Original Research Article

The inflammatory biomarkers: Are they correlated with severity of depression?

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Abstract

Background: Depression is one of the most common disorders. It has 5% prevalence worldwide and 2.8% in India. One of the etiological hypotheses for depression is inflammatory mechanism. Neutrophil lymphocyte ratio (NLR), cortisol, and vitamin D are the marker of systemic inflammation. This study assessed the association and correlation between Neutrophil lymphocyte ratio, cortisol, and vitamin D with depression and its severity.**Aim:** To see the association between Neutrophil lymphocyte ratio,cortisol, Vitamin D with depression and their correlation with the severity of Depression.**Methodology:** This study included 120 patients with depression and 120 healthy controls. Severity of depression was assessed by Hamilton Depression Rating Scale (HAM-D). N/L ratio, cortisol, and vitamin D were measured in both groups. Comparison of socio-demographic profile by independent T-test and Pearson correlation was applied to see correlation between variables. ANOVA test was applied to compare both the groups in terms of biomarkers.**Results:** N/L ratio, cortisol, and vitamin D were significantly deranged in cases compared to controls. A positive correlation was observed between severity of depression and N/L ratio and cortisol and an inverse correlation with vitamin D. **Conclusion:** There is association between N/L ratio, serum cortisol and vitamin D with depression and it also has correlation with severity of depression.

Keywords: Depression,biomarkers,NLR Ratio,cortisol,vitamin D

Introduction

Major depressive disorder is one of the most common psychiatric disorders. The prevalence of depression worldwide is 5%[1]. As per National Mental Health Survey, 2016, the prevalence of depression in India is 2.68%[2]. It is also the leading cause of disability worldwide[3].It has been associated with alteration in Central nervous system, immune response, and vascular reactivity and all these are important in the generation of a systemic inflammatory response.Many studies have seenthe relationship between depression and the immune system. These studies showed alterations in the inflammatory process like increased production of interleukin-1 (IL-1),interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-alpha)[4]. So,alteration in immune system may play a role in the etiopathogenesis of depression[5-7]. Also,Antidepressants have been shown to decrease and normalize high pre-therapeutic serum proinflammatory cytokine levels[6,8]. Stress and depression may result in an increased number of leukocytes and neutrophils, as well as decreased lymphocytes[4]. So Neutrophil lymphocyte ratio(NLR) can be a bio-marker in depression.Inverse relationship has been seen between vitamin D and depression[9]. Light therapy has been shown to improve depression, which may bedue to improved vitamin D synthesis during the light therapy[10]. So, vitamin D level can be a biomarker for depression and its deficiency can lead to poor treatment response. Supplements to the same can help in treating depression.

The increased activity of the HPA axis has found to be associated with depression[11].It may be due to reduced feedback inhibition by endogenous glucocorticoids.There are studies which showed glucocorticoid-mediated feedback inhibition is impaired in patient with depression.Successful treatment of depression is also associated with the resolution of impairment in negative feedback on the HPA axis by glucocorticoid[12].So all the above evidence suggeststhat serum cortisol increases in depression.

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Methodology

Across-sectional study which was conducted at the Outdoor and Indoor service at Psychiatric Centre,Sawai Man Singh Medical College, Jaipur.Clearance from the ethical committee was taken. The study period was from June 2019 to August 2020.

The aim of the study wasTo see the association between NL ration, cortisol, Vitamin D and depression and their correlation with the severity of Depression in patient and health controls.

Sample size was calculated where 120 cases and 120 controls were taken.

Inclusion criteria's for patient were diagnosed witha depressive episode according to ICD-10, age 18 years to 59 years, either sex, participants to give informed consent and literate enough to understand and perform a questionnaire. Patient with any inflammatory disease, hematopoietic system disorders, history of (h/o) malignancies/chemotherapy, acute infection and chronic inflammatory status, acute coronary syndrome, h/o using glucocorticoid therapy in the past 3 months, h/o of chronic renal or hepatic disease, h/o Substance other than tobacco and h/o other psychiatric disorder were excluded.

Inclusion criteria's for healthy controls wereage 18 to 59 years, either sex, participants to give informed consent, literate enough to understand and perform a questionnaire. Exclusion criteria were same for the patient and healthy controls.

Instruments of study

A written consent was taken from both the groups. A screening Performa was applied which contained all the exclusion criteria in

yes/no format. This also included name, age, sex, father's /husband's name, address, marital status, education, occupation, type of family and monthly income history of suicide attempt, family history of suicide. Then a Clinical profile Performa was applied which included number of episodes, duration of the illness, age at onset of the illness, number of hospitalizations, suicide attempts, family history of affective disorders. Hamilton Depression Rating Scale (HAM-D) was applied to quantify the severity of depression. Laboratory investigations was done which included Neutrophil/lymphocyte ratio, Serum cortisol and Serum vitamin D.

Statistical analysis: Qualitative variables included gender, marital status, educational level, socio-economic status. These variables were statistically compared between cases and controls using the Chi-square test. For normally distributed quantitative continuous variables like age, the two groups were compared using an independent T-test.Pearson Correlation was applied to see the correlation between biomarkers and severity of depression. A Scatter plot was made to graphically represent the correlation. ANOVA test was applied to compare two groups. At 95% confidence interval was taken and p <0.05 was considered to be statistically significant.

Results

Both thegroups were comparable to each other. There was no statistically significant difference among two groups.The majority of the patients were married, Hindu, males, rural background, belonging to middle socioeconomic class and living in a nuclear family.

Table 1: Comparison of bio-markers among cases and control

Category	NL Ratio	Cortisol	Vit D
Cases Mean [SD]	2.0[0.6]	27.9[5.0]	16.1[6.6]
Control Mean [SD]	1.6[0.26]	13.9[4.0]	37.5[7.9]
Test statistic & p value	7.0, 0.00	23.6, 0.00	-22.5, 0.00

Table no. 1 Showing the comparison of biomarker among depression cases and healthy controls. Table showing that Peripheral biomarkers are significantly deranged in patient with depression as compared to healthy controls.

Table 2: Correlation of HAM-D scores with biomarkers

HAM-D	NLR	Cortisol	Vitamin D
Mean value [SD]	2.04[0.6]	27.9 [5.0]	16.0 [6.6]
Correlation coeff. With HAM-D	0.47	0.27	-0.31
P value	**0.00**	**0.006**	**0.00**

Table no. 2 showing the Correlation between the severity of depression (HAM-D) and biomarkers. Results showing that NL ratioand Cortisol showing a positive correlation while Vitamin D showing a negative correlation. All typesof correlation are statistically significant.

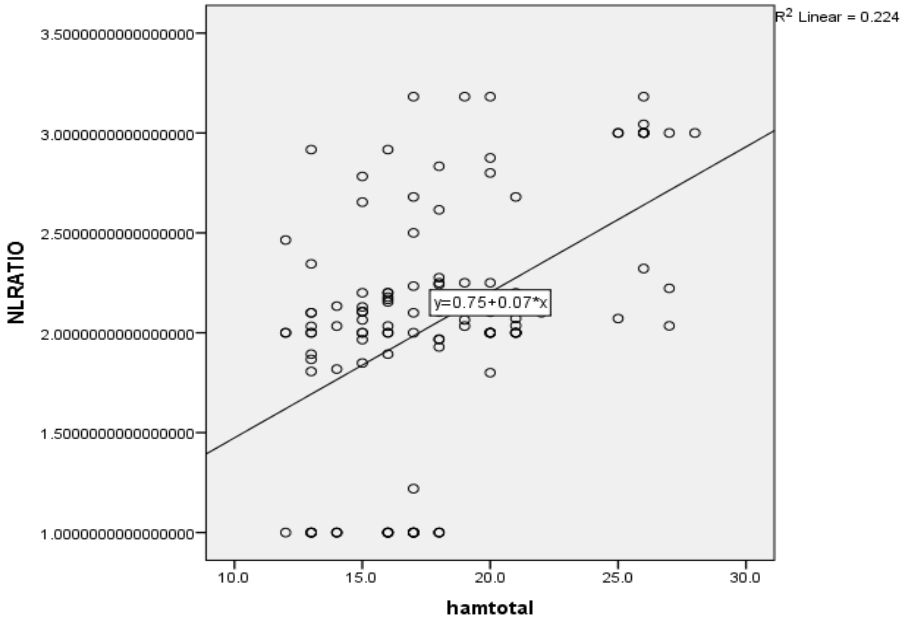

Fig 1:Scatter diagram of HAM-D and N/L ratio

Fig 1shows the positive correlation between HAM-D and N/L ratio.

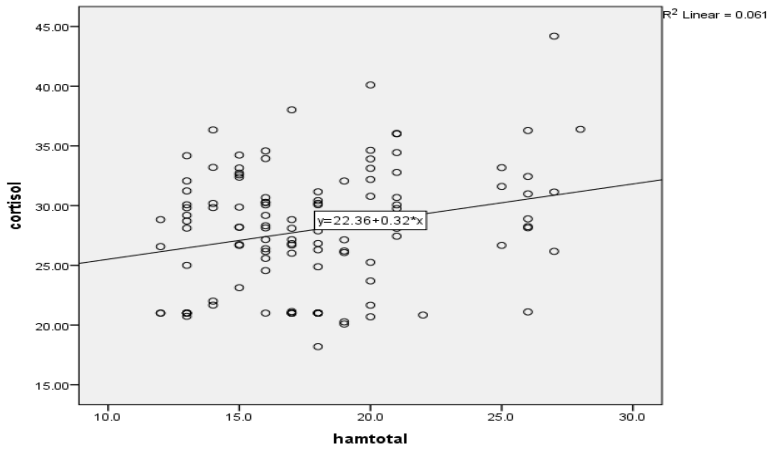

Fig 2: Scatter diagram of HAM-D and cortisol

Fig 2 showing the positive correlation between HAM-D and cortisol

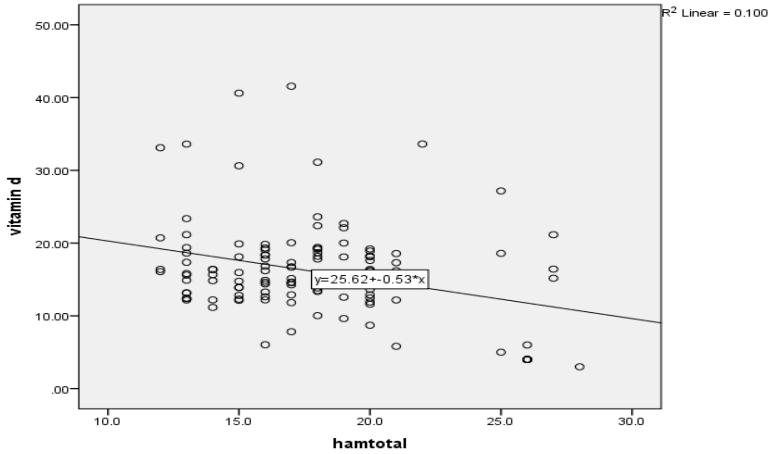

Fig 3:Scatter diagram of HAM-D and vitamin D

Fig 3showing an inverse correlation between HAM-D and vitamin D

Discussion

The major focus of the present study was to assess the peripheral biomarkers in depression and to see the correlation with severity of depression. The selection criteria were made stringent to minimize the confounding factors in the evaluation ofperipheral biomarkers. Such confounding factors were extremes of age, co-morbid psychiatric or significant physical disorders, significant substance use, co-morbid systemic inflammatory disease.Both groups were compared upon socio-demographic profile and finally, peripheral biomarkers were assessed. Two groups were comparable to each other according to the sociodemographic data and there was no statistically significant difference between the two groups. The mean age of the patient with depression and healthy controls were 36.9 (10.1), 38.60(10.3) respectively, which were not significantly different on statistical analysis (P=0.59). There were no statistically significant differences in the gender composition of the two groups in this present study(P=0.30). There were overall 93 (77.5%) married and 85(70.83%) in cases and controls respectively. All two groups did not differ significantly in terms of marital status (P value=.40) and educational status (P=0.31).In our study 24(20%) patient had mild depression, 53(44.16%) had moderate depression, and 30 (25%) had severe depression and 13 (10.8%) had very severe depression.Neutrophil lymphocyte ratio (NLR) in cases 2.04 with SD 0.6 and in controls 1.6 with SD 0.26. It was statistically significant (P=0.00)[13-16]. This study found a positive correlation between HAM-D and N/L ratio with a correlation coefficient0.47 which was statistically significant (P=0.00). As the severity of depression increases NLR ratio increases[15,16]. Possibly as the severity of depression increases inflammation increases so the NLR ratio. In this study, cases had a mean serum cortisol level 27.9 with a standard deviation of 5.0 and in controls the mean level was 13.9 with SD 4.0. The difference was statistically significant (P=0.00). Serum cortisol level was higher in cases as compared to controls[17-19]. We also observed the correlation of severity of depression and serum cortisol level(by HAM-D and serum cortisol). In this study Correlation coefficient between HAM-D and serum cortisol was 0.27 which was statistically significant (P=0.006). We observed that asthe level of cortisol level increasingso also the severity of depression[17-20]. Potential mechanisms related to these findings are unclear but it may be due to changes in theHPA Axis during the stress and depression. In this study mean Vitamin D level in cases was 16.1 with SD 6.6 and in controls was 37.5 with SD 7.9. Cases were having more vitamin D deficiency than controls. The difference was statistically significant (P=0.00)[9,10,21] In this study, the correlation between the severity

of depression and vitamin D level was observed. The correlation coefficient was -0.31 which was statistically significant (P-value =0.00). So, in this study, there was an inverse correlation between the severity of depression and vitamin D level [22-24]. however, There are negative studies also available for the same[25,26]. One study found the correlation between vitamin D and depression but found no correlation between the severity of depression and vitamin D level[21].No data on sun-exposure, dietary intake, and geographical regions were evaluated In previous studies and our study. So, the effect of confounding factors cannot be commented.

Conclusion

This is a cross-sectional study to see the association of peripheral biomarker in patients of depression and healthy controls. We also tried to find out their correlation with the severity of depression.This study found that peripheral biomarkers were significantly deranged in patients compared to healthy controls. The severity of depression had a positive correlation with NLR and cortisol and the inverse correlation with serum vitamin D.

Limitations and Future directions

This was a cross-sectional study which might not allow a definitive conclusion about the causal link between biomarkers and depression. The sample size was small.The duration of illness and number of episodes were not considered. further studies requires for definitive conclusions.

References

1. Driessen E, Hollon SD. Cognitive behavioral therapy for mood disorders: efficacy, moderators and mediators. Psychiatr Clin North Am. 2010;33(3):537–555
2. Murthy Rs. National mental health survey of India 2015–2016. Indian J Psychiatry. 2017;59(1):21.
3. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 ;392(10159):1789–858.
4. Erturk M, Cakmak HA, Surgit O, Celik O, Aksu HU, Akgul O, et al. The predictive value of elevated neutrophil to lymphocyte ratio for long-term cardiovascular mortality in peripheral arterial occlusive disease. J Cardiol. 2014;64(5):371–6.
5. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006 ;27(1):24–31.
6. Janssen DGA, Caniato RN, Verster JC, Baune BT. A psychoneuroimmunological review on cytokines involved in antidepressant treatment response. Hum Psychopharmacol Clin Exp. 2010;25(3):201–15.
7. Krishnadas R, Cavanagh J. Depression: an inflammatory illness?:J Neurol Neurosurg Psychiatry. 2012 ;83(5):495–502.
8. Hannestad J, DellaGioia N, Bloch M. The Effect of Antidepressant Medication Treatment on Serum Levels of Inflammatory Cytokines: A Meta-Analysis. Neuropsycho pharmacology. 2011;36(12):2452–9.
9. Milaneschi Y, Hoogendijk W, Lips P, Heijboer AC, Schoevers R, van Hemert AM, et al. The association between low vitamin D and depressive disorders. Mol Psychiatry. 2014;19(4):444–51.
10. Ganji V, Milone C, Cody MM, McCarty F, Wang YT. Serum vitamin D concentrations are related to depression in young adult US population: the Third National Health and Nutrition Examination Survey. Int Arch Med. 2010;3(1):29.
11. Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM, et al. Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. Proc Natl Acad Sci U S A. 1996 Feb 20;93(4):1619–23.
12. Pariante CM. The glucocorticoid receptor: part of the solution or part of the problem? J Psychopharmacol (Oxf). 2006 Jul;20(4_suppl):79–84.
13. Demir K, Avci A, Altunkeser BB, Yilmaz A, Keles F, Ersecgin A. The relation between neutrophil-to-lymphocyte ratio and coronary chronic total occlusions. 2014;6:1
14. Arabska J, Łucka A, Magierski R, Sobów T, Wysokiński A. Neutrophil-lymphocyte ratio is increased in elderly patients with first episode depression, but not in recurrent depression. Psychiatry Res. 2018;263:35–40.
15. Aydin Sunbul E, Sunbul M, Yanartas O, Cengiz F, Bozbay M, Sari I, et al. Increased Neutrophil/Lymphocyte Ratio in Patients with Depression is Correlated with the Severity of Depression and Cardiovascular Risk Factors. Psychiatry Investig. 2016 ;13(1):121–6.
16. Özyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. Psychiatry Res. 2018;268:426–31.
17. Jia Y, Liu L, Sheng C, Cheng Z, Cui L, Li M, et al. Increased Serum Levels of Cortisol and Inflammatory Cytokines in People With Depression: J Nerv Ment Dis. 2019 ;207(4):271–6.
18. Naveen GH, Varambally S, Thirthalli J, Rao M, Christopher R, Gangadhar BN. Serum cortisol and BDNF in patients with major depression—effect of yoga. Int Rev Psychiatry. 2016 ; 28(3):273–8.
19. Shabaan MAS, Shaaban I, Alatram AR, Gad EF,.The relationship of serum cortisol levels with severity of depression and age in major depression. Al-Azhar Assiut Medical Journal. 2015;13(4):4.
20. M. Abdul− Hussain M, K. Habash N, M.Alramahy M, M. Shamkhi N. Association of Cortisol with severity and duration of depression in male and female. Afr Health Res Organ. 2019;22(04):81–7.
21. Elseesy SW, Goueli T, Mostafa A, Afif A, Khalil MA. Relation between vitamin D level and severity, symptomatology and cognitive dysfunction of major depressive disorder—A sample of Egyptian patients. Neurol Psychiatry Brain Res. 2020 ;35:10–5.
22. Armstrong DJ, Meenagh GK, Bickle I, Lee ASH, Curran E-S, Finch MB. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. Clin Rheumatol. 2007;26(4):551–4.
23. Sharma N, Bharti S, Jilani AQ, Agarwal A, Singh S, Sharma R. Clinical correlation of vitamin D in depression. Int J Adv Med. 2019 ;6(4):1008–15.
24. Hoogendijk WJG, Lips P, Dik MG, Deeg DJH, Beekman ATF, Penninx BWJH. Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults. Arch Gen Psychiatry. 2008;65(5):508.
25. O'Donovan A, Rush G, Hoatam G, Hughes BM, McCrohan A, Kelleher C, et al. Suicidal ideation is associated with elevated inflammation in patients with major depressive disorder. Depress Anxiety. 2013 Apr;30(4):307–14.
26. Zhao G, Ford ES, Li C, Balluz LS. No associations between serum concentrations of 25-hydroxyvitamin D and parathyroid hormone and depression among US adults. Br J Nutr. 2010 Dec 14;104(11):1696–702.

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