DOI: 10.7860/JCDR/2021/48611.14955

Original Article

Physiology Section

Association of C-Reactive Protein with Mild and Severe Depression

SONI SINGH[1], SUNITA TIWARI[2], WAHID ALI[3], SHRADDHA SINGH[4]

ABSTRACT

Introduction: Depression is associated with increased serum C-Reactive Protein (CRP) levels in circulation. Inflammatory response is established as an important factor in the pathophysiology of depressive disorders. Increased levels of CRP are associated with Cardiovascular diseases.

Aim: The objective of the present study was to assess the changes in circulating CRP level according to severity of depression.

Materials and Methods: A cross-sectional study was conducted in Physiology Department of KGMU, Lucknow, Uttar Pradesh, India, with time duration of one year. Study group comprised of 40 drug naïve depressive patients between the age group of 18-40 years enrolled in the study. Diagnosis of depression was based on International Classification of Diseases (ICD-10). Patients were divided into two groups (mild depression and severe depression) on the basis of severity of depression accessed via Hamilton Depression Rating Scale (Ham-D). Serum CRP levels were accessed on both groups by commercially available ELISA kit.

Results: Statistically insignificant relationship was seen when age (p=0.14), Blood Pressure (BP) {Systolic Blood Pressure (SBP) (p=0.102) and Diastolic Blood Presure (DBP) (p=0.270)}, Body Mass Index (BMI) (p=0.539) were compared with both mild and severe depression group. Serum CRP levels and both the depression group (mild depression and severe depression) showed statistically significant relationship (p=0.015).

Conclusion: It can be concluded that there exist a significant association of serum CRP levels with severity of depression. Patients with severe depression have lower levels of CRP as compared to patients with mild depressive symptoms.

Keywords: Body mass index, Cardiovascular morbidity, Inflammatory cytokine

INTRODUCTION

Depression is a highly prevalent disease with significant risk of cardiovascular morbidity and mortality [1,2]. According to World Health Organisation (WHO), more than 264 million people are living with depression worldwide [3]. Depression has an elevated risk for recurrence and chronicity. According to ICD-10, depression is classified as mild (F32.0), moderate (F32.1) and severe depression (F32.2). Recently, it has been identified that depression is a strong and independent risk factor for cardiovascular diseases even in physically healthy individuals [4,5]. The rate of depression in patients with cardiovascular disease ranges between 20-40% [6]. It has been shown that increased levels of proinflammatory cytokines are associated with the development of major depressive disease [7,8]. It has been well-established that elevated CRP is a predictor for cardiovascular diseases, and cardiovascular risk is higher among depressed individuals than non depressed individuals. Increase in inflammatory cytokines causes reduction of serotonin and other neurotransmitters in Central Nervous System (CNS) and further reduces the activation of the hypothalamic-pituitary-adrenal axis, leading to elevated oxidative stress in the brain. This visceous cycle continues causing worsening of symptoms of depression [9]. This increased oxidative stress leads to increased cardiovascular morbidity and mortality which include diseases like hypertension, stroke, atherosclerosis, myocardial infarction and congestive heart failure. A study suggested that the brain-cytokine system can alter neurotransmitters and neuronal circuits that lead to pathological behaviour of an individual [7].

However, the changes in CRP levels according to severity of depression has not been studied till now. Therefore, the objective of the present study is to find out whether severity of depression has any effect on circulating serum CRP levels.

MATERIALS AND METHODS

In this cross-sectional observational study, 40 drug naïve, newly diagnosed patients suffering from depression were recruited. Patients were from Outpatient Department of Psychiatry, King George's Medical University Hospital, Lucknow, Uttar Pradesh, India. Time period for conducting the study was one year.

Ethical clearance was taken from Ethical committee KGMU before the start of research activity (Ref. code- 97 ECM II B- Thesis/P16, dated: 29/9/2019). Informed written consent was obtained from each patient. All the patients were interviewed by experienced psychiatrists. The patients were divided into two groups {mild depression (F32.0) and severe depression (F32.2)} according to the severity of symptoms based on ICD-10.

Sample size calculation: Sample size was calculated on the basis of proportion of raised CRP level among the population under study using the formula:

$$n=\frac{Z_{\alpha}^{2}pq}{L^{2}}$$

Where, p=20.5% (average of 13.7 in males and 27.3% in females) proportion of raised CRP level [10]

q=100-p,

Type I error α=5%, for the significance level of 95%.

Allowable error L=10% absolute for detecting the results with 80% power of study,

The minimum sample size required came out to be n=65.

Forty patients were included due to COVID-19 pandemic. Out of 40 cases, 22 were males and 18 were females.

Inclusion criteria: Age between 18-40 years; irrespective of gender were included. Diagnosis and classification of depressive patients according to severity of symptoms was based on ICD-10

Classification of Mental and Behavioural Disorders [11]. For assessing the severity of depression Hamilton Depression Rating Scale (Ham-D) was used on all patients via a structured interview.

Exclusion criteria: Patients with history of any metabolic syndrome, history of any cardiovascular disease, history of any other psychiatric illness, epilepsy, head injury, alcohol intake and smoking were excluded.

The BP was measured manually by sphygmomanometer. Height and weight of each patient was taken and BMI was calculated by the formula wt (in kgs)/Ht^2 (in mtrs). Peripheral blood sample of about 2 mL was obtained from each patient by venipuncture and collected in a plain vial between 9 am to 12 noon. Serum was isolated from blood via centrifugation at 3000 rpm for five minutes and stored at -24°C. This procedure was followed till all the samples were collected and then quantification of CRP levels was done at once by Enzyme Linked Immunosorbent Essay (ELISA) method. Serum levels of CRP were measured by commercially available ELISA Kit in Pathology Department (manufactured by Bioassay Technology Laboratory, Korain Biotech Co., Ltd.,).

STATISTICAL ANALYSIS

Statistical analysis was accomplished using SPSS 23 statistical software. Descriptives were stated as the mean±Standard Deviation (SD). Comparison of serum CRP levels between mild depression patients and severe depression patients was done with "unpaired t-test." A p-value ≤0.05 was considered to be statistically significant.

RESULTS

A total of 40 cases were enrolled in the study, 20 with mild depression and 20 with severe depression. Mild depressive group comprised of 13 males and 7 females with mean age of cases 34.7 years (SD-5.87). Severe depressive group comprised of 9 males and 11 females with mean age of cases 31.9 years (SD-6.36). There was no statistically significant relationship in age and severity of depression (p=0.14). Most of the patients belonged to sedentary type of occupation followed by housewife and few belonged to field work [Table/Fig-1-3].

Depression	Age in years		t-value	Unpaired t-test value
	Mean	SD		
Mild	34.75	5.87	1.472	0.149
Severe	31.90	6.36		

[Table/Fig-1]: Age distribution of patients.

Depression	Male		Female		Total	
	No.	%	No.	%	No.	%
Mild	13	65.0	7	35.0	20	100.0
Severe	9	45.0	11	55.0	20	100.0
Total	22	55.0	18	45.0	40	100.0

[Table/Fig-2]: Sex distribution of patients.

Occupation	No.	%
Sedentary	19	47.5
Field work	9	22.5
Housewife	12	30
Total	40	100.0

[Table/Fig-3]: Distribution of patients according to occupation.

Since, the present study focused on comparison of serum CRP levels between mild and severe depression cases, therefore moderate group was not employed in the study. Also, few cases with moderate depression were seen during OPD visits.

On comparing BP in mild depression group to severe depression group, it showed statistically insignificant relationship. For SBP (p=0.102) and for diastolic (p=0.789). When gender based comparison of systolic and diastolic BP were made between mild and severe depression group, statistically insignificant values were obtained [Table/Fig-4-5].

Group	Depression	SBP		t-value	Unpaired t-test value
		Mean	SD		
Overall	Mild	131.80	8.80	1.675	0.102
	Severe	126.90	9.68		
Male	Mild	130.00	10.17	1.772	0.092
	Severe	122.89	7.69		
Female	Mild	135.14	4.30	1.208	0.245
	Severe	130.18	10.22		

[Table/Fig-4]: Distribution of Patients according to SBP.

Group	Depression	DBP		t-value	Unpaired t-test value
		Mean	SD		
Overall	Mild	82.70	7.18	0.270	0.789
	Severe	82.10	6.88		
Male	Mild	80.77	7.73	0.181	0.859
	Severe	80.22	5.70		
Female	Mild	86.29	4.54	0.825	0.422
	Severe	83.64	7.63		

[Table/Fig-5]: Distribution of patients according to DBP.

On comparing BMI of mild depression group to severe depression group, statistically non significant relationship was seen (p=0.539). Gender specific comparison between BMI and both depression group showed statistically insignificant values, males (p=0.500) and females (p=0.683) [Table/Fig-6].

Group	Depression	BMI		t-value	Unpaired t-test value
		Mean	SD		
Overall	Mild	21.65	1.12	-0.620	0.539
	Severe	21.85	0.94		
Male	Mild	21.35	1.16	-0.687	0.500
	Severe	21.66	0.84		
Female	Mild	22.21	0.88	0.415	0.683
	Severe	22.01	1.03		

[Table/Fig-6]: Distribution of patients according to BMI.

The mean value of serum CRP in mild depression patient group was 1.23 and in severe depression group was 2.60. Statistically, significant relationship was found between Serum CRP levels and both (mild and severe) depression group (p≤0.015). In males, statistically significant relationship was obtained between serum CRP levels and both (mild and severe) (p=0.027). Similar result was seen in female patients with p=0.04 [Table/Fig-7].

Group	Depression	CRP		t-value	Unpaired t-test value
		Mean	SD		
Overall	Mild	1.23	1.15	-2.556	0.015
	Severe	2.60	2.10		
Male	Mild	1.54	1.33	-2.391	0.027
	Severe	3.35	2.22		
Female	Mild	0.66	0.13	-2.335	0.041
	Severe	1.99	1.89		

[Table/Fig-7]: Distribution of patients according to CRP.
Statistically significant <0.05

DISCUSSION

In our country depression is increasing because of stressful lifestyle. WHO also states that 6.5% of Indian population suffers from depression [12]. Increased levels of proinflammatory cytokines

are associated with the development of depressive disease [7,8]. Multiple and recurrent episodes of depression are reported to be associated with elevated CRP level [13,14].

In the present study, no significant association was seen between age and severity of depression. In mild depressive patients mean age was 34.75±5.87 years whereas, in the severe depressive patients mean age was 31.90±6.36 years. The probable reason for this might be that elderly people are more receptive to the unavoidable physical illnesses and if they come, they cope up with them strategically. It is demonstrated in the previous studies that major depression is more frequent in young age group than the older one which is consistent with our findings [15].

It was observed that majority of the cases were males as compared to females. The probable reason for increased male to female ratio might be that more number of males attended the OPD and the females were more restricted to household work and did not seek any medical help. Findings of the present study did not match to the previous data available which shows that females are more prone to develop depression at any age group [16,17]. The underlying cause for gender difference in depression might be hormonal and neurodevelopmental changes that vary by sex during the pubertal transition. On the other hand women dedicate themselves to both work and family and thus, they are exposed to a double stress.

Distribution of patients according to their occupation depicted that most of the cases were having a sedentary type of occupation which included teachers, students, shopkeepers. The probable reason for this may be that work constitute an objective source of stress in a person's life and it could facilitate the occurrence of depressive symptoms. As most of the females are engaged in household work, they have little time for self-reported leisure-time and physical activity. It is demonstrated in previous studies that individuals who have enough time for self-reported leisure-time and practice moderate level of physical activity in their life are less prone to develop depression during their lifetime [18,19].

The mean SBP was found to be 131.80±8.80 mmHg among mild depressive patients whereas among severe depressive patients mean SBP was 126.90±9.68 mmHg. The mean DBP was found to be 82.70±7.18 mmHg among mild depressive patients whereas among severe depressive patients mean DBP was 82.10±6.88 mmHg. According to current findings, there is no significant association between depression severity and BP (including both SBP and DBP). As hypertension is a strong confounding factor for the increase in serum CRP levels, we excluded the patients who were diagnosed with hypertension for minimising the error in our result. George DS et al., conducted a study which showed that hypertension is associated with increased serum CRP levels [20]. He J and Whelton PK and Stamler J et al., concluded that high BP plays an important role as a risk factor in development of cardiovascular disease [21,22]. Study conducted by Barrett-Connor E and Palinkas LA, on elderly population found an inverse relationship between low diastolic BP and depressive symptoms. He also demonstrated that higher levels of depressive symptoms and more diagnosis of depression were found in subjects with DBP <75 mm Hg [23].

The mean BMI was found to be 21.65±1.12 in mild depression patients whereas among severe depressive patients mean BMI was 21.85±0.94. According to present findings, there was no significant association between BMI and depression severity. As it is postulated from previous data that obesity is a strong confounding factor for increase in serum CRP levels, we excluded the patients who were having BMI in range of overweight and obese category. Sample was collected in a resting state after overnight fasting for minimising the error in the results. Both males and females were having nearly equal BMI levels. Previous data shows bidirectional association between depression and obesity [24,25]. The underlying cause for increase of BMI may be neuroendocrine disturbances that occur in patients of depression.

CRP is one of the most broadly researched acute phase reactant. Several studies exhibited increased serum CRP levels in patients suffering from severe depression [26,27]. Valkanova V et al., conducted a meta-analysis which demonstrated a significant association between increased CRP and depressive symptoms [28]. In the present study, however we found statistically significant association between serum CRP levels and severity of depression. This may be explained that depression is multifactorial chronic stress. This leads to altered hypothalamic-pituitary-adrenal axis resulting in dysfunction in immune and endocrine system of the body. These changes may alter inflammatory response. Few previous studies found positive association of raised CRP level when compared to patients with mild and severe depression [29,10]. Previous studies are not consistent with the present findings. Till now, to the best of our knowledge, no study has been found in which CRP levels according to the severity of depression has been studied. Thus, we can prevent landing of mild into the severe form by estimating CRP levels in early phase of depression. We need larger sample size and longer duration study in future to establish negative corelation between CRP levels and severity of depression.

Limitation(s)

COVID-19 Pandemic was a major limitation of the study. Time period was inadequate for conducting the present study. Larger sample size would have been recruited for obtaining more reliable and accurate results.

CONCLUSION(S)

It is concluded that severity of depression is negatively associated with CRP levels. Thus, CRP level estimation in early diagnosed cases of depression may be helpful in therapeutic management.

Acknowledgement

The authors are grateful to the management of King George's Medical University for providing all the necessary support during the course of this study

REFERENCES

[1] Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease- A systematic quantitative review. Psychosomat Med. 2003;65:201-10.
[2] Barth J, Schumacher M, Herrmann LC. Depression as a risk factor for mortality in patients with coronary heart disease: A meta-analysis. Psychosom Med. 2004;66:802-13.
[3] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. 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;392:1789-858.
[4] Gan Y, Gong Y, Tong X, Sun H, Cong Y, Dong X, et al. Depression and the risk of coronary heart disease: A meta-analysis of prospective cohort studies. BMC Psychiatry. 2014;14:371.
[5] Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. Lancet. 2013;382:1575-86.
[6] Gonzalez MB, Snyderman TB, Colket JT, Arias RM, Jiang JW, O'Connor CM, et al. Depression in patients with coronary artery disease. Depression. 1996;4:57-626.
[7] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. Nat Rev Neurosci. 2008;9(1):46-56.
[8] Vogelzangs N, Duivis HE, Beekman AT, Kluft C, Neuteboom J, Hoogendijk W, et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. Transl Psychiatry. 2012;2:e79.
[9] Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain BehavImmun. 2009;23(7):936-44.
[10] Ma Y, Chiriboga DE, Pagoto SL, Rosal MC, Li W, Merriam PA, et al. Association between depression and C-reactive protein. Cardiol Res Pract. 2011;2011:286509.
[11] International Classification of Diseases ICD-10. 10th Revision. Geneva: World Health Organization; 1992. World Health Organization.
[12] Philip SW, Sergio AG, Jordi A, Matthias CA, Guilherme B, Evelyn JB, et al. Use of mental health services for anxiety, mood, and substance disorders in 17 countries in the WHO world mental health surveys. The Lancet. 2007;370(9590):841-50.

[13] Liukkonen T, Silvennoinen KS, Jokelainen J, Räsänen P, Leinonen M, Meyer-Rochow VB, et al. The association between C-reactive protein levels and depression: Results from the northern Finland 1966 birth cohort study. Biological Psychiatry. 2006;60:825-30.
[14] Copeland WE, Shanahan L, Worthman C, Angold A, Costello EJ. Cumulative depression episodes predict later C-reactive protein levels: A prospective analysis. Biological Psychiatry. 2012;71(11):15-21.
[15] Deborah SH, Renee DG, Frederick SS, Bridget FG. Epidemiology of major depressive disorder: Results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry. 2005;62(10):1097-106.
[16] World Health Organization. Depression in India Let's talk. Rev.cdr Published 2017; Last accessed by 22nd July 2020. https://ruralindiaonline.org/en/library/resource/depression-in-india-lets-talk/?__.
[17] Depression and Older Adults. National Institute of Aging. May 01, 2017. Last accessed by 22nd July 2020. https://www.nia.nih.gov/health/depression-and-older-adults.
[18] Brown W, Mishra G, Lee C, Bauman A. Leisure time physical activity in Australian women: Relationship with well-being and symptoms. Res Q Exerc Sport. 2000;71:206-16.
[19] Hassmén P, Koivula N, Uutela A. Physical exercise and psychological well-being: A population study in Finland. Prev Med. 2000;30:17-25.
[20] George DS, Debbie AL, Roger H, Nic T, Ann R, Gordon DOL, et al. Association of C-Reactive Protein with blood pressure and hypertension. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25:1051-56.
[21] He J, Whelton PK. Elevated systolic blood pressure and risk of cardiovascular and renal disease: Overview of evidence from observational epidemiologic studies and randomized controlled trials. Am Heart J. 1999;138:211-19.
[22] Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks-US population data. Arch Intern Med. 1993;153:598-615.
[23] Barrett-Connor E, Palinkas LA. Low blood pressure and depression in older men: A population based study. BMJ. 1994;308(6926):446-49.
[24] Floriana SL, Leonore MW, Paul FB, Theo S, Pim C, Brenda WJHP, et al. Overweight, obesity, and depression: A systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry. 2010;67(3):220-29.
[25] Gregory ES, Evette JL, Jennifer AL, Belinda HO, Laura I, Paul R, et al. Association between obesity and depression in middle-aged women. Gen Hosp Psychiatry. 2008;30(1):32-39.
[26] Ashraf T, Forough R, Amin M. The relationship between body mass index and depression among high school girls in Ahvaz. Advances in Medicine. 2016;2016:3645493.
[27] Laura AP, Debra JB. Depression and obesity in the US adult household population. NCHS Data Brief. 2014;(167):01-08.
[28] Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150(3):736-44.
[29] Jitendra J, Manu S, Devendra MM, Amandeep. Associations of number and severity of depressive episodes with C-reactive protein and Interleukin-6. Asian Journal of Psychiatry. 2017;27:71-75.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Physiology, King George's Medical University, Lucknow, Uttar Pradesh, India.
2. Professor and Head, Department of Physiology, King George's Medical University, Lucknow, Uttar Pradesh, India.
3. Professor, Department of Pathology, King George's Medical University, Lucknow, Uttar Pradesh, India.
4. Professor, Department of Physiology, King George's Medical University, Lucknow, Uttar Pradesh, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Shraddha Singh,
Department of Physiology, KGMU, Lucknow, Uttar Pradesh, India.
E-mail: drshraddhasingh@yahoo.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 16, 2021
- Manual Googling: Mar 03, 2021
- iThenticate Software: May 03, 2021 (10%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jan 20, 2021**
Date of Peer Review: **Mar 04, 2021**
Date of Acceptance: **Apr 28, 2021**
Date of Publishing: **Jun 01, 2021**