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C-Reactive Protein As A Response Indicator In Drug-Naïve Patients With Major Depressive Disorder: A Hospital-Based Study

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Abstract

Objective: C-reactive protein (CRP) is an indicator of the inflammatory process in the body, and is associated with the pathogenesis of depression through its purported effect on neurotransmitter function in the brain. Current research aims to study the relationship between the levels of CRP and the rate of remission of major depressive disorder with first-line antidepressant therapy.

Methods: This hospital-based prospective study included thirty patients by purposive sampling technique. Patients with first-episode MDD with no history of antidepressant exposure and other medical comorbidity were recruited for pharmacotherapy with escitalopram, a first-line antidepressant. Patients taking antidepressants, anti-inflammatory medicines, having co-morbid conditions or other psychiatric conditions were excluded. The baseline CRP levels were measured and depressive symptoms were evaluated using the Hamilton Rating Scale for Depression (HRSD) at weeks 0, 6 and 12. The patients with low (≤5 mg/l) and high (>5 mg/l) CRP levels were compared for remission rates at week 12 using Kaplan–Meier survival analysis.

Results: Amongst the 30 cases, 11(36.7%) were males and 19(63.3%) were female patients. The mean age was 35.95±7.85 years. Both groups were matched concerning age, gender, BMI and baseline HRSD score (p>0.05). As per Kaplan–Meier survival analysis, a significantly higher proportion of patients had remission of MDD at the 12th week having CRP levels ≤5 mg/l than the patients with CRP levels >5 mg/dl (p=0.002).

Conclusion: This research concluded that after an adequate trial with a standard antidepressant, higher levels of CRP could lead to poorer remission rates in MDD subjects and could represent a sub-group of patients with treatment resistance.

Keywords: C-Reactive Protein. Escitalopram. Inflammation. Major Depressive Disorder. Remission. Treatment-resistance.

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1. Introduction

Major depressive disorder (MDD) is a severe psychiatric condition which afflicts adults of all ages from adolescence to old age. The prevalence of MDD is as high as 20%; however, the pathophysiology of this condition is poorly understood.[1] An increasing amount of literature implicates inflammatory mechanisms in the aetiology of MDD.[2] In this regard, inflammatory processes are associated with more severe depressive symptoms, which are often refractory to the commonly used antidepressants.[3] Furthermore, several studies have reported inadequate and poor response to pharmacotherapy in those patients who have higher levels of inflammation.[4] This implies that underlying inflammation in MDD represents a sub-group of patients who have recalcitrant symptoms, which are poorly responsive to standard antidepressants.[5]

There are many laboratory tests which indicate underlying inflammation, and in this respect, C-reactive protein (CRP) is an inexpensive and easily available biomarker. CRP is released as an initial response to several types of inflammatory reactions, infective processes and tissue damage.[6] This is a non-specific marker though. While CRP values are not diagnostic on their own, these do represent an active inflammatory process contributing to the disease state. In patients with MDD, several studies have demonstrated elevated levels of CRP in comparison to the healthy controls.[7] Orsolini et al conducted a systematic review including the 56 researches.[8] He concluded that the raised CRP levels in patients with MDD have an association with severe symptoms and comparatively poor response to therapy as well. Revealing research showed that MDD cases with lower initial CRP levels (<1 mg/L) when treated with standard antidepressants had a good response and improvement in depression scores at week 4.[9] Other studies also demonstrated that this relatively inexpensive indicator of general inflammation could predict differential response to first-line antidepressant medications.[10] Antidepressant medications decrease the levels of inflammation and their past use can lower the overall inflammatory burden in MDD subjects.[11] With this background, this

research had the aims of CRP levels evaluation in drug naïve MDD cases and also to determine the outcome of anti-depressant drug treatment about the levels of the CRP.

2. Materials & Methods

This was a hospital-based prospective study conducted in the Department of Psychiatry of Rawal Institute of Health Sciences, a tertiary care teaching hospital in Islamabad. The ethical clearance was obtained from the Institute's Ethical Review Board. The data collection was conducted over 8 months duration (1st Dec. 2020 to 31st July 2021). Thirty patients presenting to the outpatient Psychiatry department with MDD were recruited for the study using a purposive sampling technique. Written informed consent was obtained from all enrolled patients.

Patients of either gender, ages between 18 and 65 years who were new cases of major depressive disorder diagnosed according to ICD-11 and DSM-5 criteria were included after informed consent. Those with past exposure to antidepressant medications, having erythrocyte sedimentation rate (ESR) more than the reference range (male >20 mm/h; female >30 mm/h), presence of other medical conditions like infective diseases, coronary artery disease, diabetes mellitus, autoimmune diseases, etc. were excluded. Also, those receiving anti-inflammatory medications, with comorbid substance use disorders or suffering from another major psychiatric disorder, for example, bipolar disorder, schizoaffective disorder, etc. were excluded.

The psychometric scale used during the study was the Hamilton Rating Scale for Depression (HRSD). This is a 21-item instrument administered by the investigator and has very good validity and reliability. It was interpreted as follows: score up to 7 – no depression; 8 to 17 – mild depression; 18 to 25 – moderate depression; 26 or above – severe depression. For the study, a score of ≤ 14 was considered as indicating clinical remission. HRSD was administered at the first visit and later at week 6 and week 12 of the follow-up. Eligible subjects were given a demographic proforma on the index visit and venous blood was withdrawn from the ante-cubital vein using aseptic measures. CRP was measured using a high-sensitivity immunoturbidimetry assay and the patients were divided into two groups: Group A with CRP ≤5 mg/l and Group B with CRP >5 mg/l. Finally, for the management of MDD, the patients were started on escitalopram, a selective serotonin reuptake inhibitor. On subsequent visits at week 6 and week 12, the clinical response of escitalopram was assessed using HRSD, and the dosing of the medication was modified if required.

The statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 21. As already mentioned, the patients were divided into groups A (CRP ≤5 mg/l) and B (CRP >5 mg/l). The sociodemographic and clinical data were compared using Chi-square tests (for categorical variables) and independent sample t-tests (for continuous variables). The patients in the two groups were compared for the time taken to achieve remission using Kaplan–Meier survival analysis.

3. Results

In total, 30 newly diagnosed cases of MDD were included in the study. These cases were drug-naïve i.e., hadn't received the therapy for MDD. There were 11(36.66%) males and 19 (63.33%) females. Amongst these, 18 cases were inducted in Group A (CRP ≤5 mg/L) and 12 cases were inducted in Group B (CRP >5 mg/L) after the informed consent. The patients received anti-depressants (i.e., escitalopram and clonazepam) as per recommended practice guidelines. The patients were followed regularly till the completion of 12 weeks. All the cases completed the follow-up and none of these dropped out. Individuals in the 2 groups had no significant differences in sociodemographic variables (p-value > 0.05; Table 1).

Table 1: Study participant's group-wise demographic characteristics (n=30).

Variable	Group A (CRP ≤5 mg/l) n = 18	Group B (CRP >5mg/l) n = 12	*P*-value
Age(mean±SD) years	35.61 plus±7.25	36.29 plus±8.44	0.39
BMI (mean±SD) Kg/m²	28.25±1.55	29.99±1.46	0.18
HRSD (mean±SD) index visit	30.74±6.59	32.77±5.89	0.64
Gender • **Male** • **Female**	07 (39%) 11 (61%)	04 (34%) 08(66%)	0.75

BMI – body mass index; HRSD – Hamilton Rating Scale for depression; SD – standard deviation

The comparison of HRSD scores between group A and B subjects is mentioned in Table 2. There wasn't any statistically significant difference in the mean baseline HRSD score between these two groups (p = 0.64). However, a significant improvement in the HSRD score was recorded in group A in the 6th week (p = 0.004) and 12th week (p = 0.005) of therapy.

While utilizing Kaplan–Meier survival analysis, the cases in group A attained significantly high remission i.e.,12(66%) as compared to group B 4(33%) at the twelfth week of therapy *(p = 0.002; Table 2)*. The cut-off point for remission of MDD for this study was considered to be HRSD ≤ 14.

Table 2: The patients undergoing pharmacotherapy with escitalopram – Hamilton Rating Scale for Depression (n=30)

Parameter		Group A (CRP ≤5 mg/l) n = 18	Group B (CRP >5 mg/l) n = 12	*P* value
HRSD score	week 0	30.74±6.59	32.77±5.89	0.64
	week 6	22.11 ± 5.78	26.39 ± 6.25	0.004*
	week 12	16.96 ± 8.37	18.11 ± 9.89	0.005*
Remission (week 12)		12(66%)	4(33%)	0.002

CRP – C-reactive protein; HRSD MDD

4. Discussion

This study has the purpose of evaluating the role of the level of CRP in the therapeutic outcome of antidepressant therapy in newly diagnosed cases of MDD. The CDC (U.S. Centers for Disease Control and Prevention) and AHA (American Heart Association) have provided the cut-off values of CRP as follows: CRP<1 mg/L has low CV (cardiovascular risk) and low level of systemic inflammation; CRP 1–2.9 mg/L has average CV risk/average systemic inflammation; CRP 3–10 mg/L has high CV risk/high systemic inflammation; and CRP >10 mg/L is associated with acute inflammatory process. Although, on clinical examination neither patients in Group A nor Group B had any signs of systemic illness, Group B subjects did have greater levels of underlying inflammation but were free from an active disease process.

After being treated with a first-line antidepressant for 12 weeks, it was observed that the MDD cases with lower CRP (≤5 mg/l) achieved significant remission as compared to patients with high CRP (>5 mg/l). A literature review showed that low baseline CRP levels were associated with significantly better treatment responses to standard antidepressants as measured by validated psychometric scales.[9,12] Cytokines are other inflammatory markers studied in treatment response in MDD. An interesting study measured pro-inflammatory cytokine and CRP levels in clinically stable MDD cases that received several anti-depressant therapy cycles trials current phase of depressive episodes. The post-hoc analyses showed that the higher concentrations of inflammatory markers before therapy were predictors of poor outcomes in terms of response. The study concluded that measurement of the inflammatory markers, targeting the inflammatory process, or the downstream inflammatory mediators may have relevance in the cases who have treatment failures or recurrence of MDD.[13] Eller et al. researched one hundred MDD cases. He found that the cytokine levels i.e., soluble (IL-2) interleukin-2 receptor, IL-8, and tumour necrosis factor (TNF) alpha were lower in patients who were responders to therapy than those who weren't.[14] The meta-analysis based on 44 studies analyzed several cytokines, chemokines and CRP levels. It was discovered that MDD cases who responded to antidepressant therapy had low baseline IL-8 levels as compared to the non-responders. Also, the antidepressant therapy significantly reduced the TNF-α levels in responders as compared to the non-responders. These findings endorsed the inflammatory hypothesis and we may interpret that the peripheral cytokine levels are linked with the treatment outcome in MDD cases receiving anti-depressant therapy.[15]

Regarding the study limitations, the sample size of this study was 30. This was conducted through purposive sampling. Hence, the study findings should be carefully generalized. It may not account for other possible confounding factors as well. It must be acknowledged that the human immune system is a complex interplay of several interconnected factors, and assessing the CRP levels as the only parameter would be a simple and logical approach. As such the findings from this study probably do not reflect the entire picture. The authors recommend that the results of this study should be interpreted and verified in the context of the above-mentioned limitations.

The strength of this study was the prospective study design. Also, the selection of MDD cases that were not exposed to antidepressant therapy earlier. Hence, we could avoid various confounding factors that could be because of the incomplete drug history, which has been considered a limitation in earlier published literature. Future research should evaluate the potential scope of CRP levels as a biomarker of response, that may be extended to a variety of antidepressants and also may include the inflammatory markers beyond CRP. Although in current research, we included only escitalopram, conceivably future research could investigate the relationship between CRP levels and

response/non-response with other classes of antidepressants apart from SSRIs.

5. Conclusion

In the current study, higher CRP levels were associated with a significantly lower rate of remission at the 12th week of escitalopram therapy. Hence, we may conclude that elevated levels of CRP could lead to a low rate of remission in MDD subjects and could represent a sub-group of patients with treatment resistance.

CONFLICTS OF INTEREST- None

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Contributions:
A.M, N.M, N.S, U.G, N.A - Conception of study
A.M, N.S - Experimentation/Study Conduction
N.S, M.I, U.G, N.A - Analysis/Interpretation/Discussion
A.M, N.S, U.G - Manuscript Writing
N.S, M.I, N.A - Critical Review
N.M, M.I, U.G - Facilitation and Material analysis

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