



Research Article

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A comparative study of serum C-reactive protein in patients with Generalised Anxiety Disorder and Depression

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Abstract

Background: There is yet limited research and dearth of study on immune dysregulation and Generalised Anxiety Disorders (GAD) & Depression in India till date. Very few studies have investigated the relationship between GAD, Depression and inflammatory biomarkers, in particular C-reactive protein (CRP). **Aims and Objectives:** This study aimed to assess and compare serum C-reactive protein (CRP) level in Generalized Anxiety Disorder (GAD), Depression & Control group. **Study Design:** This was a prospective, comparative hospital based cross sectional study. **Setting:** The study was conducted only on the indoor patients admitted in the Department of Psychiatry, Assam Medical College and Hospital, Dibrugarh. **Materials and Methods:** 50 GAD and 50 Depression patients diagnosed as per ICD-10 in the age group 18-65 years admitted in the Department of Psychiatry, AMCH were included for the study. A control group of 50 individuals was selected from age & sex matched people from normal healthy population. C-reactive protein level was estimated in all respondents by particle enhanced turbidimetric immunoassay (PETIA) technique. **Statistics:** Statistical analyses were done using Analysis of Variance (ANOVA), Chi square test and Fischer's exact test (where the cell count was <5). P value <0.05 was taken as significant. **Results:** Mean serum CRP level of GAD and Depression patients were higher than Control group and it was also noted that mean serum CRP level of Depression patients were significantly elevated than GAD patients. **Conclusions:** Our study findings are consistent with the role of inflammation in GAD and Depression. So, future study in this aspect with a larger sample and follow up is needed to explore the existence of a possible "psychoneuroimmune link" between GAD, Depression and inflammatory markers.

Keywords: C-reactive protein, Depression, Generalized Anxiety Disorder, Inflammation.

INTRODUCTION

Generalized Anxiety Disorder (GAD) is characterised by excessive anxiety and worries regarding some events or activities. The duration, intensity, or frequency of the worries and anxieties are out of proportion to the actual impact of the anticipated event [1]. Symptoms must be persistent and continuing, duration of at least six months, is required for diagnosis of GAD to be established [1, 2]. In a year, approximately 6.8 million adult American population and 2% European adults suffer from GAD [3]. Lifetime prevalence rates range from 0.8% to 6.6% in the general population and 3.8% to 11.9% in primary care settings (Maier *et al.*, 2000) [4]. In fact, GAD is considered to be the most frequently occurring of all anxiety disorders in primary care (Wittchen & Hoyer, 2001; Wittchen *et al.*, 2002) [5, 6]. 1-year prevalence rates of GAD in the general population range from 1.0% to 4.4%, and rates found in the primary care population are approximately 8%. The vast majority (17%–40%) of patients with GAD also have at least one other psychiatric diagnosis (Kessler *et al.*, 1999) [7].

Lifetime rates of co-morbidities in GAD patients can reach as high as 90% (Wittchen *et al.*, 1994) [8]. Major depressive disorder (MDD) is the most common co-morbidity associated with GAD, ranging in lifetime prevalence from 38.6% to 80% (e.g., Kessler *et al.*, 1994; 1999; Kessler *et al.*, 2002) [6, 7, 8]. In Indian context, Ganguli (2000) [9] analyzed 15 epidemiological studies on psychiatric morbidity in which prevalence rate of anxiety neurosis was found to be 16.5 per thousand. In a metaanalysis of 13 Indian epidemiological studies on psychiatric morbidity (Reddy and Chandrashekhara, 1998) [10] with overall sample size of 33, 572 subjects, the prevalence rate of GAD was found to be 5.8%. Madhav (2001) [11], after analysing 10 India based studies on psychiatric illness, found that prevalence rate of anxiety neurosis was 18.5 per thousand population. In a study conducted in Dibrugarh, Assam Chaudhury *et al.*, 2006 found that over a period of 12 months, disability due to anxiety was significant [12].

Depression is a major public health problem, due to its prevalence and the dysfunction, suffering, morbidity and economical burden. According to the report on Global Burden of Disease, the

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point prevalence of unipolar depression is 1.9% for males and 3.2% for females, and 1 year prevalence is found to be 5.8% for men and 9.5% for women. If the current trend of demographic and epidemiological transition continues, It is estimated that by the year 2020, the burden of depressive disorder will increase to 5.7% of the total burden of disease and it will be the second leading cause of Disability Adjusted Life Years (DALYs), next after Ischemic Heart Disease (IHD) [13]. Many Indian studies estimated the prevalence of depressive disorder in community samples which varied from 1.7 to 74 per 1000 population [10, 14]. Reddy and Chandrasekhar (1998) have done a meta-analysis, which included 13 psychiatric epidemiological studies on 33572 subjects from the community and found the prevalence of depression to be 7.9 to 8.9 per 1000 population and the prevalence rate was approximately twice in the urban areas compared to rural population [10]. A population based South Indian study on more than 24, 000 subjects in Chennai using Patient Health Questionnaire (PHQ)12 found the prevalence of depression to be 15.1% after age adjustment using 2001 census data [15]. Nandi *et al.*, 2000 [14]. compared the prevalence of depression in the same catchment area in an interval of 20 years (in 1972 and 1992) and found that the prevalence of depression increased from 49.93 per 1000 population to 73.97 per 1000 population. Studies on primary care centres have reported a prevalence rate of 2140.45% [16-19]. Studies in hospital settings have shown that 5 to 26.7% of patients attending the psychiatric OPD have depression [20-23]. In the study mentioned earlier that was conducted in Assam, Chaudhury *et al.*, 2006 found that like anxiety, disability due to depression was also significant and was a major public health burden in upper Assam [12].

CRP is an inflammatory marker which is produced by hepatocytes mainly under transcriptional control by the pro-inflammatory cytokine interleukin 6 (IL-6) (Pepys & Hirschfield, 2003) [24]. Inflammatory cytokines have potent effects on the neuroendocrine system (mainly on the Hypothalamic-Pituitary-Adrenal [HPA] axis) and the CNS where they may produce many symptoms of illness like fever, decreased appetite, withdrawn behaviour, and sleep changes [25].

Depression is associated with activation of the inflammatory response. The 'monocyte T-cell theory' for pathophysiology of mood disorders, such as unipolar and bipolar depression [26, 27] considers activation of the immune response system as the driving force behind mood disorders. Some studies suggest that the existence of a possible "psychoneuroimmune link" between negative affectivity (depression, anger and anxiety [28], poor subjective wellbeing [29]), inflammatory markers and the development and progression of Coronary Heart Disease (CHD) [30].

It is hypothesized that inflammation is associated with anxiety disorder. There is also a high comorbidity of anxiety with depression [31], which is associated with immune dysregulation [32, 33]. Besides, chronic stress may cause alteration in the Hypothalamic-Pituitary-Adrenal (HPA) axis and the immune system, which can eventually cause depression and anxiety [34]. Hypothalamic-Pituitary-Adrenal (HPA) axis and Autonomic Nervous System (ANS) activity is found to be associated with depressive symptomatology and CRP production (Raison *et al.*, 2006; Dantzer *et al.*, 2008) [35, 36]; these two systems are also involved in anxiety disorders (Toker *et al.*, 2005; Pitsavos *et al.*, 2006; O'Donovan *et al.*, 2010) [37-39]. In experiment on animals, it was noticed that immune activation in mice was associated with anxiety symptoms and increased proinflammatory cytokines in peripheral circulation as well as in brain (Gibney *et al.*, 2013; Rossi *et al.*, 2012) [40-41]. Moreover, it was seen that intra-cerebroventricular (ICV) administration of IL-1b (a proinflammatory cytokine) receptor antagonist can block anxiety symptoms if given immediately after stress exposure (Rossi *et al.*, 2012) [41].

Generalised Anxiety Disorders (GAD) and Depression are the two mental illnesses which together comprise a major burden of public

health importance. But Very few studies have investigated the relationship between Generalised Anxiety Disorders (GAD), Depression and inflammatory biomarkers, in particular C-reactive protein (CRP). As there is yet limited research and dearth of study on immune dysregulation (characterised by increased inflammatory biomarkers in particular C-reactive protein) and Generalised Anxiety Disorders (GAD), Depression in India till date, the present study is a sincere effort to compare the serum C-reactive protein level in Generalized Anxiety Disorder (GAD) and Depression.

MATERIALS AND METHODS

Aims and objectives- The study was undertaken to assess and compare serum C-reactive protein (CRP) level in Generalized Anxiety Disorder (GAD), Depression & Control group.

Place of Study

The study was done in the Department of Psychiatry, Assam Medical College & Hospital. Assam Medical College & Hospital is a tertiary care institute situated in Dibrugarh and receives patient from entire Assam as well as neighboring North-eastern states.

Duration of Study

The study duration was one year starting from June 2015 to May 2016.

Study Design

The study was a hospital based cross sectional study.

Ethical Issues

The study proposal was submitted to the Institutional review board for review and appraisal. Study was undertaken after the approval. A written consent was obtained from every participant and they were free to withdraw the consent at any point of time.

Selection of Sample

The study group was selected from only the indoor patients admitted in the Department of Psychiatry, Assam Medical College and Hospital, Dibrugarh. Consecutive cases were taken for study.

Group A: 50 newly diagnosed patients of Generalized Anxiety Disorder (GAD) admitted in the Department of Psychiatry, AMCH, fulfilling the inclusion and exclusion criteria.

Group B: 50 newly diagnosed patients of Depression admitted in the Department of Psychiatry, AMCH, fulfilling the inclusion and exclusion criteria.

Group C: 50 age & sex matched people from normal healthy population, fulfilling the inclusion and exclusion criteria.

SELECTION CRITERIA

Inclusion Criteria

Study Group

- Patients of age group between 18 to 65 years.
- Patients of both the sexes.
- Newly diagnosed cases of Generalized Anxiety Disorder (GAD) & Depression admitted in the Department of Psychiatry, AMCH, diagnosed as per ICD-10 and confirmed by a Consultant Psychiatrist, Department of Psychiatry.
- Patients giving informed consent for the study.

Control Group

- Control of age & sex matched people from normal healthy population.
- Persons giving informed consent for the study.

Exclusion Criteria

The patients with the following conditions were excluded from the study and control groups which might cause raised serum C-reactive protein (CRP) level-

- Raised Erythrocyte Sedimentation Rate (ESR)
- Acute respiratory tract infections
- History of Malignant tumors especially of breast, lung and gastrointestinal tract
- Acute pancreatitis
- History of surgery or Burn in last 1 month
- History of Leukaemia
- Tobacco smoking
- Hormone replacement therapy (HRT) and oral contraceptive pill (OCP) use
- Obesity (BMI ≥ 30)
- Metabolic syndrome
- Known case of Rheumatoid arthritis, Systemic Lupus Erythematosus (SLE) and other Connective tissue diseases
- Recent Myocardial infarction in last 3 months
- Known case of Inflammatory bowel disease (IBD)
- Recent History suggestive of Rheumatic fever

Tools used

- 1) Informed Consent form
- 2) Semi-structured Proforma for socio-demographic data developed and used in the Department of Psychiatry, Assam Medical College & Hospital, Dibrugarh, Assam
- 3) Kuppuswamy's Socioeconomic Status Scale (2014)
- 4) International Classification of Diseases, Revision-10 (ICD-10) diagnostic guidelines

STATISTICAL ANALYSIS OF DATA

The statistical analysis of data was done using the Statistical Package for Social Sciences (SPSS for Windows, version 21.0. Chicago, SPSS Inc.) and Microsoft Excel (Redmond, Washington: Microsoft, 2003. Computer Software). Results on continuous measurements are presented as mean \pm standard deviation are compared using Analysis of Variance (ANOVA). Where the p value was found significant ($p < 0.05$) among 3 groups, post hoc Bonferroni test was done to find out the significance between 2 individual groups. Discrete data are expressed as number (%) and are analysed using Chi square test and Fischer's

exact test (where the cell counts were < 5).

Procedure

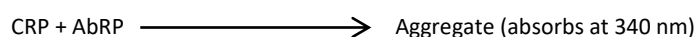
All patients in the age group 18-65 years admitted in the Department of Psychiatry, AMCH and diagnosed as Generalized Anxiety Disorder (GAD) & Depression as per ICD-10, confirmed by a consultant psychiatrist were included for the study as Group A & Group B respectively. A control group (Group C) was selected from age & sex matched people from normal healthy population. An informed consent was taken from each participant. A socio-demographic data of each patient was recorded in the demographic sheet. C-reactive protein level was estimated in all respondents by particle enhanced turbidimetric immunoassay (PETIA) technique. Analysis of the observed data was done and specific statistical tools were used as and when necessary.

Estimation of Serum C-reactive Protein (CRP)

The estimation of serum C-reactive protein (CRP) was done by the C-Reactive Protein Extended Range (RCRP) method in the advanced clinical Biochemistry laboratory under Department of Biochemistry, AMCH.

Principle: The RCRP method was based on a particle enhanced turbidimetric immunoassay (PETIA) technique and the following principles was followed-

Serum C-reactive protein (CRP) causes agglutination of the synthetic latex particles coated with antihuman C-reactive protein. The agglutination of the latex particles is proportional to the CRP concentration and can be measured by turbidimetry.



Normal Reference Value : 0–0.5 mg/dl

RESULTS AND OBSERVATION

Socio-demographic variables

Age Characteristics of the Sample

Age distribution of both study and the control groups had been tabulated in Table–1 and graphically represented in Fig-1. It was found that majority of the patients (42%) of GAD belonged to 30-39 years age group whereas depression was most common among 20-29 years age group (34%). Most of the controls were from 30-39 years (30%) and 20-29 years (30%) age group. Mean age of the GAD cases was 37.96 ± 10.70 years and depression cases was 36.82 ± 12.49 years. Mean age of the control group was 37.00 ± 12.08 years.

Table 1: Distribution of Case and Control on the Basis of Age

AGE GROUP (in years)	GROUP–A (GAD)		GROUP–B (Depression)		TOTAL CASES		GROUP–C (Control)		t value	p value
	n	%	n	%	n	%	n	%		
<20	1	2.00	2	4.00	3	3.00	1	2.00		
20–29	9	18.00	17	34.00	26	26.00	15	30.00		
30–39	21	42.00	9	18.00	30	30.00	15	30.00	0.192	0.424
40–49	10	20.00	11	22.00	21	21.00	10	20.00		
50–59	6	12.00	9	18.00	15	15.00	7	14.00		
≥ 60	3	6.00	2	4.00	5	5.00	2	4.00		
TOTAL	50	100.00	50	100.00	100	100.00	50	100.00		

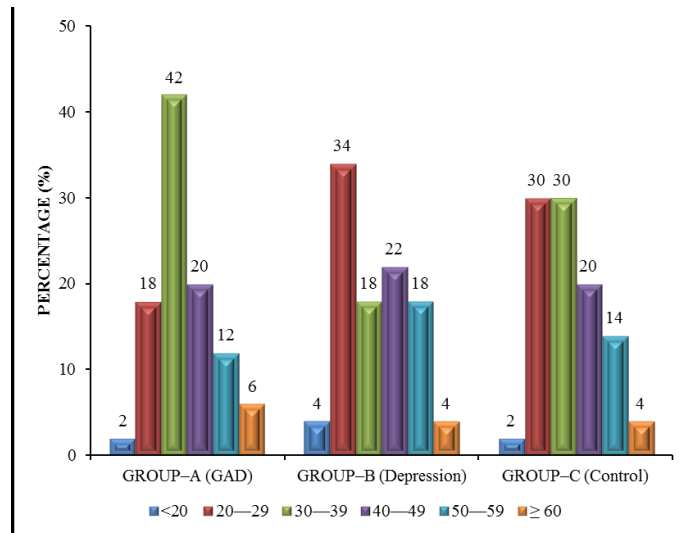


Figure 1

Sex Characteristics of the Sample

Sex distribution of both the study and control groups had been tabulated in Table-2 and graphically represented in Fig-2. It was found

that majority of the GAD (54%) cases were female whereas depression was more common in males (60%). 54% of the control group were males and 46% were females.

Table 2: Distribution of case and Control on the basis of Sex

SEX	GROUP-A (GAD)		GROUP-B (Depression)		TOTAL CASES		GROUP-C (Control)		Chi-square (χ^2)	p value
	n	%	n	%	n	%	n	%		
Male	23	46.00	30	60.00	53	53.00	27	54.00	0.013	0.908
Female	27	54.00	20	40.00	47	47.00	23	46.00		
TOTAL	50	100.00	50	100.00	100	100.00	50	100.00		

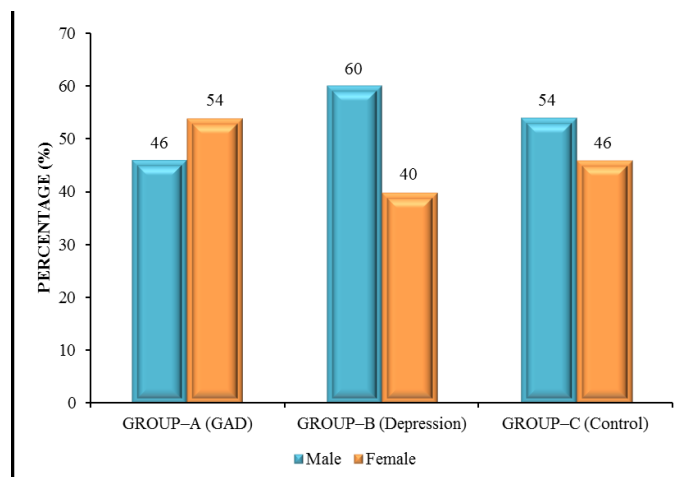


Figure 2

Socio-demographic parameters of case and control groups

The socio-demographic parameters of the case and the control group had been tabulated in the Table-3 and graphically represented in Fig-3.1-3.5. Most of the participants were Hindu by religion (86% of GAD patients and 88% of depression patients and 92% of control group). Among the GAD patients, 8% were Christian and 6% were Islam by

religion. 10% of the depression patients were Islam by religion and only 2% belonged to some other religion. In the control group, 6% were Islam by religion and 2% belonged to Christian religion. The distribution of religious status of the participants for both the study and control groups showed statistically insignificant difference (Chi-square (χ^2) = 8.0325 and p value >0.05).

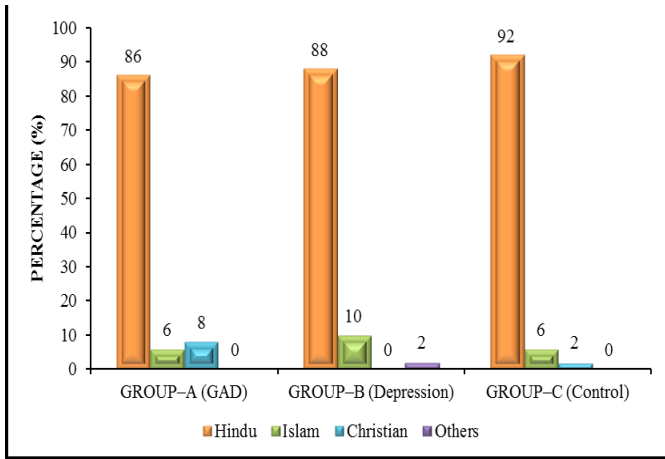


Figure 3.1

Majority of the cases and control were married. 78% of GAD cases, 66% of depression cases and 58% of control group were married. In contrast only 22% of GAD cases, 30% of depression cases and 38% of control group were unmarried. 4% each of depression and control group were widow. The statistical analysis depicted an insignificant difference ($Chi\text{-square } (\chi^2) = 5.6383$ and p value >0.05) between marital status in the study and control group.

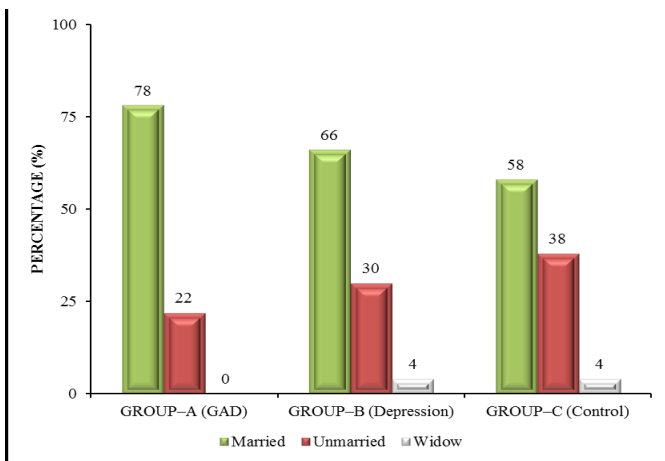


Figure 3.2

Majority of the GAD (86%), depression (84%) and control (76%) groups were from nuclear family. Only 14% of GAD cases, 16% of depression cases and 24% of control group belonged to joint family. Statistically no significant difference was found between the two groups according to their type of family ($Chi\text{-square } (\chi^2) = 1.897$ and p value >0.05).

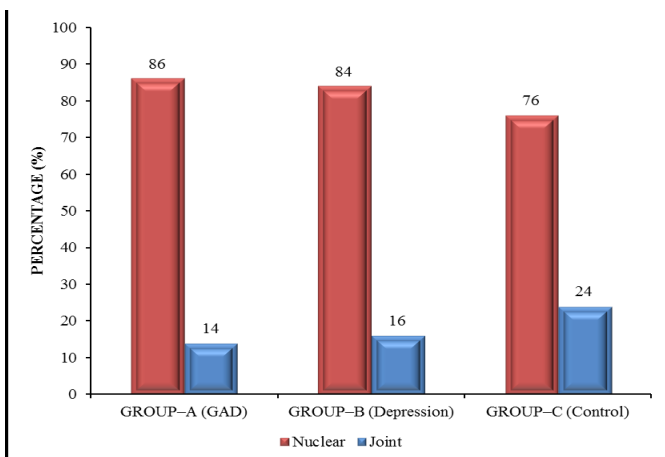


Figure 3.3

In both GAD and Depression patients, 64% were from rural background whereas 36% belonged to urban locality. But in control group, the people from rural and urban background were equal in number (50% each). The distribution of domicile of participants was statistically insignificant ($Chi\text{-square } (\chi^2) = 2.7077$ and p value >0.05) among all the groups.

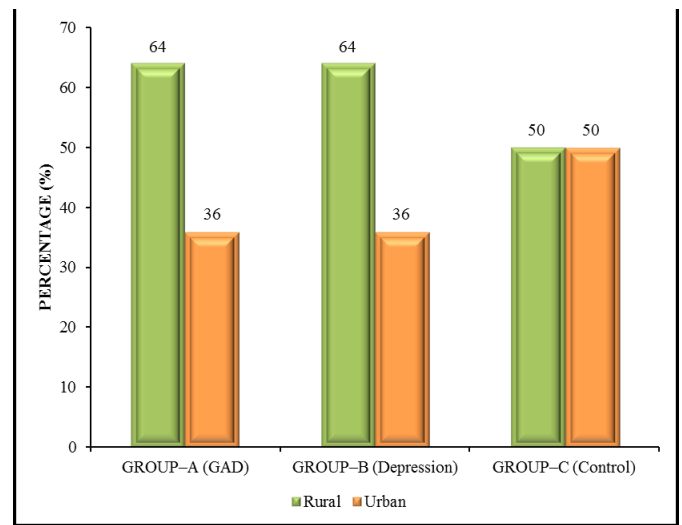


Figure 3.4

Most of the GAD patients (44%) were from Upper Lower (IV) socioeconomic status and 26% each belonged to Upper Middle (II) and Lower Middle (III) socioeconomic status whereas only 4% were from Upper (I) socioeconomic status. Among depression cases, 34% each were from Lower Middle (III) and Upper Lower (IV) socioeconomic status. 20% belonged to Upper Middle (II), 10% belonged to Upper (I) and only 2% were from Lower (V) socioeconomic status. In control group majority (34%) were from Upper Lower (IV) socioeconomic status, 32% belonged to Lower Middle (III) and 26% were from Upper Middle (II) socioeconomic status whereas only 8% belonged to Upper (I) none were from Lower (V) socioeconomic status. The difference of socioeconomic status among GAD, depression and control groups were statistically insignificant ($Chi\text{-square } (\chi^2) = 5.2308$ and p value >0.05).

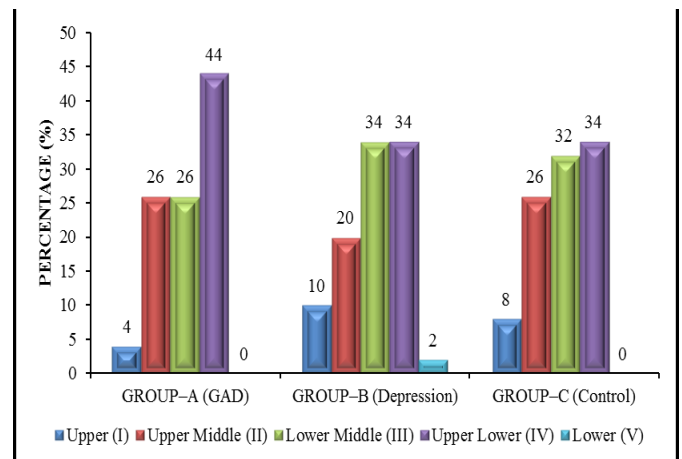


Figure 3.5

Table 3: Socio-Demographic Variables Between Case and Control

VARIABLES	GROUP-A (GAD)		GROUP-B (Depression)		GROUP-C (Control)		Chi-square (χ^2)	P value
	n	%	n	%	n	%		
Religion:								
♦ Hindu	43	86.00	44	88.00	46	92.00	8.0325	0.236
♦ Islam	3	6.00	5	10.00	3	6.00		
♦ Christian	4	8.00	0	0.00	1	2.00		
♦ Others	0	0.00	1	2.00	0	0.00		
Total	50	100.00	50	100.00	50	100.00		
Marital Status:								
♦ Married	39	78.00	33	66.00	29	58.00	5.6383	0.228
♦ Unmarried	11	22.00	15	30.00	19	38.00		
♦ Widow	0	0.00	2	4.00	2	4.00		
Total	50	100.00	50	100.00	50	100.00		
Family Type:								
♦ Nuclear	43	86.00	42	84.00	38	76.00	1.897	0.387
♦ Joint	7	14.00	8	16.00	12	24.00		
Total	50	100.00	50	100.00	50	100.00		
Locality:								
♦ Rural	32	64.00	32	64.00	25	50.00	2.7077	0.258
♦ Urban	18	36.00	18	36.00	25	50.00		
Total	50	100.00	50	100.00	50	100.00		
Socioeconomic Status:								
♦ Upper (I)	2	4.00	5	10.00	4	8.00	5.2308	0.733
♦ Upper Middle (II)	13	26.00	10	20.00	13	26.00		
♦ Lower Middle (III)	13	26.00	17	34.00	16	32.00		
♦ Upper Lower (IV)	22	44.00	17	34.00	17	34.00		
♦ Lower (V)	0	0.00	1	2.00	0	0.00		
Total	50	100.00	50	100.00	50	100.00		

Distribution of cases and control according to serum crp level

Distribution of cases and control according to serum CRP level had been tabulated in the Table-4 and graphically represented in Fig-4. It was found that 94% of GAD patients, 70% of depression patients and 98% of control group had normal (0.0–0.5 mg/dl) serum CRP level. Serum CRP level was found to be elevated (> 0.5 mg/dl) in 6% cases of GAD, 30% cases of depression and 2% of control group. By applying Freeman-Hatton extension of the Fischer’s exact test, these differences were found to be statistically significant ($p < 0.001$).

Table 4: Distribution of cases and Control According to Serum CRP Level

SERUM CRP LEVEL	GROUP-A (GAD)		GROUP-B (Depression)		GROUP-C (Control)		p value
	n	%	n	%	n	%	
Normal (0.0–0.5 mg/dl)	47	94.00	35	70.00	49	98.00	<0.001
Elevated (> 0.5 mg/dl)	3	6.00	15	30.00	1	2.00	
TOTAL	50	100.00	50	100.00	50	100.00	

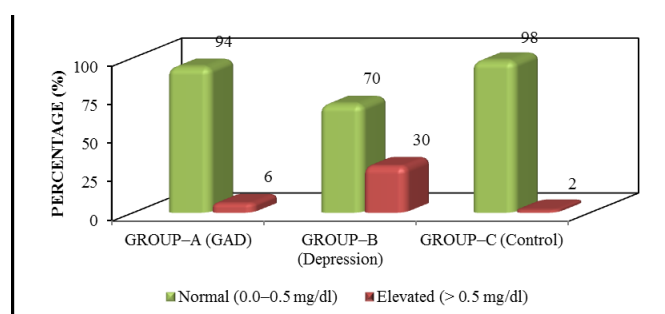


Figure 4

Comparison of Serum CRP level in GAD, depression and control groups

Comparison of serum CRP level in patients of GAD, Depression and Control group had been tabulated in the Table-5. Mean serum CRP level of GAD (0.29 ± 0.14 mg/dl) and Depression (0.42 ± 0.22 mg/dl) patients were higher than control group (0.20 ± 0.10 mg/dl). By performing ANOVA test, the higher level of serum CRP level in both

GAD and Depression cases compared to control group was statistically found to be significant (p value <0.001). By applying post-hoc Bonferroni test, these differences in serum CRP level among the 3 individual groups were also found to be statistically significant (p value <0.001).

Table 5: Comparison of Serum CRP Level In Patients of GAD, Depression and Control

SERUM CRP LEVEL	GROUP-A (GAD)	GROUP-B (Depression)	GROUP-C (Control)
Mean ± S.D. (mg/dl)	0.29 ± 0.14	0.42 ± 0.22	0.20 ± 0.10
Range (mg/dl)	0.08–0.58	0.07–0.95	0.02–0.53
<i>p</i> value		<0.001	
GAD Vs. Depression		0.001	
GAD Vs. Control		0.000	
Depression Vs. Control		0.000	

DISCUSSION

It was found that majority of the patients (42%) of GAD belonged to 30-39 years age group but Tanja *et al.*, 2007 [42] found that the average first manifestation of GAD was between 25 and 30 years which was slightly lower than that of our finding. In our study, depression was most common among 20-29 years age group (34%). As per DSM-5 the most common age of depression is 18-29 years age group which is similar to our finding [43]. Mean age of the GAD cases was 37.96 ± 10.70 years and Depression cases was 36.82 ± 12.49 years. These findings support the observation of Chaudhury *et al.*, 2006 [12] where they found that the mean age of the GAD patients was 35.5±10.54 years and the mean age of Depression patients was 39.87±11.03 years.

It was found that majority of the GAD (54%) cases were female. This finding was consistent with that of Wittchen *et al.*, 2002 [6], Reddy and Chandrashekhara (1998) [10]. As per DSM-5 females are more prone to GAD than males which is in agreement with our study finding. In our study, depression was more common in males (60%) which was contradictory to the various previous findings where depression was found to be more common in females [14, 15, 21, 44, 45].

Most of the participants were Hindu by religion (86% of GAD patients and 88% of depression). In contrary to our finding Nandi *et al.*, 1979 [14] found more prevalence of depression among Muslims. Our finding might reflect the predominance of Hindu population in our study area 78% of GAD cases and 66% of depression cases in our study were married. In contrast only 22% of GAD cases and 30% of depression cases and 38% of control group were unmarried. 4% of depression patients were widow. So, marriage did not seem to be a protective factor against the development of psychiatric morbidities like GAD and Depression.

Majority of the GAD (86%) and Depression (84%) patients were from nuclear family. Sethi *et al.*, 1980 [46] observed similar finding in case of depression. Lower rate of psychiatric morbidity like GAD and depression in joint family might be explained in terms of better social support and good interpersonal relationship among family members in joint family.

Regarding domicile, in both GAD and Depression patients, 64% were from rural background whereas 36% belonged to urban locality. Overall, it was seen that the majority of the study population in both the groups had come from rural background. This might be because of the location of the hospital which mainly caters to the rural population in the vicinity.

Most of the GAD patients (44%) were from Upper Lower (IV) socioeconomic status and 26% each belonged to Upper Middle (II) and Lower Middle (III) socioeconomic status. Higher prevalence of GAD in lower socio-economic status was also observed by Tanja *et al.*, 2007 [42]. Among depression cases, 34% each were from Lower Middle (III) and Upper Lower (IV) socioeconomic status. Our findings replicated the findings of many previous studies where depression was found to be more common in subjects from poor socioeconomic background [15, 21, 47] Thus, majority of the cases in our study belonged to the lower socio-economic groups. This could be because the place of study is a government hospital where the facilities are almost free and as such mostly poor people come here.

In our study mean serum CRP level of GAD (0.29 ± 0.14 mg/dl) was significantly (p value <0.001) higher than control group (0.20 ± 0.10 mg/dl). This finding is in agreement with the report of Bankier *et al.*, 2009 [48]; Liukkonen *et al.*, 2011 [49] and Costello *et al.*, 2012 [50]. Our finding also replicated the findings of the previous studies by Vogelzangs *et al.*, 2013 [51]; Khandaker *et al.*, 2016 [52]. But in contrary to our finding, Kheirabadi *et al.*, 2013 [53] found no relationship between anxiety and serum C-reactive protein level.

We have also found that mean serum CRP level of depression (0.42 ± 0.22 mg/dl) patients were significantly (p value <0.001) elevated than control group (0.20 ± 0.10 mg/dl). This finding strengthens the observation of Huang Tiejun (2004) [54] who found that Serum CRP levels were higher in depressive AMI patients than those in nondepressive ones. Similar finding was also noted by previous studies done by Penninx *et al.*, 2003 [55]; Jack Sawyer 2016 [56]; Miller *et al.*, 2005 [57]; and Mohamed A.A & Mansoura. S (2007) [58]. Our finding is also consistent with the observations of Danner *et al.*, 2003 [59], Edward C. Suarez (2004) [60] but in contrary to our finding Kheirabadi *et al.*, 2013 [53] found no relationship between depression and serum C-reactive protein level.

We have also compared the serum CRP level between GAD and Depression cases and found that mean serum CRP level of Depression (0.42 ± 0.22 mg/dl) patients were significantly (p value <0.001) elevated than GAD (0.29 ± 0.14 mg/dl). To our knowledge, this is an unique finding in our study as no study till date compared the serum CRP level between GAD and Depression.

So, our study findings support the role of inflammation (characterised by increased CRP) in GAD and Depression. This can be explained in various ways. Peripheral cytokines can reach the brain in many ways causing neuropsychiatric manifestations of depression and anxiety. Dantzer *et al.*, 2008 [36]; Khandaker and Dantzer, 2015 [61]; Stolk *et al.*, 2007 [62]; D'Mello and Swain, 2014 [63]; Quan and Banks, 2007 [64]. Possible connections between peripheral immune system and brain are (i) leaky areas of blood brain barrier (e.g. circumventricular Organs) (ii) active transport mechanism by soluble transport molecules, (iii) activation of macrophages and endothelial cells in cerebral vasculature (which in turn produce cytokines and cause transmigration of inflammatory cells in the brain), and (iv) retrograde axonal transport via peripheral afferent nerve fibres. When the cytokine signal reaches the brain, it can cause changes like (i) accelerated metabolism and reuptake of serotonin and other neurotransmitters, (ii) activation of the HPA axis and release of corticotrophin releasing hormone (CRH) in the amygdala and hypothalamus, (iii) increased oxidative stress and reduction of synaptic plasticity (Dantzer *et al.*, 2008; Miller *et al.*, 2009) [36, 65]. The above changes can lead to neuropsychiatric manifestations of anxiety and depression.

Limitations

- 1) The study involved one-time cross sectional assessment and lacked follow up. It would be better if the GAD and depression patients

would have been evaluated for serum CRP level after pharmacotherapy.

- 2) The sample size of the study was relatively small and this study is a hospital based study. So, the findings cannot be generalized to a larger community population.
- 3) Cases were restricted to only those patients who were admitted in Department Of Psychiatry, AMCH in the specified period of time.

CONCLUSION

Our study findings are consistent with the role of inflammation in GAD and Depression. The association between GAD, Depression and inflammation raises the possibility of a tantalizing line of future theories and treatment options. The strong relationship between inflammation and GAD & Depression supports the inflammatory hypothesis in causation of these two mental illnesses. So, there is the possibility of successful intervention and treatment of GAD and depression by directly treating inflammation with anti-inflammatory agents. The relationship between inflammation and GAD and Depression is rapidly unfolding, but the full intricacies have not yet described. However, this beginning awareness of the interplay among inflammation, and GAD and Depression can broaden our approach to care and treatment. So, future study in this aspect with a larger sample and follow up is needed to explore the existence of a possible “psychoneuroimmune link” between GAD, Depression and inflammatory markers.

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Conflict of Interest

There was no conflict of interest among authors involved in this study.

Authors' Contribution

The first author has conceptualized the hypothesis and designed the study under the active supervision and guidance of the second author. The first author has collected the study data. Analysis with interpretation of data and final preparation of the original article are done by both the authors.

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