Clinical and Experimental Health Sciences

Elevated Matrix Metalloproteinase 9 in Treatment Resistant Bipolar Depression

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ABSTRACT

Objective: Matrix metalloproteinase is a family of proteases with different pathophysiological roles. Matrix metalloproteinase 9 (MMP9) plays an enzymatic role in the restructuring of the extracellular matrix and adhesion molecules. MMP9 is upregulated in pro-inflammatory states and leads to breakdown of tight junctions thereby increasing blood-brain barrier (BBB) permeability. MMP9 may contribute to the pathophysiology of bipolar disorder (BD) via proteolysis of the BBB thus allowing entry of cytokines and neurotoxic agents into CNS. Polymorphisms of the MMP9 gene may pose increased risk for BD and schizophrenia. In this study we sought to determine MMP9 levels in treatment resistant bipolar depressed patients before and after treatment.

Methods: Treatment resistant bipolar depressed patients were treated with escitalopram, in combination with the COX-2 inhibitor, celecoxib. It was hypothesized that combination treatment would reverse resistance and augmented treatment responses. This was a 10-week, randomized, double-blind, two-arm, placebo-controlled study.

Results: MMP9 levels were higher in bipolar depressed patients compared to healthy controls at baseline, however, the difference did not reach significance. Levels decreased after treatment reaching significance in the escitalopram plus placebo group. Female patients had significantly lower MMP9 levels at end of treatment. MMP9 was higher in carriers of the MMP9 SNP, rs3918242, than in noncarriers, but the difference did not reach statistical significance.

Conclusion: MMP9 decreased in bipolar depressed patients with treatment. Age, sex and the rs3918242 polymorphism play a role in MMP9 levels. Future studies should confirm the role of MMP9 in the pathogenesis and pathophysiology of bipolar disorder, as a potential diagnostic biomarker.

Keywords: Bipolar depression, treatment resistance, MMP9, blood-brain barrier, inflammation, celecoxib

1. INTRODUCTION

Psychiatric disorders are highly prevalent around the world and represent a significant health burden (1). Lifetime prevalence of bipolar disorder (BD) is estimated to be 0.5 – 5% for both type I and II, but rates vary significantly across studies (2). BD is the sixth leading cause of disability worldwide (3). BD places a significant burden on affected individuals and their families with serious socioeconomic consequences; it is associated with significant impairment in work, family, and social life, not only during the acute phases of the illness, but also between episodes.

A better understanding of the pathophysiology of BD can lead to better treatment options and quality of life for these patients. There are abundant theories about the pathophysiology of the disorder. Heritability that is calculated to be 56.7% after adjusting for sex and age, plays an important role, with the concordance rate for monozygotic twins being 57% compared to 14% for heterozygotic twins (4). Studies suggest involvement of different brain regions. PET imaging and functional MRI studies have shown elevated activity in amygdala and diminished activity in the hippocampus and prefrontal cortex in BD patients. Structural studies have associated BD with above-average amygdala volume and below-average prefrontal cortex, basal ganglia, hippocampus, and anterior cingulate volume (5). Dysregulation of multiple neurotransmitters, notably serotonin, norepinephrine

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and dopamine, has been suggested as a contributory etiopathological causes of mood disorders (6). There is also evidence that infection with HSV-1 is an independent predictor of cognitive impairment in patients with BD or Schizophrenia (3).

A growing body of evidence supports the role of inflammation and oxidative stress in BD pathophysiology. Studies have shown peripherally measured elevated levels of pro-inflammatory cytokines, such as IL-1b, IL-6 or TNFα, in BD patients in comparison to healthy controls, and these increases occur during both manic and depressive episodes. Cognitive decline as well as abnormalities observed in gray and white matter are considered to be mediated, at least in part, by increased neuro-inflammation. Evidence of increased neuroinflammation through excessive microglial activation has been found in many imaging and postmortem studies (7-9). These pathophysiological changes are in line with numerous studies showing elevated mortality rates due to conditions associated with inflammation and oxidative stress. BD patients die on average 9 years younger than the general population. Moreover, several studies have provided evidence of the role of psychotropic agents, such as lithium, in the modulation of pro-inflammatory and anti-inflammatory pathways (10).

Increasing attention is being given to the role of the blood brain barrier (BBB) disruption in numerous neuropsychiatric disorders. The BBB functions as a diffusion barrier, regulating the transport of micro – and macro-molecules between peripheral blood and the CNS. It is formed primarily by endothelial cells of the capillary wall, astrocyte end-feet ensheathing the capillary, pericytes embedded in the capillary basement membrane, perivascular macrophages and a basal membrane. A tightly sealed monolayer of endothelial cells with tight junctions (TJ) and adherent junctions (AJ) form its barrier. Small lipophilic molecules can freely pass-through the BBB, whereas passage of large and hydrophilic solutes is limited. Specific transporters and receptor mediated endocytosis allow certain complex molecules to pass through it. Thus, a disruption of its integrity can lead to the transport of inflammatory mediators from the periphery to the CNS. Both manic and depressive episodes in BD are associated with increased levels of proinflammatory cytokines in blood, leading to a transient disruption in the permeability of the BBB during each episode.

Matrix metalloproteinase (MMP) is a large family of zinc-dependent, extracellularly acting endopeptidases with several different roles (11). These proteins are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling. At the same time, these proteins play a role in disease processes, such as cardiovascular disease, arthritis, cancer and neuropsychiatric disorders (BD, schizophrenia, and multiple sclerosis (12). MMPs are secreted as inactive pro-proteins which are activated when cleaved by extracellular proteinases.

Matrix metalloproteinase 9 (MMP9), also known as gelatinase B, 92 kDa gelatinase, or 92 Da type collagenase, plays an enzymatic role in the restructuring of the extracellular matrix and adhesion molecules (11). Experimental studies have shown that MMP9 plays a role in the plasticity of the central nervous system, as demonstrated by studies with MMP9 null mutant mice that have behavioral impairments in hippocampal dependent memory. (13). Moreover, MMP9 has been suggested in animal models to have a role in the pathogenesis of temporal lobe epilepsy (11).

Of key interest is the upregulation of MMP9 in pro-inflammatory states. In this proinflammatory milieu, MMP9 plays an important role in the breakdown of tight junctions, basal lamina, and extracellular matrix, thus increasing the permeability of the BBB, which can potentially have an impact on CNS milieu (10).

The human MMP9 gene was mapped in the 20q11.2-q13.1 chromosome area. There is a single nucleotide polymorphism (rs3918242), a C to T substitution at – 1562 bp, which results in a functional effect on gene transcription. This polymorphism leads to loss of binding of a nuclear protein to this region and an increase in transcriptional activity in macrophages. Lower transcriptional activity of the gene is associated with C/C genotype, while C/T and T/T genotypes resulted in higher transcriptional activity. Research has linked the T allele with increased severity of coronary arteriosclerosis, increased cardiac mortality and increased risk of more severe progression of some types of cancer and predisposition to BD, schizophrenia, and multiple sclerosis (14). BD patients had significantly higher frequency of the T allele of the polymorphism compared to healthy controls, especially evident in a subgroup of patients with BD type II.1 This could be the genetic link between BD and some somatic illnesses (15). A recent study produced strong evidence that a SNP related to the MMP9 gene, rs3918242, was significantly associated with susceptibility to anxiety disorders (16).

Another study showed increased levels of MMP9 and soluble intercellular adhesion molecule 1(sICAM-1), which is also involved in the restructuring of connective tissues in patients with BD in euthymic state compared to healthy controls. Significantly higher levels of MMP9 and sICAM-1 were associated with a later, progressive stage of the disease compared to earlier stages (17). We hypothesized that MMP9 may contribute to the pathophysiology of BD via proteolysis of the BBB thus exposing the CNS to a pro-inflammatory environment resulting from entry into the brain parenchyma of cytokines and neurotoxic agents. The aim of this study was to investigate the role of MMP9 in treatment resistant bipolar depression (TRBDD) and to establish whether MMP9 levels are increased in such patients. In addition, we sought to determine whether addition of an anti-inflammatory agent would augment the therapeutic response to antidepressant treatment.

2. METHODS

2.1. Study Population

The study was approved by the Institutional Review Board (IRB) of Loyola University Medical Center and was conducted according to the principles of the Declaration of Helsinki (LU # 203368, March 23, 2011). Potential candidates were screened to determine eligibility for the study based on their mental capacity to give informed consent after a study physician extensively explained the procedures of the study and the inclusion/exclusion criteria. Candidates were males and females between the ages of 21 and 65 with TRBDD who met the DSM-IV criteria for bipolar disorder (BD I or II) depressed phase and who met criteria for treatment resistance in the depressive phase of their illness.

Exclusion criteria included any comorbid medical or psychiatric diagnosis or substance abuse/dependence during the preceding 12 months. Subjects with chronic or acute inflammation, liver or kidney disease, arthritis, hypertension, diabetes, anemia or any autoimmune disorders were excluded. Study patients could not be taking stimulants, lithium, anticoagulant agents or any nicotine containing substances. Individuals who were pregnant, lactating, or taking oral contraceptives were excluded.

Treatment resistance was determined by the Maudsley Scale. The scale uses a variety of factors to determine treatment resistant depression, notably, duration and severity of symptoms, number of treatment failures and the use of psychopharmacological augmentation or electroconvulsive therapy. To be considered for the study, patients had to have failed to respond to at least two adequate lifetime trials with antidepressants and/or mood stabilizers or experienced a breakthrough depressive episode despite being maintained on a mood stabilizer and/or atypical antipsychotic agent.

For admission to the study, a minimum score of 18 on the 17-item Hamilton Depression scale (HAM-D17) was required. Moreover, the patients were required to be clinically stable before entering the study on a mood stabilizer and/or antipsychotic medication.

2.2. Study Design

This was a 10-week, randomized, double-blind, two-arm, placebo-controlled study. The study included a screening visit, a 1-week washout phase, a 1-week placebo run-in phase and an 8-week flexible dose phase (NCT0149829). During the screening visit, medical history was obtained using a Past Medical History and a Family History Questionnaire, and a physical exam was performed. Blood and urine samples were collected to obtain CBC with differential, CMP, thyroid function, lipid profile, hCG pregnancy test and toxicology screening. Subjects were evaluated with the MINI International Neuropsychiatric Interview and a variety of scales, HAM-D17, Montgomery-Asberg Depression Rating scale, Hamilton Anxiety Rating Scale, Clinical Global Severity and Improvement, and Columbia Suicide Severity Rating Scale. Once cleared and consented, patients were instructed to stop any antidepressant they were taking for a 2-week washout (4 weeks for Fluoxetine) period. They were then placed on a 1-week blinded placebo run-in phase, to identify potential placebo (PBO) responders, who were excluded from the study and offered conventional care at the same institution.

Patients who continued to meet eligibility criteria at the baseline visit were randomized to receive, on a double-blind basis, either escitalopram (ESC) and celecoxib (CBX) or ESC and PBO. ESC dosing was initiated at 10mg/day and was optimized based on efficacy and tolerability over the first 4 weeks of treatment, with a max dose of 30mg, while CBX was administered fixed at 400mg/day. No dose adjustments were made after the first 4 weeks of treatment. The randomization was done at a fixed assignment ratio 1:1. The study pharmacist generated the randomization code, kept it in sealed envelopes and only broke the seal if a serious adverse event occurred. At every visit the pharmacist prepared and handed to the subjects the study medications. Subjects were required to return the empty vials at every visit to ensure compliance.

A HAM-D17 score of 18 or greater was required for study eligibility. At least a 50% reduction in baseline HAM-D17 score by week 8 of treatment was considered response to treatment as long as the total score was above 7, while remission was defined as a total score less than 7 in HAM-D17 by treatment end. Forty-six patients completed the study; however, MMP9 data for baseline and completion of 8 weeks of treatment was available for only 39 patients. From these 39 patients, 14 were in the placebo group, while 24 were in the Celecoxib group. Healthy control subjects (N=21) were used for comparison of baseline measures, but only 13 of them had MMP9 values.

2.3. Healthy Control Subjects

Potential healthy control (HC) subjects were required to provide written informed consent as approved by the IRB. They then underwent the same screening assessments; routine laboratory tests had to be within normal limits while the main exclusion criterion was any history of psychiatric disorder in themselves or their first-degree relatives. Other exclusion criteria included presence of any medical condition, any inflammatory condition and substance abuse, current or past. HAM-D17 and BDI scores had to be less than 5. A cohort of 21 HC subjects were recruited to match the age range of the study subjects. We obtained MMP9 data for 13 of the 21 HC subjects (Table 1).

2.4. Biochemical Analysis

After an overnight fast, blood draws occurred between 8 and 10 am at baseline, at week 4 and week 8 for patients and once for healthy controls. Peripherally measured MMP9 levels exhibit a diurnal rhythm. The peak is upon awakening and the trough during the nighttime; levels are stable during midday

and into the evening hours. Blood samples were separated into plasma or serum and samples were immediately stored at – 80° C until analyzed. Serum samples were analyzed for cytokines and MMP9 levels by the technique marketed by Randox Technologies using "Evidence Investigator™". Procedures were followed according to the protocols for these assays. Statistical analyses were conducted with GraphPad Prism version 8.0.2 and SPSS version 20. Paired and unpaired t-test was used to compare the mean value of a quantitative parameter between 2 groups, while ANOVA was used to compare 3 or more groups. Pearson correlation was used to investigate the correlation between MMP9 levels and the scores of different scales that were used in the study.

Table 1. *Demographics for TRBDD patients and healthy controls*

		Patients with TRBDD	Healthy controls	p value
Female		61%	54%	0.649[a]
Male		39%	46%	
Age		41.82	42	0.9665[b]
Weight (in Kg)		89.65	73.9	0.0222[b]
BMI		31.85	26	0.0101[b]
Ethnicity	Caucasian	24	10	0.3126[a]
	Non-Caucasian	15	3	
Tobacco users	Yes	13	0	0.0162[a]
	No	26	13	

[a] *Chi-square test*
[b] *t-test*

3. RESULTS

Baseline MMP9 levels in the TRBDD group (n=39) were elevated compared to the HC subjects (n=13), but the difference did not reach statistical significance (P = 0.1668, unpaired t-test), means of 67.81 ng/ml and 43.94 ng/ml, respectively (Figure 1). MMP9 levels in patients with TRBDD declined significantly after 8 weeks of treatment with ESC whether combined with CBX or PBO. Mean week 8 MMP9 level for the entire TRBDD cohort was 50.62 ng/ml compared to 67.81 ng/ml at baseline (p=0.025, paired t-test) and still slightly above the mean of HC subjects (Figure 2).

We compared MMP9 values at baseline and week 8 for the two treatment groups. Surprisingly, there was a statistically significant difference in the ESC + PBO group (p=0.018, paired t-test; Figure 3), but not in the ESC + CBX group (p=0.348, paired t-test; Figure 4). Mean MMP9 value for the ESC + PBO group was 86.41 at baseline and 56.32 at week 8. For the ESC + CBX group the mean MMP9 value was 56.18 at baseline and 47.06 at end of treatment. Both treatment groups showed declines in MMP9 values with treatment. When comparing HC at baseline with the two groups, ESC+PBO and ESC+CBX, there was no statistically significant difference at MMP9 levels. (HC vs ESC + PBO group, p=0.0896; HC vs ESC + CBX, p=0.7744; ESC + PBO group vs ESC + CBX, p=0.1920).

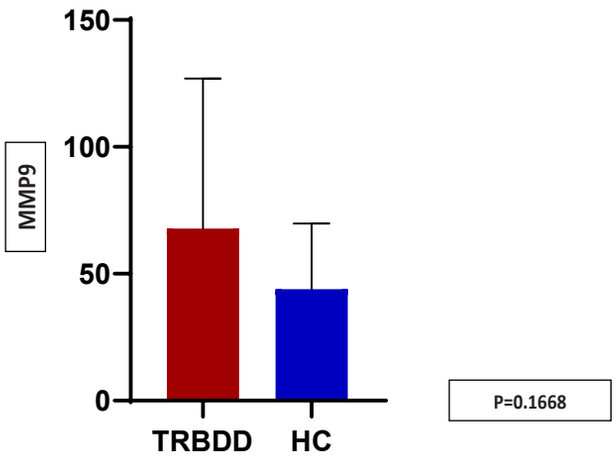

Figure 1. *MMP9 levels at baseline for patients with treatment resistant bipolar depression (Mean=67.81 ng/ml, SD= 59.17) and Healthy controls (Mean=43.94 ng/ml, SD=25.89)*

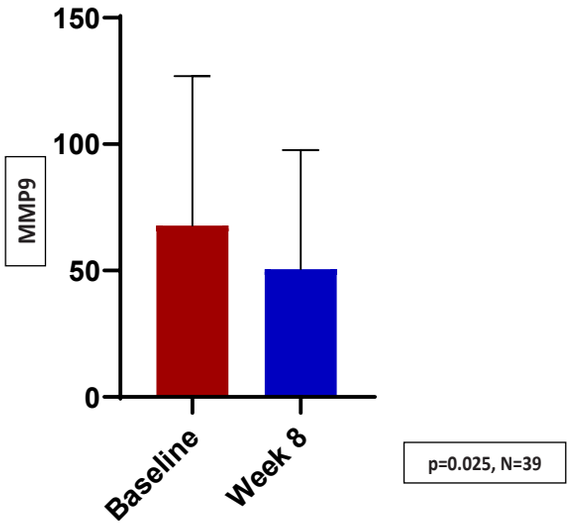

Figure 2. *MMP9 levels for patients with treatment resistant bipolar depression at baseline (Mean MMP9=67.81 ng/ml, SD=59.17) and week 8 (Mean MMP9=50.62 ng/ml, SD=47.04)*

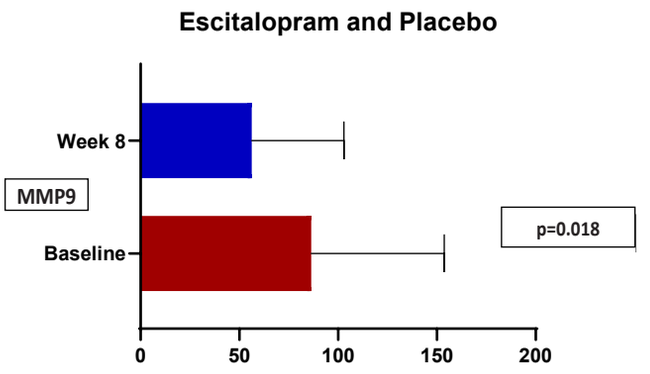

Figure 3. *Placebo group at baseline (Mean=86.41 ng/ml, SD= 67.3) and week 8 (Mean=56.32 ng/ml, SD=46.59)*

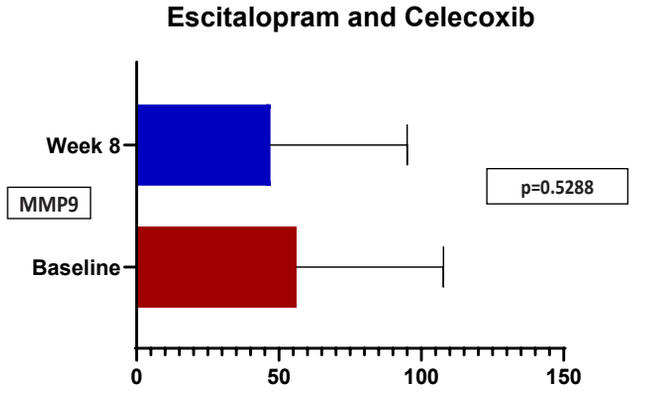

Figure 4. *Celecoxib group at baseline (Mean=56.18 ng/ml, SD=51.58) and week 8 (Mean=47.06 ng/ml, SD=47.96).*

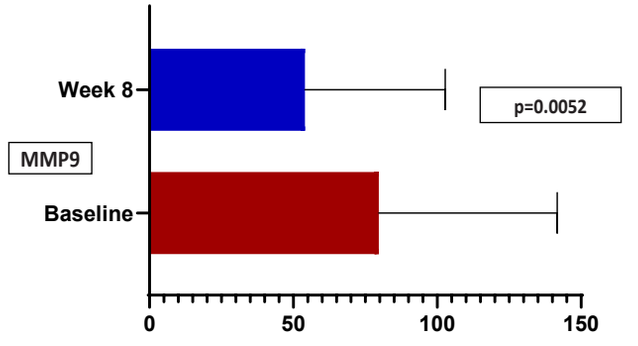

Figure 5. *MMP9 levels for females at the beginning (MMP9=79.71 ng/ml, SD=61.96) and end of treatment (54.03 ng/ml, SD=48.72)*

We then compared MMP9 levels in males (n=15) and females (n=24). There was no statistically significant difference between the two groups at baseline (p=0.113). There was no statistically significant difference when comparing female HC and baseline female BDD patients at baseline or male HC and male BDD patients at baseline. However, females showed a significant change between baseline and week 8 (p= 0.005 vs p=0.793 for men, paired t-test; Figure 5). MMP9 levels declined in the female group from 79.71 to 54.03.

Using the median age of the patient group, we divided them into two age groups, <40 (n=20) and ≥40 (n=19). MMP9 at baseline was statistically significantly higher in the ≥40 patient group (p=0.012). Mean MMP9 values were 91.64 for the ≥40 group, and 45.16 for the <40 group. There was no statistically significant difference in MMP9 levels between baseline and week 8 for the <40 group. MMP9 for the ≥40 group was higher at baseline than week 8 (p=0.075, paired t-test), means of 91.64 and 57.35, respectively (Figures 6 and 7).

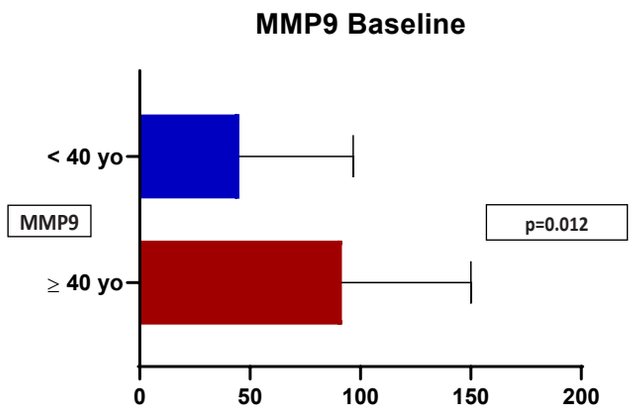

Figure 6. *Baseline levels of MMP9 for the ≥ 40 (Mean=91.64 ng/ml, SD-58.44) and <40 group of patients (Mean=45.16 ng/ml, SD=51.56)*

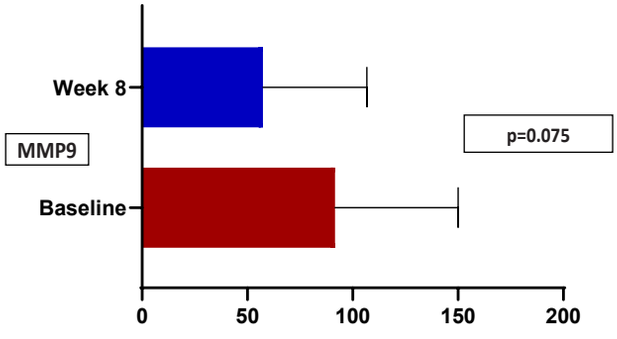

Figure 7. *MMP9 was decreased for patients ≥ 40 years old between baseline (Mean= 91.64 ng/ml, SD=58.44) and week 8 (Mean= 57.35 ng/ml, SD=49.34)*

There was no statistically significant correlation between MMP9 and HAM-D17, HAM-A, MADRS and PSS-14 at baseline, week 4 or week 8. We also assessed the MMP9 SNP rs3918242. Of a total of 39 patients, 30 were non-carriers and 9 were carriers of the SNP rs3918242. In the no-carrier group, 44.1% were males and 55.9% females, whereas in the carrier group 20% were males and 80% females (p=0.169). When adjusting for confounding factors (age, sex, and body mass index), the mean value for MMP9 at baseline was higher for carriers of the MMP9 SNP (80.16) than for the noncarriers (64.09) but the difference did not reach statistical

significance (p=0.486). This is likely due to the small sample size, and we believe that a larger sample size will likely reach statistical significance. Future studies should explore differences in MMP9 levels in carriers and non-carriers of the SNP rs3918242, as it may relate to BBB function. Additionally, in the non-carrier group 38.2% showed no response, while 61.8% responded to treatment. In the carrier group, 30% were non-responders while 70% responded to treatment. That difference was not statistically significant (p=0.634). When we investigated remission, for the non-carrier group 61.8% did not remit while 38.2% were remitters. In the carrier group 40% did not remit while 60% reached remission (p=0.222). We do believe that a greater sample size can reach statistical significance and this difference may have clinical implications.

4. DISCUSSION

In order to more accurately diagnose and more effectively treat BD, we need to better understand its complex pathophysiology. Currently, the diagnosis of BD is established by DSM criteria, that are based on the patient's report and clinical judgement, both of which are subjective. Recent studies have clearly revealed increased levels of pro-inflammatory mediators, such as TNF-a and IL-1b, and decreased levels of anti-inflammatory ones, such as IL-4 and IL-10, in patients with mood disorders. This supports the hypothesis that inflammation plays an important role in the pathophysiology of BD. Biochemical markers can potentially serve as diagnostic markers for mood disorders or even as an adjunctive tool for staging of BD (18).

A potential biomarker that may be used in BD diagnosis, if confirmed in future and larger studies, is matrix metalloproteinase-9 (MMP9), an endopeptidase that plays a role in the plasticity of the central nervous system. Studies have shown an association between MMP9 and unipolar depression (19) as well as symptoms of depression in middle-aged normal population assessed by means of the Center for Epidemiological Studies Depression Questionnaire (CED-S) (20). Increased MMP9 levels are also associated with cardiovascular disease, cancer, multiple sclerosis, schizophrenia and bipolar disorder (11,15).

Our results show a significant association between blood levels of MMP9 in patients with TRBDD compared to HC subjects at baseline. Our findings are in line with the growing body of evidence suggesting a role of neuro-inflammation in the pathogenesis and pathophysiology of BD. Many studies are showing that inflammatory markers are increased in patients with BD in comparison to healthy controls. Therefore, MMP9 can be an adjunctive tool in BD diagnosis In addition, anti-inflammatory treatment could be used to augment antidepressant effectiveness in TRBDD.

Our study showed that women and patients ≥40 years of age rather than men or patients <40 years of age had significantly higher levels of MMP9 at baseline compared to HC subjects. In another study (17), MMP9 levels are higher for BD patients in euthymic state than in HC and patients at a later stage of BD had higher levels of MMP9 levels than patients in earlier stages. More studies with a greater number of patients are needed in order to determine what role MMP9 can play in the diagnosis of BD, its subtypes, the stage of the disorder and treatment resistance. Several polymorphisms of the MMP9 gene have been identified, the MMP9 SNP (rs3918242) seems to have a functional effect on the transcription of the gene. Even though our analysis did not reach statistical significance, the trend shows that MMP9 levels were increased in the carrier group. There was also a trend showing that the group of carriers had greater remission rates. Future studies should focus on the effect of this SNP in the pathogenesis of BD and the response to different types of treatment.

The search for peripheral biomarkers has not, as of yet, resulted in reliable, non-invasive tests that can be used for the diagnosis of psychiatric disorders. The heterogeneity of the pathophysiology and the overlap across different psychiatric disorders make it impossible for a single test to be specific or applicable for any disorder. However, the different biomarkers can be used in addition to the scales and clinical criteria to assist the clinician with the practice of personalized medicine thereby leading to more accurate diagnosis and patient congruent treatment modalities.

There is growing evidence that certain antidepressants and mood stabilizers exert anti-inflammatory and antioxidant effects. In our study, patients were treated with ESC in combination with either CBX or PBO. MMP9 levels were reduced after both treatments. However, the difference was, surprisingly, statistically significant only for the ESC + PBO group. A statistically significant decrease of MMP9 levels was noted for the patients ≥40 years of age and women after treatment. There was a decrease in patients <40 years of age and men as well, but it did not reach statistical significance. Clearly, age and sex are apparent important confounding factors along with the SNP rs3918242 polymorphism; we strongly recommend they should be included in the design of future studies along with further exploration of the MMP9 and potential role of anti-inflammatory treatments.

Limitations: *Relatively small sample size and a short observation period (8 weeks).*

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Conflicts of interest: *The authors declare that they have no conflict of interest.*

Ethics Committee Approval: *This study was approved by the Ethics Committee of Loyola University Medical Center (Approval date: February 4, 2011 and number: LU # 203368)*

Peer-review: *Externally peer-reviewed.*

Author Contributions:

Research idea: AH

Design of the study: AH

Acquisition of data for the study: EF, AT, DH, DH

Analysis of data for the study: DH, DH, JS

Interpretation of data for the study: AH, JF, DH, JS
Drafting the manuscript: EF, AT, DH, JS
Revising it critically for important intellectual content: AH
Final approval of the version to be published: AH

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