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Original Article

Biochemistry Section

Metabolic Syndrome and Cardiovascular Disease Risk in patients with Depressive disorder on Antidepressive Medication

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ABSTRACT

Introduction: Depression and Metabolic syndrome both are the two major public health issues. The depressive patients are at higher risk for Cardiovascular Disease (CVD). The use of antidepressant medication has been linked to CVD. Major depression is associated with activation of the inflammatory response.

Aim: To investigate the presence of metabolic syndrome, cardiovascular risk and inflammatory marker levels in depressed patients and compare it with healthy population without depression.

Materials and Methods: Cross-sectional analysis was undertaken on 94 patients with the diagnosed depressive disorder from Department of Psychiatry, Sawai Man Singh Medical College Jaipur, Rajasthan, India and 50 healthy controls from the general population. The Body Mass Index (BMI), waist circumference, blood sugar, lipid parameters and high sensitive C-Reactive Protein (hs-CRP) were measured in both groups. Depressive symptoms were measured using Montgomery-Asberg Depression Rating Scale (MADRS), antidepressant medication use {Selective Serotonin Reuptake Inhibitor (SSRI)} was also reported. Metabolic syndrome prevalence was assessed based on International Diabetes Federation (IDF) guidelines.

Results: The depressive subjects showed statistically significant increased blood glucose (p=0.007), and decreased High Density Lipoprotein Cholesterol (HDLC) (p=0.001) values. There were statistically significant increased hs-CRP values (3.30±2.61 mg/L) in users of SSRI antidepressant medication compared to healthy controls (1.96±0.70 mg/L). The prevalence of metabolic syndrome in depressed patients was 42.36%.

Conclusion: Depressive patients are at higher risk for CVD due to a high prevalence of metabolic syndrome. These patients should be regularly monitored for CVD risk factors.

Keywords: High sensitive C-Reactive protein, Selective serotonin reuptake inhibitor

INTRODUCTION

Major Depressive Disorder (MDD) is the most prevalent psychiatric disorder and is also amongst the most severe and debilitating. It has become the second most prevalent cause of illness-induced disability, affecting 350 million people worldwide [1]. Antidepressant medication is commonly prescribed for mental health problems. The use of antidepressant medication has been linked with a greater risk of weight gain [2], Diabetes [3], and with an increased risk of CVD events in most studies [4,5]. Studies have shown that the prevalence of Metabolic Syndrome (MetS) is greater in individuals with MDD symptoms [6,7]. MetS is a cluster of CVD risk factors including central obesity, elevated blood pressure, hypertriglyceridemia, hyperglycaemia and decreased HDLC. The link between depression and coronary heart disease may be mediated through inflammation. Atherosclerosis is preceded by inflammation with increasing production of acute phase proteins, including C-Reactive Protein (CRP) and pro-inflammatory cytokines [8].

C-reactive protein is one of the positive acute phase reactant protein which is produced by hepatocytes when exposed to certain pro-inflammatory cytokines especially interleukin IL-6, which play a key role in inflammation. Increased levels of CRP have been associated with chronic infections and inflammatory conditions, as well as with increased risk of inflammatory CVD [9]. A hs-CRP is a sensitive marker for low-grade systemic inflammation and raised levels in blood independently predict the future risk of CVD [10-12].

However, the relationship among cardiovascular risk, inflammatory markers and MetS is not much explored in Indian patients with depression. The present study aimed to investigate if there are any differences in parameters that constitute MetS, as well as in hs-CRP levels, total cholesterol, and BMI in patients with depressive disorder treated with SSRI medication, compared to healthy controls.

MATERIALS AND METHODS

The present cross-sectional study was conducted at the Department of Psychiatry, SMS Medical College and Hospital, Jaipur, Rajasthan, India, in the month of July-September 2016. Institutional Ethical Committee Approval was obtained before the commencement of the study. Informed consent was obtained from the guardians and families of the subjects.

A total of 94 patients suffering from depression (64 males, 30 females between the age of 20 and 60 years) were recruited in this study. There was no randomisation. The patients were enrolled on first come first serve basis. Patients were interviewed and diagnosed by the psychiatrist as per ICD-10 (International Statistical Classification of Disease and Related Health Problems, 10th Revision) criteria of mental disorders [13]. The sociodemographic profile and history of illness were recorded in self-designed semi-structured pro-forma. The severity of illness was assessed by the psychiatrist using MADRS. Each item is rated from 0 to 6 based on severity (0=no abnormality to 6= severe). Severity gradation for the MADRS have been proposed (9-17=mild, 18-34=moderate, and ≥35=severe) [14].

The inclusion criteria were the patients with diagnosis of depression and those who wanted to participate in the study. Exclusion criteria were mental retardation, chronic inflammatory conditions, treatment with mood stabilisers, pregnant or lactating women.

A total of 50 sex and age matched controls, preferably first-degree relatives, were psychiatrically evaluated and enrolled in the study with no past history of psychiatric illness.

Anthropometric and metabolic assessment: Body weight (in kilograms), height (in meters) and waist circumference (in centimetres) were measured by a calibrated scale. At the end of

normal expiration in standing position, waist circumference was measured at midway between the inferior costal margin and the superior border of the iliac crest. The blood pressure was measured using sphygmomanometer. Under the aseptic condition, fasting venous blood sample was collected to measure their blood glucose (by GOD-POD method) [15], lipid parameters Cholesterol by CHOD-POD method [16], Triglyceride by GPO-POD Endpoint method [17], HDL by direct liquid enzymatic method [18] and hs-CRP levels [19].

International Diabetes Federation (IDF) guideline criteria were used for defining metabolic syndrome. According to the IDF definition, for a person to be defined as having the metabolic syndrome they must have central obesity (defined as waist circumference with ethnicity specific values) plus any two of the following four factors: (i) Raised triglyceride, i.e., ≥150 mg/dL (1.7 mmol/L); (ii) Reduced HDL cholesterol, i.e., <40 mg/dL (1.03 mmol/L) in males, <50mg/dL (1.29 mmol/L) in females; (iii) Raised blood pressure, i.e., Systolic BP≥130 or diastolic BP ≥85 mm; (iv) Raised fasting serum glucose, i.e., FS ≥100 mg/dL (5.6 mmol/dL) [20].

hs-CRP assay: Serum hs-CRP was measured by a typical sandwich type assay of Immuno-Biological Laboratories (IBL-America). Approximately 0.1 mL of serum is required per duplicate determination. The assay makes use of two highly specific monoclonal antibodies: A monoclonal antibody specific for CRP is immobilised on to the microwell plate and another monoclonal antibody specific for a different region of CRP was conjugated to Horseradish Peroxidase (HRP). CRP from the sample and standards were allowed to bind to the plate, washed with wash buffer and subsequently incubated at room temperature with HRP conjugate. After the second washing, enzyme substrate was added. The enzymatic reaction was terminated by addition of the stop solution. The absorbance was measured on a microtitre plate reader at 450 nm. The cut-off value was 1.1 mg/dL. The intensity of the colour formed by the enzymatic reaction was directly proportional to the concentration of the CRP in the sample [19].

STATISTICAL ANALYSIS

The numerical data were presented as Mean±Standard Deviation (mean±SD). Independent t-test was used for comparison of both the groups. Correlation analysis was undertaken using Pearson correlation coefficients (r). The analyses were done using SPSS 20 (Armonk, NY). The probability level of $p<0.05$ was considered to be statistically significant.

RESULTS

The socio-demographic characteristics of the study groups are presented in [Table/Fig-1]. The mean age of depressive patients was 39.24±11.63 (20-60) years and of control subjects was 38.17±10.92 years. Most of the subjects were married {patient group 66 (70.2%), controls 33(66%)}, belonged to joint families {patient group 66 (70.2%), control 31(62%)} and from rural background {(patient group 55(58.5%), control 24(48%)}.

The statistical comparison of physical and laboratory parameters are shown in [Table/Fig-2]. Waist circumference (p=0.001), fasting glucose levels (p=0.007), cholesterol (p=0.002), HDL, LDL and hs-CRP (p=0.001) were significant in-patient group as compared to healthy controls while body mass index (p=0.652), systolic BP (p=0.621) and diastolic BP (p=0.672), triglyceride (p=0.668) was not statistically significant. Correlation of hs-CRP with MADRS, total duration of illness and SSRI length is shown in [Table/Fig-3].

All subjects from the depressive groups were on antidepressant SSRI medication (mean value 4.29±6.13 years). The severity of depressive symptoms measured by MADRS scale showed that there were 12 (12.76%) severe depressive patients, 37 (39.36%) moderate and 45 (47.87%) mild depressive patients. Total duration of illness was 6.78±5.26 years. hs-CRP was positively significant correlated with total duration of illness (p=0.004) and length of SSRI therapy (p=0.008), however there was no significant correlation with MADRS score (p=0.712). 42.6% of present samples fulfilled the IDF criteria for metabolic syndrome.

Variable	Mean±SD	Healthy controls
	Patient group	
	n=94	n=50
Age (years)	39.24±11.63	38.17±10.92
Marital Status		
Single	17 (18.0%)	16 (32%)
Married	66 (70.2%)	33 (66%)
Widower/Divorced/	11 (11.7%)	01 (2%)
Employment		
Employed	58 (61.7%)	32 (64%)
Unemployed	36 (38.2%)	18 (36%)
Education		
Secondary	61 (64.8%)	31 (62%)
University	33 (35.1%)	19 (38%)
Family Type		
Nuclear	28 (29.7%)	19 (38%)
Joint	66 (70.2%)	31 (62%)
Locality		
Urban	39 (41.4%)	26 (52%)
Rural	55 (58.5%)	24 (48%)

[Table/Fig-1]: Socio-demographic comparison in depressive patients and Control.

Variable	Mean±SD	Healthy controls	p-value
	Patient group		
	n= 94	n=50	
BMI (kg/m^2)	22.27±4.88	21.81±3.34	0.652
Waist circumference (cm)	95.57±10.0	84.6±12.78	0.001
Fasting glucose (mg/dL)	99.43±53.47	82.54±20.34	0.007*
Systolic BP (mmHg)	123.5±9.4	121.4±8.7	0.621
Diastolic BP (mmHg)	83.8±10.4	79.2±8.9	0.672
Total cholesterol (mg/dL)	198.96±39.67	171.99±52.82	0.002*
Triglyceride (mg/dL)	153.60±96.51	144.61±129.58	0.668
HDL (mg/dL)	38.24±2.86	40.40±1.45	<0.001*
LDL (mg/dL)	128.12±40.02	102.69±29.68	<0.001*
hs-CRP (mg/dL)	3.30±2.61	1.96±0.70	<0.001*

[Table/Fig-2]: Statistical comparison of physical and biochemical parameters in depressive patients and controls.
*Correlation is significant at the 0.05 level

Variable	hs-CRP	
	Pearson correlation	p-value
MADRS	0.039	0.712
TDI	0.295	0.004**
SSRI duration	0.271	0.008**

[Table/Fig-3]: Correlation of hs-CRP with different variables.
**Correlation is significant at the 0.05 level
TDI: Total Duration of Illness; SSRI: Selective Serotonin Reuptake Inhibitor

DISCUSSION

MetS is a cluster of symptoms with higher prevalence in psychiatric patients compared to the general population [21]. Numerous pathophysiological mechanisms have been proposed to explain this occurrence. Majority of the studies have focused on drug-treated psychiatric population and on the role of psychotropic drugs in the causation of MetS.

The prevalence of Mets in present experimental group of patients with depressive disorder was 42.6%. The present finding is similar to previous reports. For instance a study by Stanojevic A et al., found that the prevalence was 48.6% compared to 28% in the healthy control group of patients (p= 0.11) [22]. Among the US adults, 24% have MetS, and the prevalence increases with age (44% at age 60 years) [23]. Fagiolini A et al., evaluated 171 patients and found the MetS prevalence of 30% [24]. Another study reported the MetS prevalence rate of 32% in a group of 125 bipolar patients [25].

In a study in Northern India conducted on psychiatric in-patients by Mattoo SK and Singh SM, the prevalence of MetS as per IDF criteria was 37.8% for the entire sample, while it was 29.8% for males and 46.5% for females [26]. In the depressive disorder group, the reported prevalence was 13.3% overall, while it was 4.4% in male depressives and 8.9% in female depressive patients. The two other studies from the United States [27] and Brazil [28] using ATP III criteria for the MetS found prevalence rates of 38.6% and 29.4% respectively.

The finding of this research of higher levels of inflammation protein hs CRP in depressed patients with metabolic syndrome is in line with the study by Maes M., who showed that increased inflammation with influence on lower serotonin levels, and metabolic abnormality in depression could be in the circle in which serotonin and proinflammatory cytokines are interwined and mutually induce one another [29]. Numerous studies have now confirmed that CRP levels are elevated in patients with MetS [30,31].

The cut-off point for an elevated value of CRP in the present study was 6 mg/L. The relationship among high CRP values and variable such as severity of depression measured by MADRS scale, length of SSRI therapy and length of illness duration was also explored. There was no significant correlation between MADRS and hs-CRP. It means in the present study it is not necessary that the person who is severely depressed have high hs-CRP level however, hs-CRP was positively correlated with total duration of illness and length of SSRI therapy, so depression is associated with activation of inflammatory response. Some studies also found an association between increased CRP levels with the severity of depressive symptoms [32] and normalisation after antidepressant treatment [33], however findings are not consistent across studies. Measurement of inflammatory markers in depressive patients with MetS may be beneficial in prediction, detection and management of cardiovascular events.

LIMITATION

The limitation of the present study was that all patients who enrolled for the study were taking SSRI medication. Also, for patient population, the factors like physical activity or dietary habits were not controlled hence, the effect of these factors on CVD risk could not be described.

CONCLUSION

One of the outcomes of the study is that measurement of serum inflammatory parameters in depressive patients with MetS may be beneficial in the prediction, detection and management of cardiovascular events. Depression requires a systemic approach, rather than a solely psychiatric treatment scheme.

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