| Retired                  | 15±14.6 | 7±7.4   |      |      |
| Housewife                | 33±32.0 | 21±22.3 |      |      |
| Marital status           |        |         |      |
| Single                   | 33±32.4 | 39±40.6 | 0.037 | 6.61 |
| Married                  | 56±54.9 | 54±56.3 |      |      |
| Widow or divorced        | 13±12.7 | 3±3.1   |      |      |
| Education                |        |         |      |
| Illiterate/elementary    | 52±50.5 | 32±33.3 |      |      |
| High school              | 23±22.3 | 17±17.7 |      |      |
| University               | 28±27.2 | 47±49.0 |      |      |
| Residence                |        |         |      |
| Rural                    | 35±34.7 | 23±24.0 | 0.1   | 2.71 |
| Urban                    | 66±65.3 | 73±76.0 |      |      |
| Family history of psychiatric illness |  |      |
| No                       | 57±55.9 | 79±82.3 | <0.001 | 16.04 |
| Yes                      | 45±44.1 | 17±17.7 |      |      |
| Alcohol                  |        |         |      |
| No                       | 99±95.2 | 72±75.8 | <0.001 | 15.46 |
| Yes                      | 5±4.8   | 23±24.2 |      |      |
| Smoking                  |        |         |      |
| No                       | 58±55.8 | 64±66.7 | 0.114 | 2.49 |
| Yes                      | 46±44.2 | 32±33.3 |      |      |
| Obesity                  |        |         |      |
| No                       | 58±58.6 | 76±80.0 | 0.001 | 10.4 |
| Yes                      | 41±41.4 | 19±20.0 |      |      |
| Body weight (kg)         | 81.1±16.5 | 71±16.4 | <0.001 | 4.09 |
| Height (cm)              | 167±39.5 | 166±28.6 | 0.391 | 0.86 |
| BMI (kg/m²)              | 29.0±5.6 | 25.9±5.7 | <0.001 | 3.85 |
| Waist circumference (cm) | 101.6±14.0 | 84.6±14.4 | <0.001 | 8.42 |

| BD - bipolar disorder, BMI - body mass index |

### Table 2 - Distribution of the study variables among bipolar disease patients.

| Variables               | Mean ± SD |
|-------------------------|-----------|
| GAF                     | 76.5 ± 12.6 |
| YMRS                    | 3.6 ± 4.8 |
| HDRS                    | 4.7 ± 5.1 |
| CGI-severity            |           |
| 1                       | 24 ± 28.6 |
| 2                       | 23 ± 27.4 |
| 3                       | 29 ± 34.5 |
| 4                       | 6 ± 7.1   |
| 5                       | 2 ± 2.4   |
| Additional disease      |           |
| No                      | 78 ± 76.5 |
| Yes                     | 24 ± 23.5 |
| Antipsychotic           |           |
| No                      | 93 ± 89.4 |
| Yes                     | 11 ± 10.6 |
| Polyparmacy              |           |
| No                      | 11 ± 10.6 |
| Yes                     | 93 ± 89.4 |
| Antidepressant           |           |
| No                      | 88 ± 84.6 |
| Yes                     | 16 ± 15.4 |
| Mood modifier            |           |
| No                      | 13 ± 12.5 |
| Yes                     | 91 ± 87.5 |
| Dual mood modifier       |           |
| No                      | 90 ± 86.5 |
| Yes                     | 14 ± 13.5 |

YMRS - young mania rating scale, HDRS - hamilton depression rating scale, GAF - global assessment of functioning score, CGI - clinical global impression
Discussion. In this study, the plasma levels of YKL-40 in BD patients is determined higher than healthy controls. The ROC curve analysis displayed an optimum cutoff point of >2307.1 to support that YKL-40 is a useful potential biomarker in BD. Although we had an adequate sample size in this study, there may be some limitations due to study design.

The general limitations of questionnaire studies applies for the demographic questions and the scales. On the other hand, the cases and controls were matched by age and gender to rule out confounding. However, some other confounders may still be present. Calculations of kappa or intraclass correlation (ICC) reliability coefficients could provide estimates regarding the degree of error in the bipolar diagnosis. Besides, the lack of information about the accuracy of the diagnosis can be considered as a weakness in this research. The fact that there is no difference between BD patients and the occupational distribution of the control group may imply that BD is not related to the occupations and working lives of patients. The research findings of Adejumo et al.\textsuperscript{27} are similar to the distribution of occupations in our research, where they reported the unemployment rate in BD patients as 15.5%. The proportion of widow or divorced patients in the BD group was higher compared to the control group, indicating that BD patients may have difficulties in maintaining their marriages. Adejumo et al.\textsuperscript{27} found 18.4% divorce among BD patients. Also, Metsa-Simola et al.\textsuperscript{28} reported that psychiatric morbidity is a persistent risk factor of divorce. The lower levels of education among BD patients compared to the control group suggested that BD adversely affects the education of patients. Although we cannot claim a causal relationship, the lower educational attainment of BD patients compared to the controls, may be an indicator that BD may adversely affect educational status. On the other hand, a low level of education can make it difficult for patients to benefit from psychoeducation and health education. There is an agreement, that well clinical management of BD patients includes an significant training factor for patients and also for their relatives.\textsuperscript{29}

The place of residence of BD patients was similar to the control group, indicating that settlement is not a risk factor for BD. However, in a large international survey using the internet, the rural residence of BD patients was reported to be lower (14.9%) than our study.\textsuperscript{30} The higher rates of psychiatric illnesses in the BD group suggest genetic influences in the etiology of the disease. Jakobsen et al.\textsuperscript{31} found the rate of family history of BD between 29.1% and 38%. There are many studies supporting the genetic etiology of BD.\textsuperscript{3,32,33} The lower rate of alcohol use in BD patients compared to the control group is important in protecting patients from the neurodegenerative effects of alcohol dependence.
Although smoking was more prevalent in the BD patients (44.2%) compared with the healthy controls (33.3%), the difference was not statistically significant. Wintemberg et al.\textsuperscript{34} reported smoking prevalence in Turkey as 27%. However, in our study, the rate of smoking was higher in both groups. In this study, obesity indicators such as BMI and waist circumference of BD patients were higher than the control group. Ertekin et al.\textsuperscript{35} have found similar alcohol use, smoking, and obesity rates compared to our findings. Obesity is more prevalent in BD patients compared to the average population. In one study, the prevalence of obesity was found to be 55% in BD patients.\textsuperscript{36} The prevalence of obesity in Turkey was found in 28% of BD patients.\textsuperscript{37} We found no associations between the presence of comorbidities, use of antidepressants, antipsychotics, mood modifiers, dual mood modifiers, GAF scores, BMI, YMRS, HDRS, or CGI-severity scores and serum YKL-40 levels. However, the reason behind lower YKL-40 levels among patients under polypharmacy requires further elucidation. One meta-analysis has shown increased CRP levels in bipolar disorder regardless of the mood state.\textsuperscript{38} However, our study demonstrated normal levels of CRP in both study and control groups. As to the main outcome measure compared to the controls, YKL-40 concentrations in BD participants were significantly increased. Similarly, YKL-40 concentrations in serum and cerebrospinal fluid (CSF) in BD participants against control group.\textsuperscript{31} YKL-40 serum levels have been adversely affected with manic/hypomanic episodes and with presence of psychotic symptoms.\textsuperscript{39} As a CSF neuroinflammation biomarker, YKL-40 is related with management performance in euthymic bipolar disorder; however, not in control group.\textsuperscript{40} In conclusion, we have observed a strong relationship between YKL-40 and BD with relatively high predictive power and an OR of above 7. Thus, we conclude that with acceptable sensitivity and specificity levels, the YKL-40 can be utilized as a marker in the diagnosis and follow-up of BD. Future research should concentrate on testing and confirming the YKL-40 as a marker in different contexts and patient populations.

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