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PERIPHERAL INFLAMMATORY BIOMARKERS IN DEPRESSION: A REVIEW

Pathology

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ABSTRACT

Use of biomarkers is a routine clinical practice in medicine to provide objective evidence of normal and pathological biological process, response to therapeutic interventions and relapse of disease. However, in field of psychiatry, clinicians mainly rely on clinical interview and psychological tools for diagnostic and therapeutic purposes. Inflammatory biomarkers present a valuable and promising aid to advance better understanding of pathogenesis, diagnosis, treatment and prevention of depression. This review provides a summary of available literature on inflammatory biomarkers in major depression with specific focus on peripheral inflammatory biomarkers which have a potential to be easily used in routine clinical practice.

KEYWORDS

Depression, inflammatory biomarkers, CRP, Cytokines

1. INTRODUCTION

Depressive disorder is the most prevalent psychiatric disorder and World Health Organization estimates that more than 350 million individuals of all ages suffer from depression.[1]Recently concluded National Mental Health Survey reported that overall weighted prevalence of depressive disorders in India was 2.7% for current experience and 5.3% for lifetime experience.[2] Diagnosis of major depression is made on the basis of clinical interviews assisted by various psychological questionnaires. These are generally derived from a list of symptoms derived from Diagnostic and Statistical Manual of Mental Disorders (4th ed.; DSM-IV),[3] its recently revised 5th edition, DSM-5[4] and International Classification of diseases-10th Edition (ICD-10).[5] However a debate is still raging on the value, objectivity of this symptom-based approach to diagnosis[6-8] as well as limitations around making individual treatment plans.

Also, a significant proportion of individuals affected with depression fail to show adequate response to standardized proposed treatment of the disorder, thus contributing to the major proportion of disability associated with major depressive disorder.[9] Also it can take weeks before patients feel full antidepressant effect and there is high rate of relapse and treatment resistance, highlighting the problems with use of antidepressants. So there is need to identify various peripheral biomarkers which can be easily measured and can aid in diagnosis as well as management of major depression in clinical practice.[10,11,12]

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[13]Another definition describes biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease".[14] In medicine, biomarkers are used for predictive, diagnostic, therapeutic, prognostic assistance in various diseases.[15,16,17] Biomarkers also have a potential to overcome some of concerns associated with current symptom-based assessments in psychiatry.

Unfortunately, research on biomarkers in psychiatry is hindered by extensive heterogenicity associated with constellation of symptoms as well as their severity. It is further complicated by high degree of psychiatric and medical comorbidities,[18] and other biological as well as psychosocial factors associated with psychiatric illnesses.

In recent past, significant work has been done and reported on role of immunity and inflammation in the pathogenesis of depression and mechanisms of antidepressant response. Several studies have reported an association of levels of inflammatory biomarkers with depression.[19,20,21,22] Also, it has been reported that inflammatory biomarkers can be used as useful tools in prediction of general and differential response to antidepressants.[23,24] Since peripheral biomarkers can be easily measured, they can prove to be a useful tool in clinical practice. In this paper, many of the most commonly researched peripheral inflammatory biomarkers in major depression are reviewed.

2. A summary of potential diagnostic biomarkers in depression

Various inflammatory biomarkers may be used to assist clinical decision making. Individual inflammatory biomarkers are reviewed here, but it is likely that combination of biomarkers will be needed to achieve sensitivity and specificity rates to the levels required for diagnostic purposes.[17]

2.1. C-reactive protein (CRP)

In a recent meta-analysis, a significant association was found between CRP and major depression **(d = 0.47, p < 0.0001).** This meta-analysis reported that heterogenicity between studies was moderate and no apparent publication bias was notified. Sensitivity analysis of only high-quality studies and subjects free of antidepressant confirmed the positive association between CRP and major depression.[22]Findings from other meta-analyses have also confirmed that major depression is associated with increased CRP levels.[20, 25] In a meta-analysis on longitudinal studies it was also established that there was significant association between baseline increased levels of CRP and depressive symptoms at follow-up even after adjustment for various factors associated with increased levels of CRP and depression.[25]

In a recent study, hs-CRP was found to be elevated in patients with MDD, and more so in treatment-resistant patients.Childhood adversity and specific depressive and anxious symptoms were other phenotypes associated with elevated CRP.[26]

However, these findings are not uniform and a large study has reported CRP levels are elevated in adults with atypical MDD and not nonatypical depression and no MDD, even after adjustment for potential cofounders, anxiety disorders, body mass, and smoking.[27] Another study reported that association of depressive symptoms with higher levels of CRP, was mainly driven by somatic symptoms. For anxiety, somatic symptoms were associated with raised levels of inflammatory markers, whereas cognitive anxiety symptoms were associated with CRP (men only).[28]On subgroup analysis, other studies have reported high CRP in depressed patients with childhood adversity,[29] and cumulative depressive episodes.[30]

2.2. Cytokines

Apart from CRP, cytokines are the most studied inflammatory markers studied in patient with depression. In a recent meta-analysis, IL-1β (pooled standardized mean difference [SMD]: 0.642) and IL-6 (pooled

SMD: 0.377) were significantly elevated in depression as compared to controls. However, there was no difference in TNF-α (p = 0.351) and CRP (p = 0.05)levels between patients with depression and controls.[31]Another meta-analysis involving high quality studies also confirmed an association between IL-6 concentrations and major depression. It also reported a link between TNF-α and depression, but cited inconsistencies between subgroups and extensive heterogeneity in study specific estimates leading to uncertainty about cumulative effect. No association was found between interleukin-1b levels and major depression (d = 0.05, p = 0.86).[22]

Another meta-analysisinvolving cross-sectional studies of IL-6 and IL-10 in people with and without depression was conducted. It reported elevation of IL-6 in depressed compared to non-depressed groups (d = 0.46), with greater effect in subgroups with diagnosed depressive disorders as compared to those with only depressive symptoms. The effect was greater in the group of patients who were not selected for a particular comorbidity as compared to those selected for cardiovascular disease. Effect size for IL-10 was not significant (d = -0.31).[32]

A meta-analysis by Liu et al found that levels of sIL-2R, TNF-α and IL-6 in MDD patients were significantly higher than those of healthy controls (SMD=0.555, p<0.001, SMD=0.567, p=0.010; SMD=0.680, p<0.001); reporting age, samples source and ethnic origins may play a potential role in heterogeneity.[33]

2.3. Neopterin

There has not been consistency as per levels of neopterin levels in patients with depression are concerned. Various studies have reported increased levels of plasma neopterin in depressed patients[34-39];particularly in patients with melancholic symptoms of depression.[36,40]Also higher number of episodes of depression was associated with higher levels of neopterin.[35]These findings are in contradiction with other studies which reported no difference between patients with depression and healthy controls.[41] However, conclusion on levels of neopterin in depression is marred by low number of sample in various studies and lack of meta-analysis.

2.4. TRYCATs (tryptophan catabolites along the IDO pathway)

Various studies have found that depression is associated with lowered tryptophan, increased indoleamine-2,3-dioxygenase (IDO) activity and reduced levels of the neuroprotectiveTRYCAT, kynurenic acid (KYNA). However, these findings are not uniform, [42,43,44] with studies indicating that increased TRYCAT activity may be related to specific subtypes of depression or depressive symptoms. Also studies have reported that increased IDO activity is found in patients suffering from somatisation; concluding that abnormality in TRYCAT pathway is in fact attributable to somatization rather than to depression per se.[43,44] Another study has reported that KYNA level was higher in the subgroup of major depression with suicide attempt as compared to non-attempters, who did not differ from healthy volunteers.[45] However, evidence of findings on TRYCATs is limited by smaller sample size of studies and lack of meta-analysis.

3. Biomarkers associated with the treatment of depression

3.1. The potential of biomarkers as a measure of treatment response

It is need of hour to identify and use treatment responsive biomarkers to add objectivity to clinical interview and use of psychological tools in assessing treatment response.Validation of such markers can be helpful in assessing treatment efficacy by monitoring changes in their levels over time with treatment.

A recent meta-analysis has concluded that treatment with antidepressant significantly decreased plasma levels of IL-4, IL-6 and IL-10 patients with major depression. However, decrease in the IL-1β was significant exclusively for SSRI drugs and no significant effect was found on IL-2, TNF-α IFN-γ and CRP levels with antidepressants.[46]

Another recent meta-anlysis with large data and exclusion of studies on bipolar depression and comorbidities found that levels of of IL-6, IL-10, TNF-α, and CCL-2 are significantly decreased with antidepressants. Although this analysis indicated that these effects may not be associated consistently with response with antidepressant treatment.[47]

Another meta-analysis confirmed that antidepressants lead to significant decrease in IL-6, marginally significant decrease in CRP and a non-significant decrease in IL-10 and higher baseline IL-6 and CRP was associated with greater reduction in depressive symptoms.[48]

Electroconvulsive therapy (ECT) has also been found to affect levels of inflammatory biomarkers in depressed patients. In a recent study on patients with treatment resistant depression higher levels of IL-6 at baseline were associated with lower end-of-treatment MADRS score. IL-6 remained a significant predictor and CRP emerged as a significant predictor for women, but not men after stratification for sex.[49]A study demonstrated that clinical improvement with repeated ECT was accompanied with significant decline in TNF-α in gradual way reaching to levels comparable to healthy controls. Treatment with ECT has also been found to be associated with significantly elevated neopterin levels in depressed responders.[41] Anderson et al. (1992) found that a reduced neopterin:biopterin ratio in psychotic depression was associated with therapeutic response with ECT.[50] A recent review has reported that findings of various studies suggest that a single session of ECT induces an acute, transientimmune activation, whereas repetitive ECT treatment results in long-term down-regulation of immune activation. However, definitive conclusion is precluded by various inconsistencies in findings and methodological issues.[51]

3.2. The potential of inflammatory biomarkers for enhancing personalised treatment

Current practice guidelines recommend prescription of antidepressants based on either clinical factors (such as previous response , side-effect profile) or non-clinical factors (such as patient's preference, cost, availability of drug),[52] despite lack of evidence that such clinical or non-clinical factors can guide antidepressant medication.[53]

It raises the need to identify various biomarkers that can guide the clinician in decision making for most appropriate antidepressant treatment for a particular individual with major depression. Inflammatory biomarkers can be useful as a guiding factor and are poised to profoundly change the current clinical practice. In recent times, a significant amount of research has been taking place in this area and the evidence that is emerging is encouraging.

In a recent study, Uher et al used data from multicentre Genome-Based Therapeutic Drugs for Depression (GENDEP) study to show that CRP, which is an easily available and widely used biomarker can be used as differential predictor of response to different antidepressants. It was found that depressed patients with pre-treatment CRP levels less than 1 mg/L experienced significantly greater reduction in depression as assessed with Montgomery-Åsberg Depression Rating Scale (MADRS), administered weekly. On the contrary, depressed patients with pre-treatment CRP levels ≥1 mg/L had significantly greater improvement with nortriptyline as compared to escitalopram.[24]

Another recent study has reported that baseline CRP levels can predict differential response to different antidepressant treatments. In this study, patients with lower levels of CRP (<1 mg/L) had greater reduction with SSRI monotherapy as compared to SSRI-Bupropion combination. For patients on SSRI monotherapy, improvement was significantly greater in patients with lower levels of CRP (<1 mg/L) as compared to those with CRP levels ≥ 1 mg/L. However, higher baseline CRP levels were associated with greater reductions in depression severity with bupropion-SSRI combination treatment. This study reported that for SSRI monotherapy group, rate of remission were higher in participants with with CRP level <1 mg/L had higher rates of remission as compared to those with ≥1 mg/L CRP level (remission rate=57.14% versus 29.73%). Conversly, for Bupropion-SSRI treatment arm, CRP levels ≥1 mg/L CRP level were associated with higher rates of remission as compared to <1 mg/L CRP level (remission rate=51.35% versus 33.33%). In this study, remission rate with baseline CRP guided treatment assignment was 53.10% as compared to 30.9% remission in biomarker mismatched arm.[54] This finding is valuable as CRP matched remission rates are significantly higher than remission rates of 33% in the first step of STAR*D study.[55]

A previous study has also (Harley et al) reported that higher pre-treatment CRP is a predictor of poor response to psychotherapy (cognitive–behavioral or interpersonal psychotherapy), but a good response to pharmacological treatment (nortriptyline or fluoxetine).[56] Although CRP is a practical biomarker for treatment selection, its

levels are raised in multiple acute and chronic conditions. So, there is need to identify more inflammatory biomarkers that are more specific and easily measurable. Recently, a study has reported that higher baseline levels of more specific IL-17 was associated with greater reduction in depression severity in patients treated with bupropion-SSRI combination. However, no such association was seen in patients treated with SSRI monotherapy and venlafaxine-mirtazapine combination treatment arms.[57]Another recent study has found that greater baseline platelet derived growth factor level was associated with greater improvement in depression and anhedoniawith Bupropion- SSRI but not with SSRI monotherapy or venlafaxine-plus-mirtazapine.[58]

3.3. Anti-Inflammatory Drugs as Novel Antidepressants

Along with identifying various predictors of clinical response to antidepressant treatment, there is also need to identify newer medications with novel mechanism of action for patients with treatment-resistant depression (TRD). A meta-analysis has highlighted the potential usefulness of anti-inflammatory drugs in depression. It reported that adjunctive use of celecoxib, a NSAID, led to greater reduction in depression severity as well as greater remission and response rated as compared to placebo.[59]Anti-cytokine drugs targeting inflammatory pathways implicated in pathogenesis of depression have emerged as potential novel antidepressants. In a study, Raison et al found that while there was no overall difference between Infliximab or placebo in patients with TRD, infliximab was superior to placebo in improvement of depression severity in subgroup of TRD patients with CRP $\geq$ 5 mg/ml.[60]

A recent meta-analysis concluded that patients receiving anti-inflammatory agents had lower post-treatment depressive symptom scores as compared to those receiving placebo and has recommended further high quality trials for the routine clinical use of anti-inflammatories in depression.[61]Recently, trials of various humanized monoclonal antibodies against IL-6 and IL-17 receptor have shown promising results in their effects on depressive symptoms.[62,63,64] However, these trials were not conducted in depressed patients without autoimmune diseases as substantial risk is associated with anti-cytokine treatment.

4. The potential of biomarkers to predict the onset of depression

Several biopsychosocial factors are known to be associated with an increased risk of depression or relapse of depression. Measurement of biomarkers also offers an additional option for risk identification, enabling various preventive strategies, early identification, treatment and relapse prevention.

Higher levels of CRP have been identified as independent risk marker for de novo depression in women[65] and predicts increased risk for hospitalisation with depression.[66] Valkanova et al have reported that raised CRP, and to a lesser extent IL-6,was associated with an increased risk of subsequent depressive symptoms.[25]A study on people undergoing IFN-α treatment for hepatitis C has also reported that KYNA levels are positively associated with increased risk of depression.[67]

5. Literature from India

Although late, but Indian researchers are also coming up with studies assessing inflammatory biomarkers in depression. Recently, many studies have been published from India, which needs special mention in this review.

In a recent study on Indian population, significantly raised baseline levels of TNF-α and IL-6 but not TGF-β were found in drug naïve depressed individuals as compared to apparently healthy controls. Males and females were comparable on levels of inflammatory biomarkers.[68]A study from North India reported that serum levels of hs-CRP were significantly higher in drug-naïve patients with depression as compared matched healthy controls, underlying the presence of low-grade inflammation in patients with depression.[69]

A short term study from South India has reported that there was statistically insignificant chage in levels of TNF-α, IL-6 and TGF-β and reduction in depression severity scores was not accompanied by corresponding decline in these inflammatory markers.[70]Another Indian study has reported levels of CRP and IL-2 decreased significantly after 8 weeks of treatment with antidepressants. Although, levels of IL -6 were significantly raised in the subjects after treatment.[71]

6. Conclusion

Although measurement of inflammatory biomarkers has great potential, the research on its clinical utility is still in early days. Inflammatory biomarkers provide an alternative and objective way for assistance in diagnosis, prognosis and selection of individualised treatment of major depression. Inflammatory biomarkers still lack the sufficient sensitivity and specificity to use them in isolation for clinical practice. This signifies the need for further future studies which have large sample size, covers more number of ethnic and racial groups, takes various patient and disease variables into account and addresses various inconsistencies in specimen collection, storage and measurement. Also research on biomarkers has primarily focussed on treatment with antidepressants and ECT and there is need for further research in other treatment modalities such as psychotherapy and lifestyle interventions. Initial and encouraging findings obtained from the research of effects of anti-inflammatory medications have opened scope for further research on newer antidepressants with novel mechanisms.

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