Association of Inflammatory and Liver Markers with Cardiometabolic Risk Factors in Patients with Depression

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Abstract Metabolic syndrome (MS) is found to be more prevalent in patients with psychiatric disorders including depression. This study aimed to assess the association of inflammatory and liver markers with cardiometabolic risk factors in patients with Depressive disorders. Prevalence of MS by using Modified NCEP ATP-III Criteria and liver enzymes and CRP were assessed in 382 patients with depressive disorders. MS prevalence was 27.7% and lower HDL level was the commonest metabolic abnormality. ALT, GGT, and CRP levels were positively correlated with weight and BMI. ALT, GGT, and CRP levels were significantly greater in patients with abnormal waist circumference, triglyceride levels and raised blood pressure, compared to patients with normal indices. Such association was not found with abnormal HDL cholesterol and hyperglycemia. Levels of GGT and CRP were significantly greater in patients with MS compared to patients without MS and CRP was significant predictor for MS. To conclude, one-fourth of depressed patients had MS. MS and metabolic abnormalities were associated with inflammatory marker and liver enzymes. Patients with depression should be regularly evaluated for cardiovascular risk factors, liver enzymes, and inflammatory markers.

Keywords Metabolic syndrome · Liver enzymes · Inflammatory markers · Depression · India

Introduction

Depression is second common cause of disability [1]. It is associated with increased morbidity, mostly due to cardiovascular diseases. Metabolic syndrome (MS) partly mediates the association as depression increases the risk of MS by twofold [2].

Prevalence of MS in patients with depression or depressive symptoms is reported in the range of 11–57%. A recent systematic review and meta-analysis by Vancampfort et al. [3] reported pooled MS prevalence of 31.3% in patients with depressive disorders.

Liver enzymes like aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), glutamyltransferase (GGT), and alkaline phosphatase (ALP) may predict metabolic syndrome [4], with the good evidence base for ALT [4] and GGT [5, 6].

A prospective cohort study of 5984 employed adults reported association of elevated ALT with the risk of developing depression and suggested non-alcoholic fatty liver disease (NAFLD) as an independent modifiable risk factor for depression [7]. A population-based cohort of 1439 subjects reported predictive value of ALT for coronary events (hazard ratio = 1.88) independent of traditional risk factors and metabolic syndrome [8].

Greater risk of cardiovascular disorder is reported in patients with MS and high GGT compared to patients with MS and low GGT or patients without MS (odds ratio = 2.66) [4]. For better cardiovascular risk prediction, inclusion of raised GGT criteria for MS diagnosis is also recommended [5].

Inflammatory markers, especially C reactive proteins (CRP) was found to be associated with lower high-density lipoprotein and overweight/obesity and elevated in patients with depressive disorders [9].

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However, Indian literature is scarce on the relationship of inflammatory and liver markers with cardiometabolic risk factors in patients with depression. The present study was aimed to assess the association of inflammatory and liver markers with metabolic abnormalities in patients with depressive disorders.

Materials and Methods

After obtaining approval from Institutional Ethics Review Committee, this study was carried out at the Psychiatry outpatient clinic of a tertiary-care hospital in North-Western India. The study included consecutive patients of either gender aged between 18 and 60 years, with depressive disorder (first episode depression, or recurrent depressive disorder, or Dysthymia) as per International Classification of Diseases (ICD-10) [10] consulted to outpatient psychiatry clinic from March 2015 to August 2016. Written informed consent was obtained from all the patients and all the assessments were done at their first visit. All the patients with depressive disorder were included except patients with bipolar depression, psychotic depression, and any other comorbid psychiatric or chronic physical disorders were excluded from the study. Diagnostic confirmation was done by Psychiatry Consultant by using Mini International Neuropsychiatric Interview (MINI) [11].

Total 382 patients with depressive disorders were consecutively recruited and assessed for their inflammatory marker [high sensitivity C reactive protein (hsCRP)], liver enzyme (AST, ALT, GGT) and metabolic abnormalities. Metabolic profile of 170 patients has been published earlier as preliminary estimate [12].

Including demographic and clinical profile sheet following instruments were used.

Mini International Neuropsychiatric Interview (MINI)

It is a clinician based, brief structured interview for diagnosis of major axis I psychiatric disorders and found to have high validity and reliability [11].

Hamilton Depression Rating Scale (HDRS)

It is a clinician rated 17 items likert scale to assess severity of depression [13].

Anthropometric and Metabolic Assessments

Body weight, height and waist circumference were measured by a calibrated scale. At the end of normal expiration,

waist circumference was measured at midway between the inferior costal margin and the superior border of the iliac crest. Blood pressure was measured by standard mercury manometer.

Under aseptic condition, fasting venous blood sample was collected to measure their blood glucose (FBS), triglycerides (TG), high density lipoprotein (HDL), C-reactive protein (hsCRP), Aspartate transaminase (AST, SGOT), Alanine aminotransferase (ALT, SGPT), and Gamma-glutamyltransferase (GGT) levels.

Modified NCEP ATP-III criteria was used for diagnosing MS, in which 3 out of following 5 abnormalities should be present to establish MS diagnosis: high waist circumference (≥ 80 cm for females and ≥ 90 for males of Asian origin), high systolic blood pressure ≥ 130 and/or high diastolic blood pressure ≥ 85 mm of Hg (or on treatment for hypertension), high triglyceride levels ≥ 150 mg/dl (or on specific treatment for this abnormality), low HDL cholesterol < 40 mg/dl for male and < 50 mg/dl for females (or on specific treatment for this abnormality), and high fasting blood sugar ≥ 100 mg/dl (or on treatment for diabetes mellitus) [14].

Statistical Analysis

SPSS version 14.0 for Windows (Chicago, Illinois, USA) was used for analysis. Frequencies and percentages were calculated for categorical variables whereas mean and standard deviation were calculated for continuous variables. Subjects with and without metabolic syndrome were compared by using Chi Square test and t-tests and in case of skewed data non-parametric tests (Mann–Whitney U test for continuous variables and Fisher exact test for categorical variables) were employed. Correlational analysis was employed to find out association of metabolic syndrome with demographic and clinical variables and regression analysis was done to assess the predictors of MS.

Results

Socio-demographic Profile

The study group comprised of 382 patients with depressive disorders. As depicted in Table 1, mean age and education were 36 and 8 years respectively. Majority were married and Hindu by religion, nearly one-third of patients were from nuclear family and rural locality and two-fifth of patients were males and on paid employment.

Table 1 Socio-demographic variables

Variable	Mean (SD)
Age (years)	36.08 (10.52)
Education (years)	8.96 (5.65)
	Frequency (%)
Sex	
Male	166 (43.4)
Female	216 (56.6)
Marital status	
Currently single	51 (13.3)
Married	331 (86.7)
Occupation	
On paid jobs	161 (42.1)
Home makers/not on paid jobs	221 (57.9)
Religion	
Hindu	343 (89.8)
Non-hindus	39 (10.2)
Family type	
Nuclear	143 (37.4)
Non-nuclear	239 (62.6)
Locality	
Urban	241 (63.1)
Village	141 (36.9)

Clinical Profile

Mean age at onset, duration of depression, and HDRS score were 32 years, 40 months, and 17 respectively. The most common psychiatric diagnosis was first episode depressive episode (62%). Small proportion of patients (N = 68, 17.8%) were receiving psychotropics (mostly antidepressants and anxiolytic combination) at the time of intake (Table 2).

Table 2 Clinical profile of patient group

Variable	Mean (SD)
Age at onset of depression (years)	32.70 (10.22)
Duration of depression (months)	40.45 (49.97)
Depression severity (HDRS score)	17.11 (5.74)
	Frequency (%)
Depression subtype	
First episode depression	261 (62.4)
Recurrent depressive disorder or Dysthymia	121 (28.9)
On psychotropics	68 (17.8)

Profile of Inflammatory Marker, Liver Enzymes and Metabolic Abnormalities

Mean levels of AST, ALT, GGT, hsCRP and proportion of abnormal levels of these indices are depicted in Table 3. Lower HDL level was the commonest metabolic abnormality followed by raised waist circumference and the least common abnormality was abnormal blood pressure. 106 patients with depressive disorder (27.7%) fulfilled the criteria for MS and another 108 (28%) patients fulfilled 2 out of the 5 criteria for MS and another 119 (31%) fulfilled 1

Table 3 Profile of metabolic abnormalities, liver enzymes, and inflammatory marker

Variable	Mean (SD)
AST	23.43 (10.53)
ALT	24.29 (16.42)
GGT	22.99 (23.65)
hsCRP	0.27 (0.49)
	Frequency (%)
Abnormal AST (> 50 U)	11 (2.87)
Abnormal ALT (> 50 U)	22 (5.75)
Abnormal GGT (> 30 U)	31 (8.11)
Abnormal hsCRP (> 2 U)	5 (1.30)
Abnormal waist circumference (≥ 90 M, ≥ 80 F)	176 (46.1)
Abnormal blood pressure (≥ 130/≥ 85 mmHg)	72 (18.8)
Abnormal Triglyceride (≥ 150 mg/dl)	93 (24.3)
Abnormal HDL (< 40 mg/dl M, < 50 mg/dl F)	249 (65.1)
Abnormal fasting blood sugar (≥ 100 mg/dl)	104 (27.2)
Obesity (BMI ≥ 25)	134 (35.1)
Metabolic syndrome (consensus criteria)	106 (27.7)

BMI body mass index, *HDL* high density lipoprotein

criterion for MS. Nearly one-third of the patients (35%) were obese [body mass index (BMI) ≥ 25].

Association of Inflammatory Marker and Liver Enzymes with Metabolic Syndrome and Metabolic Abnormalities

Metabolic Syndrome

GGT (26.22 ± 21.17 vs. 21.77 ± 24.44 , Mann–Whitney (MW) U value = 4.15, $p < 0.001$) and hsCRP (0.43 ± 0.48 vs. 0.20 ± 0.48 , MW value = 6.24, $p < 0.001$) levels were significantly greater in patients with MS compared to patients without MS. hsCRP was significant predictor for MS (B = 1.03, SE = 0.286, Wald = 13.14, $df = 1$, $p < 0.001$, OR = 2.82, CI 1.611–4.945).

Waist Circumference

ALT (25.51 ± 15.20 vs. 23.24 ± 17.30 , MW value = 2.80, $p = 0.005$), GGT (25.97 ± 28.55 vs. 20.47 ± 18.23 , MW value = 4.23, $p < 0.001$), hsCRP (0.43 ± 0.63 vs. 0.13 ± 0.24 , MW value = 8.22, $p < 0.001$) levels were significantly greater in patients with greater waist circumference compared to patients with normal waist circumference.

Blood Pressure

ALT (27.26 ± 17.73 vs. 23.60 ± 16.05 , MW value = 2.24, $p = 0.025$), GGT (28.08 ± 25.12 vs. 21.82 ± 23.18 , MW value = 2.87, $p = 0.004$), hsCRP (0.36 ± 0.46 vs. 0.24 ± 0.49 , MW value = 3.34, $p = 0.001$) levels were significantly greater in patients with raised blood pressure compared to patients with normal blood pressure.

Triglyceride

AST (26.87 ± 12.01 vs. 22.32 ± 9.78 , MW value = 4.46, $p < 0.001$), ALT (31.27 ± 21.10 vs. 22.04 ± 13.91 , MW value = 5.02, $p < 0.001$), GGT (31.07 ± 23.94 vs. 20.44 ± 23.02 , MW value = 6.28, $p < 0.001$), hsCRP (0.33 ± 0.45 vs. 0.25 ± 0.50 , MW value = 3.69, $p < 0.001$) levels were significantly greater in patients with raised triglyceride compared to patients with normal triglyceride level.

Obesity

ALT (25.94 ± 16.01 vs. 23.40 ± 16.60 , MW value = 2.62, $p = 0.009$), GGT (27.02 ± 30.85 vs.

20.81 ± 18.37 , MW value = 4.54, $p < 0.001$), hsCRP (0.44 ± 0.44 vs. 0.17 ± 0.49 , MW value = 8.98, $p < 0.001$) levels were significantly greater in obese patients compared to non-obese patients.

Weight

Mean weight was positively associated with ALT (Pearson correlation coefficient = 0.216, $p < 0.001$), GGT (correlation coefficient = 0.193, $p < 0.001$), and hsCRP (correlation coefficient = 0.262, $p < 0.001$).

Body Mass Index

Mean BMI was positively associated with ALT (Pearson correlation coefficient = 0.115, $p = 0.025$), GGT (correlation coefficient = 0.167 $p = 0.001$), and hsCRP (correlation coefficient = 0.347, $p < 0.001$).

AST, ALT, GGT, and hsCRP levels were not associated with HDL and fasting blood sugar.

Discussion

Both depression and MS are major public health problems, with significant disease burden and substantial physical comorbidity, especially cardiovascular [15]. A recent meta-analysis by Vancampfort et al. [3] reported greater risk of MS (relative risk = 1.57) in patients with depression compared to healthy controls. Index study evaluated MS in 382 patients with depression and the association of liver enzymes (AST, ALT, and GGT) and inflammatory marker (hsCRP) with MS.

Index study found 27.7% prevalence of MS in patients with depression which was within the reported range of 17–46% of other Indian studies [16–20] and similar to mean MS prevalence (29.7%) reported by a meta-analysis by Vancampfort et al. [21].

In line with earlier studies [5, 6, 9], index study found significant association of MS and metabolic abnormalities with liver enzymes and inflammatory marker, therefore supported the hepatic mechanism for MS.

Similar to earlier studies [22, 23], we have also found significantly raised GGT levels in depressed patients with MS compared to patients without MS. We could not find such association with other liver enzymes (ALT, AST), while few studies have reported raised ALT and AST with MS [24, 25]. Index study found significant association of liver enzymes (GGT and ALT) with metabolic abnormalities like abnormal waist circumference, blood pressure, triglyceride, obesity, weight and BMI. Similar association of GGT with adiposity [25], BMI [26] and cardiovascular risk factors [27] were reported by earlier studies.

Liver enzymes (especially ALT and GGT), even within the reference range, were found to be significantly associated with MS [24, 25]. Similarly in index study majority of our patients had liver enzymes within the reference range (elevated AST in 2.8%, elevated ALT in 5.7%, and elevated GGT in 8.1% patients). ALT and GGT were significantly associated with metabolic abnormalities and GGT was significantly associated with MS in our patients with depression.

In line with earlier studies [6, 28], we also found significant association of raised hsCRP with MS and metabolic abnormalities like waist circumference, blood pressure, triglyceride, BMI and obesity. Index study reported hsCRP as significant predictor of MS (OR = 2.82), similarly Rethorst et al. [29] labeled CRP as predictor for MS (OR 2.81 for those with CRP levels ≥ 3.0 mg/L). Similar to findings from other study [29], index study found significant association between elevated inflammation (CRP) and presence of MS components/metabolic abnormalities (Pearson's correlation coefficient = 0.219, $p < 0.001$). A study by Rethorst et al. [29] did not find any association of age and gender with CRP levels, but index study found significantly raised hsCRP levels with greater age and female gender.

Other studies have also reported association of depression severity with CRP, reduction in CRP levels with weight loss and with improvement in depression [28].

Inflammation is reported to be an important link between depression and MS, and inflammation, obesity and MS substantially increase the risk of medical comorbidities in patients with depression. Inflammation is linked with depression in different ways such as several inflammatory disorders frequently co-occur with depression, levels of inflammatory activity are elevated in depression, inflammatory challenges evoke depressive symptoms, and anti-inflammatory agents can help to alleviate depressive symptoms. Cytokines have been found to reduce levels of serotonin by reducing the availability of tryptophan and antidepressant treatments have been found to reduce levels of proinflammatory cytokines.

Index study report significant association of MS with elevated liver enzymes and inflammatory marker, which highlights the similarity of findings in Indian patients as mentioned in other studies conducted outside India [5, 6, 9]. It needs further replication in larger sample for more evidence and generalizability.

Strengths of our study are larger sample of 382 patients with depression, exclusion of patients with physical and psychiatric comorbidities, incorporation of liver enzymes (AST, ALT, GGT) and inflammatory marker (hsCRP) to find out their association with MS in depression.

Index study has following limitations: cross-sectional design, hospital based sample, could not assess treatment

refractoriness, other life style factors, and other inflammatory markers and their association with MS or metabolic abnormalities. Future studies should overcome above limitations and to be conducted in larger multicentric sample from hospital and community setting. Studies should also explore the underlying mechanisms for MS, with hepatic derangement and raised inflammatory markers, and should guide for effective strategies for management and prevention of these morbidities. Prospective studies with robust methodology should prove vital in determining the importance of liver enzymes and inflammatory markers to predict cardiovascular risk factors and MS.

To conclude, index study reported 27.7% prevalence of MS in patients with depression and lower HDL level was the commonest metabolic abnormality. ALT, GGT, and hsCRP levels were positively correlated with weight and BMI. ALT, GGT, and hsCRP levels were significantly greater in patients with abnormal waist circumference, triglyceride levels and raised blood pressure, compared to patients with normal indices. Such association was not found with abnormal HDL cholesterol and hyperglycemia. Levels of GGT and CRP were significantly greater in patients with MS compared to patients without MS and CRP was the significant predictor for MS.

Clinicians should thoroughly evaluate liver enzymes, inflammatory markers, metabolic abnormalities and MS in patients with depression for comprehensive treatment and prevention of cardiovascular risk factors and morbidity. The significant association of hepatic and inflammatory markers with MS in index and earlier studies and ease of processing blood sample for liver and inflammatory markers from patients with MS, and better cardiovascular risk prediction further emphasize for incorporation of liver and inflammatory markers in diagnosing and predicting MS.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflict of interest.

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